GlaxoSmithKline

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PERIODIC BENEFIT RISK EVALUATION REPORT/EU PERIODIC SAFETY UPDATE REPORT

Department	Vaccines Clinical Safety and Pharmacovigilance, GlaxoSmithKline Global Vaccines Development Site de Wavre Nord, Avenue Fleming 20, B- 1300 Wavre, Belgium
Generic Name/ Trade Name	Combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine / Infanrix™ hexa
International Birth Date	23 February 2000 (Colombia)
EU Birth Date	23 October 2000 (European Union)
Reporting Period	23 October 2011 to 22 October 2014
Report date	15 January 2015

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PREFACE

On 29 September 2014 GSK implemented a new safety database, Argus Safety. Entry of ICSRs onto the previous GSK safety database, OCEANS, continued through EOB 26 September 2014. All cases from OCEANS have been migrated into Argus Safety.

As the data presented in this report consist of cases migrated from OCEANS as well as cases entered directly into Argus Safety, there may be differences in the presentation of data in outputs compared to those in previous reports.

In particular, changes to the presentation of event seriousness in the summary tabulation outputs have been made. This was previously presented according to whether or not the case in which the event resided was serious. Event seriousness in the new outputs is based on the event level assessment from Argus Safety. As a result, variations in event counts in summary tabulations may be observed when compared with previous reports.

QPPV DELEGATION STATEMENT

As the European Qualified Person for Pharmacovigilance for Infanrix™ hexa, I confirm I have delegated the task of preparation and signature of the attached Periodic Benefit Risk Evaluation Report/EU Periodic Safety Update Report to the person who has signed that document. That person is an appropriately qualified and trained individual for the purposes of performing that task.

Contact Details

EU Qualified Person
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EXECUTIVE SUMMARY

- This is the Periodic Benefit-Risk Evaluation Report (PBRER) / EU Periodic Safety Update Report (EU-PSUR) for GlaxoSmithKline's (GSK's) combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine / Infanrix™ hexa, hereafter referred to as *Infanrix hexa*. It summarises benefit and risk information regarding *Infanrix hexa* both cumulatively and for the current reporting period of 23 October 2011 to 22 October 2014.
- *Infanrix hexa* is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b.
- *Infanrix hexa* has been approved for marketing in over 100 countries.
- During the period under review, there have been no dosage modifications, changes in target population, formulation changes, restriction on distribution, clinical trial suspension, neither have there been any withdrawal, revocation, rejection or failure to obtain a renewal of a Marketing Authorization. However, the following actions were taken during the period for safety reasons:
  - GSK Biologicals' initiated a voluntary recall on 05 October 2012 for specific batches of *Infanrix hexa* in different countries due to a potential microbiological contamination. The safety data reviewed during the period did not show any clinical evidence of the potential presence of a contamination of the vaccine.
  - Temporary suspension of *Infanrix hexa* batch **A21CC054A** in Czech Republic as a consequence of a reported case with a fatal outcome. GSK reviewed the manufacturing investigation results and concluded that there was no deviation or manufacturing incident that could have an impact on the safety of the subjects vaccinated with batch **A21CC054A**. The case that led to the temporary suspension has been reported by a physician who stated that the child died of probable sudden death and that there was a possibility of aspiration. Sudden infant death syndrome was confirmed by autopsy. A Dear Health Care Professional Letter was submitted with this information. Information received after the DLP of the report confirmed that the batch was released on 27 November 2014.
  - Submission of a Dear Health Care Professional Letter as a result of a request/complaint to GSK Austria from a customer regarding *Infanrix hexa* batch **A21CC196A** which contains shorter needles than the ones currently used for this market: 25G 5/8" (= diameter 0.5mm / length 16mm) instead of 25 G1" (= diameter 0.5mm / length 25mm). Both needle sizes lead to a comparable immunogenicity although the use of a shorter needle for vaccination may lead to a higher risk of local reactions. The benefit of the vaccination with *Infanrix hexa* remains favourable over the risk of experiencing injection site adverse events.

- The following updates to the reference safety information (RSI) were made during the period:
  - In the 'Adverse events' section, in subsection 'Experience with hepatitis B vaccine', 'Mimicking serum sickness' was replaced by 'Allergic reactions mimicking serum sickness' to be in line with the Hepatitis B RSI.
  - In the 'Use and Handling' section, the instruction to shake the mixture until the powder is completely dissolved in the suspension was added to subsection 'Wording for vial and pre-filled syringe presentation', to be in line with subsection 'Wording for vial and vial presentation' of the *Infanrix hexa* GPI.
  - Template related changes impacting RSI in the *"Use and Handling"* section. These changes were not the result of new safety data received.
  - Post-marketing data identified a potential increased risk of convulsion (with or without fever) and hypotonic-hyporesponsive episode (HHE) when *Infanrix hexa* is co-administered with Prevenar13™. Frequency categories for the respective events following *Infanrix hexa* - Prevenar13™ co-administration are expected to remain unchanged compared to *Infanrix hexa* single administration.The RSI was updated with a warning about these potential increased risks.
- The cumulative number of subjects that have received *Infanrix hexa* within the clinical development programme (CDP) is 14,109 (plus 585 blinded vaccinations) in primary studies and 10,672 in booster studies. The overall number of subjects who have received *Infanrix hexa* in other CDPs is 27,430 in primary studies and 11,025 in booster studies.

  Note that subjects from booster studies may have participated in priming studies. Therefore the overall number of subjects in the entire development programme cannot be calculated by adding the number of subjects in priming studies to those in booster studies.
- As subjects can receive one to four doses of *Infanrix hexa*, the post-marketing exposure to *Infanrix hexa* in the reporting period is estimated to be between 11,723,455 and 46,893,819 subjects. The cumulative post-marketing exposure to *Infanrix hexa* is estimated to be between 29,898,921 and 119,595,685 subjects.
- According to peer reviewed literature, a risk of waning of acellular pertussis vaccine induced immunity was identified for acellular pertussis containing vaccines. GSK concludes that it is critical to maintain strong acellular pertussis immunization programs (i.e. high vaccine coverage and timeliness of vaccination) to control pertussis in this period of increased circulation of disease. GSK will continue close monitoring waning of acellular pertussis vaccine induced immunity and post-marketing lack of efficacy cases through routine pharmacovigilance.
- Important risks have been newly identified during the period: the potential increased risk of convulsion (with or without fever) and hypotonic-hyporesponsive episode when *Infanrix hexa* is co-administered with Prevenar™ 13 (see above). The potential increase of HHE and convulsions with or without fever after co-administration of *Infanrix hexa* with Prevenar™ 13 vaccine found after review of

post-marketing data, does not represent a change of the frequencies of these 'very rare' events.

- The benefit: risk profile of *Infanrix hexa* for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b continues to be favourable.
- The company continues to monitor cases of anaemia haemolytic autoimmune,thrombocytopenia, thrombocytopenic purpura, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, haemolytic anemia, Kawasaki's disease, important neurological events (including encephalitis and encephalopathy), Henoch-Schonlein purpura, petechiae, purpura, haematochezia, allergic reactions (including anaphylactic and anaphylactoid reactions), extensive swelling of vaccinated limb, cases of lack of effectiveness as well as fatal cases.
- The company ended close monitoring of Cyanosis, Gaze palsy, Haematochezia, Injection site nodule, abscess and injection site abscess.

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1. INTRODUCTION

This Periodic Benefit Risk Evaluation Report (PBRER) / EU Periodic Safety Update Report (EU-PSUR) for GlaxoSmithKline's (GSK's) combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine / Infanrix™ hexa, hereafter referred to as *Infanrix hexa,* covers the reporting period from 23 October 2011 to 22 October 2014. This PBRER is compiled in accordance with the ICH-E2C(R2) guideline and the EU Guideline on Good Pharmacovigilance Practices (GVP) Module VII – Periodic Safety Update Report and summarises benefit and risk information regarding *Infanrix hexa* both cumulatively and for the reporting interval. The International Birth Date (IBD) for *Infanrix hexa* is 23 February 2000 (Colombia). The EU Birth Date for *Infanrix hexa* is 23 October 2000.

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b. The primary vaccination schedule consists of three doses of 0.5 ml (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) or two doses (e.g. 3, 5 months). There should be an interval of at least one month between doses. The Expanded Program on Immunisation schedule (at 6, 10, 14 weeks of age) may only be used if a dose of hepatitis B vaccine has been given at birth.

After a vaccination with 2 doses (e.g. 3, 5 months) of *Infanrix hexa*, a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age. After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) of *Infanrix hexa*, a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

A 0.5 ml dose of vaccine contains not less than 30 IU of adsorbed diphtheria toxoid, not less than 40 IU of adsorbed tetanus toxoid, 25 mcg of adsorbed PT, 25 mcg of adsorbed FHA, 8 mcg of adsorbed pertactin, 10 mcg of adsorbed recombinant HBsAg protein, 40 D antigen units of type 1 (Mahoney), 8 D antigen units of type 2 (MEF-1), and 32 D antigen units of type 3 (Saukett) of the polio virus and 10 mcg of *Haemophilus influenzae* type b polysaccharide conjugated to tetanus toxoid as carrier protein.

This report covers all formulations and indications for *Infanrix hexa.*

2. WORLDWIDE MARKETING AUTHORISATION STATUS

Infanrix hexa was first approved on 23 February 2000 in Colombia for primary and booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and disease caused by *Haemophilus influenzae* type b and is currently approved in over 100 countries, including all European Union Member States, Norway, Iceland, Switzerland, Canada and Australia.

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

Actions related to investigational use

During the period under review, there have been no dosage modifications, changes in target population, formulation changes, restriction on distribution, clinical trial suspension/refusal, or any other action taken for safety reasons.

Actions related to marketing experience

During the period under review, there has been no withdrawal, revocation, rejection or failure to obtain a renewal of a Marketing Authorization.

However, the following actions were taken during the period for safety reasons:

- GSK Biologicals initiated a voluntary recall on 05 October 2012 for specific batches of *Infanrix hexa*, Infanrix™-IPV and Infanrix™-IPV/Hib (30 batches in total) in the following countries: Albania, Australia, Belgium, Brazil, Canada, Czech republic, Cyprus, France, Germany, Greece, Lebanon, Malaysia, Malta, Netherlands, Qatar, Romania, Slovakia, Spain, UK and Vietnam. No affected batches were distributed in other countries. This voluntary recall was triggered by a potential microbiological contamination (*Bacillus cereus*) of affected batches identified during the quality control testing on the surrounding environment: no contamination was found in the products themselves. The product impact assessment was performed by a multidisciplinary team of GSK Biologicals experts concluding that the risk of contamination theoretically exists, however this risk is low because there was no indication of contamination of the product. An initial safety evaluation of all adverse events reported with the recalled batches and non-recalled batches was performed. A comparison of the reporting rates corresponding to the recalled batches and non-impacted batches did not reveal any abnormal incidence of reported adverse events of interest. The majority of the events of interest reported in association with the recalled batches are in line with the current Reference Safety Information (RSI) of *Infanrix hexa*, Infanrix™-IPV and Infanrix™-IPV/Hib. No cases were reported with *B. Cereus* identified as a causative pathogen so far. The safety data reviewed to date did not show any clinical evidence of the potential presence of a contamination of the vaccine with *B. cereus*. A causal role of infection due to *B. cereus* is considered unlikely, as the probability of contamination in the final vaccine containers remains speculative. The company committed to provide monthly reports to the European Medicines Agency (EMA) for a period of 6 months following the voluntary recall containing a cumulative review of ADRs reported with implicated batches and any case with a suspicion of infectious aetiology. The sixth and last monthly report was submitted to EMA in time and endorsed.
- Temporary suspension of *Infanrix hexa* batch **A21CC054A** in Czech Republic as a consequence of a reported case with a fatal outcome. The regulatory authorities in Czech Republic sent a request to GSK for the investigation of the vaccine batch **A21CC054A** administered (see also APPENDIX 7A.2).

Review of available data concluded that except from a temporal relationship to *Infanrix hexa* administration there was no other scientific or medical evidence of the causal role of the vaccination in the subject's death. The physician who reported this case stated that the child died of a probable sudden death, and that there was a possibility of aspiration. Sudden infant death syndrome was confirmed by autopsy.

The batch documentation review has been performed by GSK Vaccines Quality Assurance (QA) and Quality Control (QC) and according to GSK procedures: No deviation that could impact the quality of the product has been highlighted. GSK has reviewed the manufacturing investigation results and concluded that there was no deviation or manufacturing incident that could have an impact on the safety of the subjects vaccinated with batch **A21CC054A**. A Dear Health Care Professional Letter was submitted with this information. Refer to Section 14 for further information on this investigation.

- GSK Austria received a request/complaint from a customer regarding *Infanrix hexa* batch **A21CC196A** which contains shorter needles than the ones currently used for this market: 25G 5/8" (= diameter 0.5mm / length 16mm) instead of 25 G1" (= diameter 0.5mm / length 25mm).

  Both needle sizes are registered for *Infanrix hexa* vaccination via centralized procedure. Both needle sizes lead to a comparable immunogenicity although the use of a shorter needle for vaccination may lead to a higher risk of local reactions. Therefore decisions on needle size remain under the health care professional's responsibility and depend on the subject's morphology and the vaccination technique. Even with a shorter needle (16 mm) the benefit of the vaccination with *Infanrix hexa* remains favourable over the risk of experiencing injection site adverse events. The next batch will be shipped again with needle size 25G1 from the manufacturing site. A Dear Health Care Professional Letter was submitted with this information (see also APPENDIX 7A.2).

4. CHANGES TO REFERENCE SAFETY INFORMATION

Changes to the RSI, including rationale, are communicated to Regulatory Agencies on an ongoing basis. The RSI in effect at the end of the reporting period is presented in APPENDIX 1A.

The RSI is the Global Prescriber Information (GPI) version 014 dated 13 March 2014; the RSI is highlighted in this document by shaded text.

Revision marked changes to the RSI during the reporting period are shown in APPENDIX 1B, 1C, 1D and 1E. Changes to the RSI during the reporting period are highlighted in the documents (deleted text shown as ~~**blue, bold strikethrough**~~; new text shown as ***red, bold italics***).

There were four updates to the GPI during the period under review:

- On 17 October 2012 (version 011):
  - **Adverse Reactions section**: this section includes a subsection "Experience with hepatitis B vaccine" as one of the active substances of *Infanrix hexa* is hepatitis B.

    This subsection lists adverse events reported additionally with the hepatitis B vaccine. However, part of one adverse event listed in the hepatitis B GPI has been incorrectly reflected in the *Infanrix hexa* GPI, i.e. "allergic reactions including anaphylactoid reactions and mimicking serum sickness". "Allergic reactions (including anaphylactic and anaphylactoid reactions)" is listed under the subsection post-marketing data of the *Infanrix hexa* GPI as this adverse event has been reported with the vaccine itself.

    "Mimicking serum sickness" has not been reported following vaccination with *Infanrix hexa*. "Mimicking serum sickness" is therefore listed in subsection "Experience with hepatitis B vaccine", but without being linked with allergic reactions, which is the case in the hepatitis B GPI. "Allergic reactions" was added before "mimicking serum sickness" to align the *Infanrix hexa* GPI with the Hepatitis B GPI.
  - **Use and Handling section:** this section includes reconstitution instructions for the "vial + vial" and the "vial + pre-filled syringe" presentations. In the "vial + vial" presentation, the instruction to shake the mixture until the powder is completely dissolved in the suspension is given, whereas the "vial + pre-filled syringe" presentation does not include this instruction. Therefore this instruction was added to the "vial + pre-filled syringe" presentation.

In addition to the above RSI changes, hepatitis B persistence data as assessed in clinical studies was added to section 'Pharmacodynamic Effects'.

- On 16 April 2013 (version 012):
  - Update with thermostability data (change not impacting RSI).
  - Simplification of the impacted section (change not impacting RSI).
  - Template related changes impacting RSI in the "*Use and Handling*" section. These changes were not the result of new safety data received.
  - The Hepatitis B long-term follow-up data previously included in version 011 has been deleted as this update was put on hold. The sentence mentioned previously in version 010 was put back instead: *"Protective immunity against hepatitis B has been shown to persist for at least 3.5 years in more than 90% of children administered four doses of Infanrix hexa. Antibody levels were not different from what was observed in a parallel cohort administered monovalent hepatitis B vaccine"* (change not impacting RSI).
- On 26 August 2013 (version 013):
  - Update with Hib impact of vaccination data (change not impacting RSI).
  - Simplification of the impacted section (change not impacting RSI).

- On 13 March 2014 (version 014): The GPI was updated in March 2014 to provide details in Adverse reactions, Interactions and Warning and precautions sections on the potential increased risk of convulsion and hypotonic hyporesponsive episode when *Infanrix hexa* is co-administered with Prevenar13™.

Specific information relevant to this latter change is provided in the appropriate sections of the PBRER (refer to Section 16.2, Signal evaluation).

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

The cumulative number of subjects from ongoing and completed GSK-sponsored interventional clinical trials investigating *Infanrix hexa* for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b is presented in Table 1.

Note that subjects from booster studies may have participated in priming studies. Therefore the overall number of subjects in the entire development programme cannot be calculated by adding the number of subjects in priming studies to those in booster studies.

The information for completed clinical studies is sourced from the clinical trial database. For ongoing clinical trials, the cumulative exposure is estimated using the enrolment at the data lock point and the randomization ratio for the study.

Table 1 Cumulative Number of Subjects from Ongoing and Completed Clinical Trials

Treatment	Number of Subjects in		TOTAL
	Ongoing studies	Completed studies	
Primary vaccination			
Infanrix hexa in CDP	224	13,885	**14,109**
Comparator(s) in CDP	0	4,547	**4,547**
Blinded in CDP	585	0	**585**
Infanrix hexa out of CDP	3,621	23,809	**27,430**
Not receiving *Infanrix hexa* out of CDP	0	16,103	**16,103**
TOTAL primary vaccination	**4,430**	**58,344**	**62,774**
Booster vaccination			
Infanrix hexa in CDP	657	10,015	**10,672**
Comparator(s) in CDP	0	5,444	**5,444**
Infanrix hexa out of CDP	2,581	8,444	**11,025**
Not receiving *Infanrix hexa* out of CDP	0	2,328	**2,328**
TOTAL booster vaccination	**3,238**	**26,231**	**29,469**

Data until 22 October 2014.

An estimate of cumulative number of subjects exposed to *Infanrix hexa* by age, gender and racial group for **completed** GSK sponsored interventional studies with an approved clinical study report is presented in Table 2 and Table 3 for primary and booster vaccination studies, respectively.

Table 2 Summary of demographic characteristics for completed studies (Primary vaccination)

		Infanrix Hexa In CDP N = 13885		Control In CDP N = 4547		*Infanrix Hexa* Out CDP N = 23809		Group not receiving *Infanrix Hexa* N = 16103		Total N = 58344	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age Months at vaccination dose for schedule	Mean	2.2	-	2.1	-	1.9	-	1.9	-	2.0	-
	SD	0.96	-	0.77	-	0.58	-	0.54	-	0.71	-
	Median	2.0	-	2.0	-	2.0	-	2.0	-	2.0	-
	Minimum	0	-	0	-	1	-	1	-	0	-
	Maximum	8	-	6	-	5	-	4	-	8	-
	Missing	4	-	0	-	0	-	0	-	4	-
Gender	Female	6764	48.7	2213	48.7	11698	49.1	7863	48.8	28538	48.9
	Male	7119	51.3	2334	51.3	12111	50.9	8240	51.2	29804	51.1
	Missing	2	-	0	-	0	-	0	-	2	-
Race	Black	238	1.7	89	2.0	176	0.7	123	0.8	626	1.1
	White	6866	49.4	3209	70.6	486	2.0	981	6.1	11542	19.8
	White-Caucasian	3913	28.2	690	15.2	16573	69.6	9773	60.7	30949	53.0
	White-Arabic/North African	17	0.1	1	0.0	109	0.5	47	0.3	174	0.3
	Oriental	786	5.7	321	7.1	69	0.3	41	0.3	1217	2.1
	Oriental-East/South East asian	278	2.0	0	0.0	1011	4.2	20	0.1	1309	2.2
	Oriental-Central/South Asian	268	1.9	0	0.0	10	0.0	4	0.0	282	0.5
	Oriental-Japanese	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Oriental-Chinese	363	2.6	0	0.0	0	0.0	0	0.0	363	0.6
	Hispanic	1	0.0	0	0.0	230	1.0	2	0.0	233	0.4
	American indian or Alaskan native	0	0.0	0	0.0	277	1.2	271	1.7	548	0.9
	Other	1152	8.3	236	5.2	4831	20.3	4806	29.8	11025	18.9
	Unknown	3	0.0	1	0.0	37	0.2	35	0.2	76	0.1

N = total number of subjects.
n/% = number / percentage of subjects in a given category.
Value = value of the considered parameter.
SD = standard deviation.

Table 3 Summary of demographic characteristics for completed studies (Booster vaccination)

		Infanrix Hexa In CDP N = 10015		Control In CDP N = 5444		Infanrix Hexa Out CDP N = 8444		Group not receiving Infanrix Hexa N = 2328		Total N = 26231	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age Months at vaccination dose for schedule	Mean	15.3	-	15.2	-	13.4	-	12.9	-	14.5	-
	SD	3.16	-	3.04	-	2.07	-	2.08	-	2.91	-
	Median	15.0	-	14.0	-	13.0	-	12.0	-	14.0	-
	Minimum	1	-	10	-	9	-	10	-	1	-
	Maximum	48	-	29	-	23	-	23	-	48	-
	Missing	2	-	0	-	0	-	0	-	2	-
Gender	Female	4776	47.7	2670	49.0	4152	49.2	1150	49.4	12748	48.6
	Male	5237	52.3	2774	51.0	4292	50.8	1178	50.6	13481	51.4
	Missing	2	-	0	-	0	-	0	-	2	-
Race	Black	46	0.5	24	0.4	41	0.5	11	0.5	122	0.5
	White	3436	34.3	1248	22.9	179	2.1	184	7.9	5047	19.2
	White-Caucasian	5895	58.9	3894	71.5	7665	90.8	2035	87.4	19489	74.3
	White-Arabic/North African	2	0.0	0	0.0	56	0.7	14	0.6	72	0.3
	Oriental	508	5.1	206	3.8	60	0.7	16	0.7	790	3.0
	Oriental-East/South East asian	0	0.0	0	0.0	13	0.2	8	0.3	21	0.1
	Oriental-Central/South Asian	0	0.0	0	0.0	8	0.1	3	0.1	11	0.0
	Oriental-Japanese	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Oriental-Chinese	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Hispanic	4	0.0	0	0.0	3	0.0	6	0.3	13	0.0
	American indian or Alaskan native	0	0.0	0	0.0	3	0.0	3	0.1	6	0.0
	Other	122	1.2	72	1.3	80	0.9	48	2.1	322	1.2
	Unknown	2	0.0	0	0.0	336	4.0	0	0.0	338	1.3

N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

5.2.1. Post-approval (non-clinical trial) exposure

Overall estimation of post-authorisation exposure

Information on the actual number of people exposed to *Infanrix hexa* in the different countries is not available to the MAH. Therefore, the patient exposure is approximated by the number of doses distributed which is the most reliable data available with regard to patient exposure for a vaccine in a post-marketing setting.

It is important to note that the sales database from which data are retrieved is an in-house 'living' database and is subject to updates and corrections depending on information provided by GSK local country subsidiaries (e.g. vaccine doses may be returned by subsidiaries to the central warehouse). These constant updates may result in discrepancies between consecutive queries of the database. In order to minimise the risk of inaccuracy and to better reflect the exposure data the DLP to retrieve the sales data was 30 September 2014.

From 23 October 2011 until 30 September 2014, 46,893,819 doses of *Infanrix hexa* have been distributed. Since launch until 30 September 2014 119,595,685 doses have been distributed. As vaccination with *Infanrix hexa* could vary between one and four doses per subject in accordance with local recommendations and compliance with the vaccination schedule, post-marketing exposure to *Infanrix hexa* during the PBRER/EU PSUR reporting period is estimated to be between 11,723,455 and 46,893,819 subjects. The number of subjects exposed since launch until the data lock point of this report is estimated as being between 29,898,921 and 119,595,685.

Detailed Post-marketing exposure

For *Infanrix hexa*, summary qualitative and quantitative information is difficult to determine. No summary prescription data are available to the MAH at this time to allow for a detailed breakdown of patient exposure.

Exposure in subgroups where patterns of reports indicate a safety signal

No patterns of reports were identified in the time-period that indicated a safety signal.

5.2.2. Post-Authorisation use in special populations

No significant use in special populations for *Infanrix hexa* has emerged during the reporting period.

5.2.3. Patterns of use of the medicinal product

No distinct pattern(s) of use have been observed with the use of *Infanrix hexa* that is relevant to the interpretation of safety data.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 has been used for the coding of adverse events. The primary System Organ Classes (SOCs) are ordered by decreasing number of events and the Preferred Terms (PTs) are arranged alphabetically.

6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative tabulation of the serious adverse events (SAEs) that have been reported from clinical trials up to the data lock point of this report is presented in APPENDIX 2A. The tabulation presents SAE counts under the following column headings: DTPa-HBV-IPV+Hib (i.e. *Infanrix hexa*), Blinded, Other IMPs, Non-IMPs, Placebo, No Therapy. The "Other IMPs (Investigational Medicinal Product)" column contains cases where the patient was receiving another study drug (e.g. active comparator) when the event occurred. The cases in the "Non-IMPs" column are cases where the event was suspected to be related to a medication that was not a defined study drug. No therapy refers to cases where the patient was not receiving any study drug when the event occurred e.g. event occurred during the run-in phase of a study prior to first receipt of study drug. Where the same SAE occurs twice (or more) for the same trial subject, this SAE has been counted twice (or more) at the PT level in the tabulation. However, if the subject received more than one study drug (e.g., study drug and placebo) events have been counted in only one column according to the following hierarchy: Asset name, Blinded, Other IMP's, Placebo, Non-IMPs, No therapy.

This integrated dataset does not include denominators and therefore no statistical interpretation can be made. A numerical difference in numbers of SAEs between treatment groups does not necessarily translate to an increased incidence/causal association.

6.3. Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

A cumulative and interval summary tabulation of adverse reactions reported to GSK is presented in Appendix 2B.

Data in the summary tabulations include:

- Serious and non-serious adverse reactions from spontaneous sources (including reports from healthcare professionals, consumers, scientific literature, competent authorities worldwide)
- Serious adverse reactions from non-interventional studies and other non-interventional solicited sources.

For the tabulations, all spontaneously reported adverse events are considered as adverse reactions.

The cumulative totals in the tabulations are derived from all adverse reactions for *Infanrix hexa,* irrespective of source, relationship to drug and formulation/indication/route of administration.

The interval summary tabulations include adverse reactions from spontaneous cases received during the reporting period as well as adverse reactions from cases received

prior to the reporting period for which follow-up was received during the reporting period.

7. SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING INTERVAL

Information from GSK-sponsored and interventional studies obtained during the reporting period and which highlights significant findings that impact safety, including lack of product efficacy, are included in this section. Signals that arose from clinical trial sources are tabulated in **Section 15**.

There were no completed or ongoing GSK sponsored post-authorisation trials with the primary aim of identifying, characterising or quantifying a safety hazard or confirming the safety profile of *Infanrix hexa* during the reporting period. Therefore, APPENDIX 4A and APPENDIX 4B contain no data for this report.

7.1. Completed Clinical Trials

There have been no studies completed during the period of this report that highlight any significant safety issues. No change to the RSI is warranted.

7.2. Ongoing Clinical Trials

Information obtained from clinical studies ongoing during the period of this report does not highlight any significant lack of efficacy or safety issues.

7.3. Long-Term Follow-up

No new significant safety information became available from long-term persistence studies.

7.4. Other Therapeutic Use of Medicinal Product

No patient access or other programmes such as expanded access or compassionate use have been initiated for *Infanrix hexa*.

7.5. New Safety Data Related to Fixed Combination Therapies

Currently, among products with an ongoing CDP or an open IND, the following are components of *Infanrix hexa*: Infanrix™ (DTPa), Infanrix™-IPV (DTPa-IPV), Boostrix™ (DTPa), Boostrix™-IPV (DTPa-IPV), Infanrix™-IPV/Hib (DTPa-IPV/Hib), Infanrix™ Penta (DTPa-IPV-HepB), Engerix™ B (HepB), Poliorix™ (IPV) and Hiberix™ (Hib).

There was no significant safety finding in *Infanrix hexa* component products.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

There were no GSK-sponsored non-interventional trials for *Infanrix hexa* with the primary aim of identifying, characterising, or quantifying a safety hazard, or confirming the safety profile or measuring the effectiveness of risk management measures that were completed or ongoing during the reporting period.

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

No significant safety information was identified from other clinical trial sources for *Infanrix hexa*.

Two (2) long-term *Bordetella pertussis* vaccination impact studies were also ongoing during the period in Sweden and in France (EPI-PERT-106286 ongoing in Sweden since January 1998 and EPI-PERT-108761 ongoing in France since January 2002). Both are GSK-supported observational studies.

The Swedish study aims to measure the age-specific incidence of pertussis in relation to changes in the vaccination schedule: introduction of vaccination in 1996 for infants and toddlers, then introduction of a pre-school booster in 2007 (DTPa), and adolescent vaccination with Tdap vaccines for the cohorts receiving the pre-school booster (including Boostrix™).

The French study aims to describe the numbers and age distribution of pertussis cases identified within this paediatric network, in relation to changes in the vaccination schedule. In France, a preschool booster was introduced in 2013, with vaccines of the DTPa family (including Infanrix™), and Tdap vaccines (including Boostrix™) are used in adolescents since 2013; before 2013, only adults received Tdap, the adolescents were receiving DTPa vaccines and there was no pre-school booster.

10. NON-CLINICAL DATA

There were no apparent emerging non-clinical safety data (internal or from the published literature) during the period of this report that impact the safety of patients receiving *Infanrix hexa*.

11. LITERATURE

A full review of the literature was conducted during the reporting period. Specifically, GSK uses a standard 'drug safety' routinely (at least monthly) literature search to generate an automated alert which is reviewed for new and significant safety findings, including evidence of lack of efficacy and relevant information on vaccines' adjuvants. The search is based on, Medline and/or Embase.com for literature citations and abstracts, and SearchLight for conference abstracts. The Embase published literature database, covers over 7,600 peer reviewed journals in the biomedical field, including 2,000 journals not included in Medline. Embase is updated daily and includes articles in press.

Important new data concerning waning of acellular pertussis induced-immunity was identified. See the review paper by Sheridan [2014] as well as a summary of the literature in APPENDIX 7B.1.

In addition, information of interest was identified concerning the below topics. These do not impact the overall risk benefit profile of *Infanrix hexa*.

11.1. Manuscripts

- **Short term risk of sudden unexpected death (SUD) in infancy and sudden infant death syndrome (SIDS).** A significant increased risk was observed in Italy in the 0-7 days after vacination for hexavalent vaccines in general after the first dose (RR 2.2, 95%CI 1.1-4.4), but the increased risk was not significant for *Infanrix hexa* alone (RR 1.9, 95%CI 0.8-4.2) [Traversa, 2011]. Note that this article was published prior to the current PSUR period but not reported in the previous PSUR [Matturri, 2014] assessed the risk of SIDS following hexavalent vaccination in Italy on the basis of in-depth examination of the autonomic nervous system; this study did not prove a causal relationship between the hexavalent vaccination and SIDS. See APPENDIX 7B5 for an observed-to-expected analysis of SUD in infancy based on data in the GSK safety database, where this signal is not reproduced.
- **Prophylactic paracetamol coadministered with 7-valent pneumococcal conjugate vaccine and *Infanrix hexa*** [Rose, 2013]: Paracetamol effectively prevented fever and other reactions, mainly during the infant series. However, as events were generally mild and of no concern in either group the data supported current recommendations to administer paracetamol to treat symptoms only and not for routine prophylaxis.
- **Co-administration with**
  - **Synflorix™ in 11,911 Latin American infants** in primary vaccination. Serious adverse events were reported for 21.5% and 22.6% of Synflorix and control recipients, respectively. There were 19 deaths (0.16%) in the Synflorix™ group and 26 deaths (0.22%) in the control group. After a mean follow-up of 23 months vaccine efficacy against vaccine serotype IPD, vaccine serotype clinically confirmed acute otitis media, and World Health Organization–defined consolidated community-acquired pneumonia was 100%, 67.1%, 25.7%, respectively [Tregnaghi, 2014].
  - **Synflorix™ in Vietnamese infants**: *Infanrix hexa* had a clinically acceptable safety profile when co-administered with Synflorix. The reactogenicity was comparable to that observed in other South-East Asian populations [Huu , 2013].
  - **Synflorix™ and Rotarix™ in Mexican infants** at 2, 4 and 6 months and with at 2 and 4 months. Synflorix™ was immunogenic and well tolerated, although incidences of pain at injection site was higher than in previous European studies. This might have resulted from subjective assessment of pain in small children which can be influenced by cultural perceptions of pain, as supported by

observations of similar differences reported for other studies of vaccines conducted in different populations [Ruiz-Palacios, 2011].

- **Synflorix™ and Rotarix™ in Taiwanese infants**. All vaccines were immunogenic and well tolerated [Lin, 2012].
- **Heptavalent pneumococcal conjugate vaccine (PCV7)** compared to Pediacel™ as a booster at 11-18 months of age. The vaccines had a similar safety and immunogenicity profile [Berner, 2012].
- **Prevenar™ and Rotarix™** in healthy children in Latin America compared to Hexaxim™. Both vaccines were immunogenic and safe following co-administration with Prevenar™ and Rotarix™ [Lopez, 2012].
- **NeisVac-C (MnCC-TT) and PCV13 or PCV7** in Spain. Immune responses to MnCC-TT and to the diphtheria and tetanus antigens administered with PCV13 were noninferior to the responses observed when the vaccines were administered with PCV7. Local and systemic reactions were similar between groups [Martinon-Torres, 2012].
- **MenB vaccine (4CMenB) and PCV7** in Europe. Responses to routine vaccines (Infanrix hexa and PCV7) co-administered with 4CMenB were noninferior to routine vaccines alone for all antigens, except for the responses to pertactin and serotype 6B pneumococcal polysaccharide [Gossger, 2012].
- **Nimenrix™** (quadrivalent meningococcal serogroup A, C, W and Y conjugate vaccine, utilising tetanus toxoid) [Findlow, 2013].

- **Infanrix hexa**
  - **Immunogenicity when administered at 3, 5 and 11 months of age**. According to a pooled analysis of data from four vaccination studies conducted in Europe (covering 626 subjects), *Infanrix hexa* induces an adequate immune response after 2-dose primary plus booster doses when administered according to a 3, 5 and 11 months schedule [Van Der Meeren, 2012].
  - **Immunogenicity and safety of Hexaxim™ and *Infanrix hexa*** when administered as primary and booster vaccination in healthy children in Mexico. Both vaccines were immunogenic and well tolerated [Becerra Aquino, 2012].
  - In **Italy**, *Infanrix hexa* has a demonstrated safety record extending over a decade of use; it has been associated with record levels of vaccine coverage, and with sustained disease control in vaccinated cohorts [Baldo, 2014].
- **Hepatitis B immunity.** [Zanetti, 2012] assessed responses to a challenge dose of monovalent hepatitis B vaccine in children immunised with three doses (2+1) of either Hexavac™ or *Infanrix hexa* during infancy (Italy) and showed that immune memory persists for long-term (5 years) after a primary vaccination in infancy with both hexavalent vaccines. Van Der Meeren [2014] showed similar long-term hepatitis B immune persistence in children immunised with four doses (3+1) of hexavalent vaccine.
- **Immunogenicity of the HBV component of *Infanrix hexa* when co-administered with Prevenar, and comparison of pertussis and Hib components**

in *Infanrix hexa* with Infanrix-IPV + Hib in The Netherlands. Target thresholds for immune responses were achieved for all antigens studied. The GMC of one pertussis component, filamentous hemagglutinin (FHA), of *Infanrix hexa* was significantly lower in children vaccinated with *Infanrix hexa* and Prevenar™ (302.2, CI: 274.5–332.7) than in children vaccinated with Infanrix™-IPV + Hib (422.0, CI 367.1–485.0) [Whelan, 2012].

- **Immunization in a child with cancer**. A 6-year-old boy had received the routine UK immunization schedule, including DTPa-IPV/Hib, PCV7, MenC (three doses each) and at one year of age a 4th dose of Hib and MMR (single dose). At the age of 3 years he was diagnosed with acute lymphoblastic leukaemia. Following chemotherapy, he received 4 'catch-up' vaccines at initial immunization review including DTPa-HBV-IPV/Hib, PCV13, MenC and MMR. All immunizations were well tolerated and he completed the hepatitis B course. At 1-month post the 3rd and final hepatitis B vaccine dose he had a protective level of antibodies and was seropositive for measles, mumps, rubella and varicella. His cancer remains in remission [Crawford, 2012].
- **Immunologic memory following primary vaccination with Synflorix or PCV7 at 2, 3, and 4 months of age followed by 23-valent pneumococcal polysaccharide vaccine (23vPS) booster dose at 11 to 14 months of age when co-administered with *Infanrix hexa*.** Induction of immunologic memory following Synflorix™ priming was confirmed. Additional PCV boosting in 4-year-olds did not provide strong evidence of hyporesponsiveness induced by previous 23vPS boosting. However, our results did not rule out depletion of the memory B cell pool following 23vPS vaccination, resulting in subsequent attenuated immune responses, and therefore support the use of PCV rather than 23vPS for booster vaccination in the second year of life [Knuf, 2012].
- **Antibody and cell-mediated immunity to pertussis 4 years after monovalent acellular pertussis vaccine at birth.** In the longest reported follow-up of infants who received aP vaccine at birth and Infanrix hexa at 2-4-6 months, a trend to lower pertussis toxoid IgG antibodies post booster was found compared with receipt of first dose of aP-containing vaccine at 8 weeks of age. There was no difference in injection site reactions among groups (aP vaccine at birth and 1 month, aP at birth only and no aP) following the DTaP-IPV booster at 4 years of age [Wood, 2014].

11.2. Congress abstracts

Information of interest was also identified in congress abstracts concerning:

- **Immunisation of preterm infants in the neonatal unit.**

  Presented at 17th Congress of the Perinatal Society of Australia and New Zealand (PSANZ), 14-17 April 2013, Adelaide Convention Centre, Adelaide, South Australia.

  Presented by Thompson K, Davis PG, Jacobs SE.

  Background: Preterm infants are at increased risk of morbidity from vaccine preventable diseases. Vaccinations are immunogenic in preterm infants. We aimed to

assess adherence to national immunisation guidelines for hospitalised preterm infants, and the incidence of immunisation related adverse events.

Method: Retrospective audit of preterm infants who were inpatients when eligible for immunisation, with Prevenar™, *Infanrix hexa*, and RotaTeq™ on day 60 of life. The study was conducted in Newborn Intensive and Special Care (NISC) at the Royal Women's Hospital, Melbourne from Jan 2011 to July 2012. Physiological parameters and level of support during the 48 hours pre and post immunisation were compared.

Results: 126 of 131 eligible infants (96%) were immunised in NISC; mean (SD) gestational age (GA) was 26.5 (1.9) w and birthweight 923 (291) g, corrected GA 35.6 (2.3) w and weight 2323 (504) g at immunisation. 93 (74%) were immunised on time, and 33 (26%) late. There was an increase of at least 5 apnoeic/bradycardic events per day in 13% of infants, an increase in respiratory support in 21%, and an increased rate of fever (>37.5) in 24% in the 48 hours after vaccination compared with the preceding 48 hours.

Conclusions: Compliance with the national immunisation guidelines for eligible inpatient preterm infants in NISC was excellent (96%), with 74% immunised at 2 months postnatal age. There was a significant risk of increased apnoea/bradycardic events and respiratory support after vaccination. These may be considered when determining timing of immunisation, including appropriate counseling for parents.

- **Safety and reactogenicity of Synflorix™ co-administered with Infanrix hexa in Vietnamese infants.**

  Presented at 15th International Congress On Infectious Diseases (ICID) Of The International Society For Infectious Diseases (ISID), Bangkok, Thailand, 13 June 2012

  Presented by Huu T N; Toan NT; Tuan HM; Viet HL; Thanh Binh PL; Yu T-W; Shafi F; Habib A; Borys D.

  Conclusion: A Synflorix™ 3-dose primary vaccination, co-administered with *Infanrix hexa* at 2, 3 and 4 months of age was well tolerated by Vietnamese infants. Synflorix™ reactogenicity was comparable to that observed in other South-East Asian populations.

- **Waning Pertussis Antibodies To 4 Years Among Infants Who Did And Did Not Receive Monovalent Acellular Pertussis Vaccine At Birth.**

  Presented at 7th World Congress Of The World Society For Pediatric Infectious Diseases (WSPID), Melbourne, Australia, 16 November 2011

  Presented by Wood N; Marshall H; McIntyre P

  Background: Vaccination at birth against pertussis is an attractive strategy to prevent early-onset severe disease. This is the first report following acellular pertussis (Pa) vaccine at birth to 4 years old with no doses after 6 months old.

  Methods: Newborns were randomised into 3 groups: Group 1 - Pa vaccine at birth and Pa at one month, Group 2 - Pa vaccine at birth, Group 3 - Hepatitis B vaccine

(HBV) at birth only. All groups received HBV vaccine at birth and *Infanrix hexa* at 2, 4 and 6 months of age. IgG antibody responses to pertussis toxoid (PT), pertactin (PRN) and to diphtheria, tetanus and HBV were measured pre and post DTPa at 4 years and adverse events measured.

Results: IgG geometric mean concentrations (GMC) were not significantly different between groups pre and post DTPa booster. There was no difference in injection reactions between groups.

Conclusion: Although there were no significant differences in long-term antibody responses, lower anti-PT IgG and HBV levels require further evaluation. The magnitude of any effects on subsequent infant antibody responses is a key area to compare the two most promising strategies to prevent severe infant pertussis - maternal and neonatal immunization.

- **Lasting immune memory against hepatitis B 10 years after the 2+1 primary vaccination schedule with DTPa-HBV-IPV/HiB or DTPa-IPV/Hib+HBV.**

  Presented at 30th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), Thessaloniki, Greece, May 8–12, 2012.

  Presented by Avdicova M, Crasta P, Hardt K, Kovac M.

  Conclusion: 2+1 primary vaccination with *Infanrix hexa* in infancy induces lasting immune memory against hepatitis B up to 11 years post-vaccination, and a strong anamnestic response to HBV challenge dose, which was well tolerated.

12. OTHER PERIODIC REPORTS

GSK has prepared only a single PBRER/EU PSUR covering all formulations and indications for *Infanrix hexa*. GSK is not aware of another party providing a PBRER/EU PSUR for *Infanrix hexa* during the reporting interval.

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

There were no reports of lack of efficacy in clinical trials. GSK identify pertussis waning of immunity as an important identified risk in all DTaP and Tdap (reduced pertussis content) vaccines since 2013. After review of spontaneous reports of pertussis related lack of efficacy since launch with DTaP vaccines, there is no major concern of lack of efficacy (LOE) reports among spontaneous data (see APPENDIX 7A.5).

14. LATE BREAKING INFORMATION

Infanrix hexa batch **A21CC054A** that was temporally suspended by the Czech Republic Regulatory Authority, was released on 27 November 2014. The conclusion of the investigation is that there is no safety concern with this batch (see APPENDIX 7A.2).

15. OVERVIEW OF SIGNALS; NEW, ONGOING OR CLOSED

15.1. Description of Methods of Signal Detection and Sources Screened

GSK employs a routine, pro-active process for identifying safety signals[1] with four main components:

1. Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
2. Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
3. Systematic, regular review of the literature.
4. Regular review of issues related to vaccine batch(es).

Sources screened for signals, both as part of GSK's routine pharmacovigilance and in the preparation of this PBRER, include the GSK safety database, the GSK disproportionality analysis tool (Online Signal Management, OSM), global scientific literature, clinical study data and epidemiology study data.

[1]A safety signal is defined as a report or reports of an event with an unknown causal relationship to treatment that is recognised as worthy of further exploration and continued surveillance (CIOMS VI).

15.2. Overview of signals during the reporting period

During the reporting period, four signals were evaluated:

- Waning of immunity of acellular pertussis vaccines: was categorised as a new important identified risk.
- One signal (potential increased risk of hypotonic-hyporesponsive episode (HHE) and convulsions with or without fever following co-administration of *Infanrix hexa* with Prevenar13™) was categorised as new information regarding important identified risks (HHE and Convulsions) during the period.
- Two signals (Guillain-Barré syndrome and Extensive swelling of vaccinated limb) were closed as refuted signals during the period.

According to the Guideline on Good Pharmacovigilance Practices (GVP) Product- or Population- Specific Considerations I: Vaccines for prophylaxis against infectious diseases (effective 13 December 2013), additional information is provided in APPENDIX 7A for the following events:

- Potential impact on safety of changes in the manufacturing process (APPENDIX 7A.1);
- Batch related issues (APPENDIX 7A.2);

- Age-related adverse reactions (APPENDIX 7A.3);
- Vaccination errors (APPENDIX 7A.4);
- Vaccination failure (APPENDIX 7A.5);
- Vaccination anxiety-related reactions such as syncope (APPENDIX 7A.6).

Safety evaluations performed during the period to assess signals or to address regulatory inquiries, as well as areas of special interest, are provided in APPENDIX 7B:

Signal evaluations

- Waning of immunity of acellular pertussis vaccines (APPENDIX 7B.1);
- Hypotonic-hyporesponsive episode (HHE) and convulsions with or without fever following co-administration of *Infanrix hexa* with Prevenar13™ (APPENDIX 7B.2);
- Guillain-Barré syndrome (APPENDIX 7B.3);
- Extensive swelling of vaccinated limb (APPENDIX 7B.4).

Evaluations performed in answer to regulatory inquiries for events not considered signals

- Sudden Death (APPENDIX 7B.5);
- Kawasaki's disease (APPENDIX 7B.6);
- Rash and Rash maculo-papular (APPENDIX 7B.7);
- Myocarditis (APPENDIX 7B.8A and APPENDIX 7B.8B);

Monitoring and closure of

- Cyanosis (APPENDIX 7B.9);
- Gaze palsy (APPENDIX 7B.10);
- Haematochezia (APPENDIX 7B.11);
- Injection site nodule (APPENDIX 7B.12) ;
- Injection site abscess (APPENDIX 7B.13).

Continued monitoring of

- Anaemia haemolytic autoimmune and Haemolysis anemia (APPENDIX 7B.14);
- Thrombocytopenia, Thrombocytopenic purpura, Autoimmune thrombocytopenia and Idiopathic thrombocytopenic purpura (APPENDIX 7B.15);
- Important neurological events (including encephalitis and encephalopathy) (APPENDIX 7B.16);
- Henoch-Schönlein purpura (APPENDIX 7B.17);
- Petechiae (APPENDIX 7B.18);
- Purpura (APPENDIX 7B.19);

- Allergic reaction (including anaphylactic and anaphylactoid reactions) (APPENDIX 7B.20).

16. SIGNAL AND RISK EVALUATION

16.1. Summary of Safety Concerns

Table 4 summarises the important safety concerns for *Infanrix hexa* at the beginning of the reporting period.

Table 4 Important Safety Concerns at the Start of the Reporting Period

Important identified risks	- Hypersensitivity to any component of the vaccine - Syncope - Temperature of ≥ 40.0 C within 48 hours, not due to another identifiable cause - Hypotonic-hyporesponsive episode (HHE) - Apnoea in infants born prematurely - Convulsions with or without fever, occurring within 3 days
Important potential risks	- Encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine
Missing information	None

16.2. Signal Evaluation

Closed signals categorised as new important identified risks.

- Waning of acellular pertussis vaccine-induced immunity

See Section 17.2.

Closed signals categorised as new information regarding important identified risks

- **Potential increased risk of hypotonic-hyporesponsive episode (HHE) and convulsions with or without fever following co-administration of *Infanrix hexa* with Prevenar13™**

Post-marketing data evaluated during this period supported this PRAC recommendation: a potential increased risk of HHE and convulsions with and without fever following coadministration of *Infanrix hexa* with Prevenar13™ (PCV13) was observed when compared to Infanrix hexa administered alone. Frequency categories of these events following Infanrix hexa-PCV co-administration are expected to remain unchanged compared to Infanrix hexa single administration. A Type II variation regarding this topic was submitted to EMA and accepted. Convulsions with or without fever remain listed with a frequency 'very rare'. As a result of this evaluation the company acknowledges that following the introduction of pneumococcal vaccines into infant vaccination schedules, there is an observed increase in febrile reactions and fever-associated adverse events. The RSI of *Infanrix hexa* has been updated with the following information:

'Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of Infanrix hexa with Prevenar 13 to those which reported use of Infanrix hexa alone.'

This signal was categorized as new information regarding important identified risks (HHE and Convulsions).

Closed and refuted signals

- **Guillain-Barré syndrome**

Review of a case of Guillain-Barré Syndrome (GBS) following vaccination with Infanrix-IPV-Hib reported spontaneously to GSK in November 2013 triggered an evaluation of GBS following DTPa-containing vaccines. Review of recent literature found case reports or case series describing at least a temporal association between GBS and immunization for various vaccines, however large epidemiological studies have not been able to conclusively prove a causal link. Review of GBS cases after vaccination with the Infanrix family of vaccines within GSK's database found generally poor documentation of diagnosis or reasonable alternative causes for most cases, however some cases with reasonable documentation do not have an alternative explanation. One case would appear to show a positive rechallenge to Infanrix antigens. An internal observed to expected ratio analysis found no overall excess of cases, but an excess of cases within a certain age group, but many fewer cases than expected in the age group most represented. The majority of cases used for this analysis had incomplete assessments of GBS. In addition, the observed to expected analysis was undertaken without a precise incidence rate for the largest group vaccinated.

It is GSK's position that there is currently insufficient evidence of a causal link between the Infanrix family of vaccines and Guillain-Barré Syndrome. GSK will continue to monitor all cases of GBS through routine pharmacovigilance.

- **Extensive swelling of vaccinated limb (ELS)**

In 2013 and 2014, increased ELS spontaneous reporting frequencies were observed for Infanrix™, Infanrix™-IPV, Infanrix™-IPV/Hib, *Infanrix hexa* and Boostrix™. Thirteen different countries were involved: Poland, Czech Republic, Sweden, the Netherlands, Belgium, Ireland, Italy, Slovakia, Slovenia, Poland, France, Germany and China. The following were the most likely root causes for increased ELS reporting rates observed in the above countries:

- Increased attention, specifically to ELS, by Polish authorities, also possibly triggered by pertussis outbreaks, and regardless of (increasing or decreasing) sales;
- Increased vaccine use due to introduction of GSK vaccines in local national immunization programmes leading to an overall increase in local spontaneous reporting including, but not limited to, ELS;
- National/regulatory initiatives to increase local spontaneous reporting, specifically of ELS or not;
- Pre-school boosting following switch from DTPw priming to DTPa priming;
- Pertussis vaccination catch-up programmes;

- Local studies and communications related to ELS.

GSK considers that the identified ELS signal did not indicate a safety concern and closed this signal. A complete evaluation of ELS among all DTaP vaccines is in APPENDIX 7B.4.

A summary of these safety signals can be found in APPENDIX 3, Table 5 'Safety Signals that were Ongoing or Closed in the Reporting Period'.

16.3. Evaluation of Risks and New Information

New information on important potential risks

There is no new information on important potential risks.

New information on important identified risks

New information regarding the following important identified risk was analysed during the period:

- **Waning of immunity of acellular pertussis vaccines**

See details in Section 17.2.

- **Potential increased risk of hypotonic-hyporesponsive episode (HHE) and convulsions with or without fever following co-administration of *Infanrix hexa* with Prevenar13™**

See details in Section 16.2.

There was no new information which would change the company position on other important identified risks.

New information on risks not categorised as important

There was no new information which would change the company position on risks not categorised as important.

Update on missing information

Not applicable.

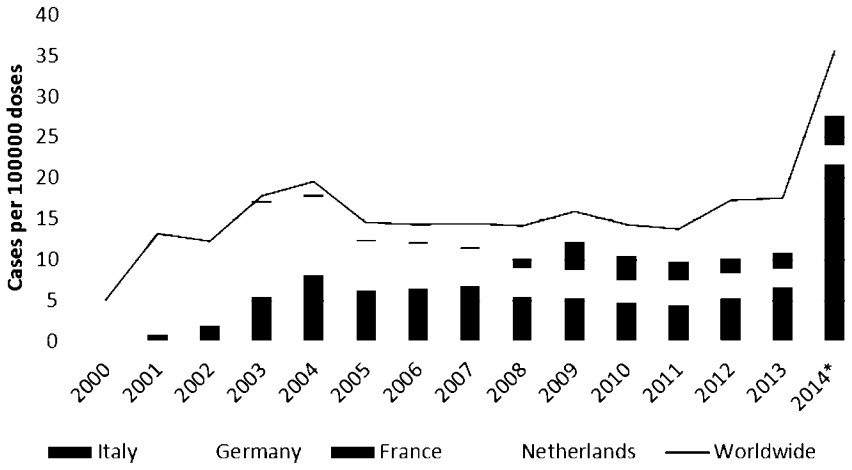
Global *Infanrix hexa* reporting frequency and proportion

In 2014 the global *Infanrix hexa* reporting frequency increased from 17.6 to 35.6 cases per 100,000 doses distributed worldwide. This increase was mainly due to cases reported from Italy (Figure 1). Between 2011 and 2014, the local Italian reporting frequency increased from 36.1 to 206.6 cases per 100,000 doses distributed in Italy. Since 2008 there has been a steady increase in the Italian case reporting frequency due to an increased attention of health care providers to report AEs as encouraged by the Italian Drug Agency (AIFA). AIFA also encouraged reporting an increasing level of detail. In March 2012, a new national vaccine plan for 2012 to 2015 was released [PNPV, 2012],

although the pertussis vaccination schedule remained unchanged (vaccines impacted by the new plan were human papillomavirus, pneumococcal, meningococcal and varicella vaccines). Altogether, these events are believed to have caused the overall increase in Italian case reporting as of 2012.

As a consequence, 20% of all cumulative spontaneous cases received worldwide since launch for Infanrix hexa were reported between January and October 2014 (Figure 2). This increased proportion is reflected in APPENDIX 2B, where the number of spontaneous events reported during the period represents near 20% of the cumulative number for most events.

Figure 1 **Global *Infanrix hexa* reporting frequency by calendar year and respective contributions of the four countries from which most *Infanrix hexa* cases were reported**



*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014.

Figure 2 **Global proportion of all cumulative cases received worldwide since launch for *Infanrix hexa***

*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014.

16.4. Characterisation of Risks

As outlined in the *Infanrix hexa* RSI and based on clinical trials and post-marketing safety data, the following AEs are recognized as well-characterized identified risks: Hypersensitivity, Syncope, Hyperpyrexia, Hypotonic-hyporesponsive episode, Apnoea in infants born prematurely, Convulsions with or without fever, Extensive swelling of vaccinated limb, or as potential risk: Encephalopathy. No risk management activities are required for these risks. No change in nature or frequency of reports indicative of these risks and assessed as causally related was observed, except a potential increased risk of hypotonic-hyporesponsive episode (HHE) and convulsions with or without fever following co-administration of *Infanrix hexa* with Prevenar13™. Therefore these events are not further characterized in this PBRER, with the exception of HHE and convulsions. As part of a routine, proactive pharmacovigilance process, GSK will continue to routinely monitor cases including all these events on an ongoing basis.

16.4.1. Important Identified Risks

Hypotonic-Hyporesponsive Episodes (HHE)

Frequency	Very rare (<1/10,000)
Impact on the Individual Patient	Risk of injury through hypotonia and loss of consciousness
Public Health Impact	May frighten caregiver resulting in non-attendance for follow-up vaccinations. May be mistaken for other adverse events, e.g. anaphylaxis
Patient Characteristics Relevant to Risk	Unpredictable
Duration of Treatment/Risk Period	From time of vaccination to around 48 hours post-vaccination
Reversibility	Usually spontaneously reverses without sequelae
Preventability	Unpredictable
Potential Mechanism	Unknown, but more common with whole-cell pertussis vaccines
Evidence source and strength of evidence	Örtqvist, 2010, Bonhoeffer, 2004.

Convulsion (with or without fever)

Frequency	Very rare(<1/10,000)
Impact on the Individual Patient	Untreated may result in brain damage, rhabdomyolysis and associated acid-base disturbance and multi-organ failure
Public Health Impact	May frighten caregiver resulting in non-attendance for follow-up vaccinations
Patient Characteristics Relevant to Risk	More common in subjects developing pyrexia.
Duration of Treatment/Risk Period	0-7 days
Reversibility	Usually amenable to anti-pyretic treatment and anti-convulsant treatment
Preventability	May be prevented in some patients through regular anti-pyretic post vaccination
Potential Mechanism	Elevated temperature leading to neurological dysfunction.
Evidence source and strength of evidence	Sun, 2012

16.4.2. Important Potential Risks

No change in nature or frequency of reports indicative of encephalopathy and assessed as causally related was observed; therefore this event is not further characterized in this PBRER.

16.4.3. Missing Information

Not applicable.

16.5. Effectiveness of Risk Minimisation

Currently no additional risk minimisation activities other than routine risk minimisation activities are implemented for *Infanrix hexa.*

The company believes that the warnings and statements given in the product information and patient leaflet are adequately informing prescribers and patients of the risks and of the missing information and thereby serve to minimise any potential risks. No evidence was gained during the reporting period suggesting limitations of the risk minimisation activities implemented.

17. BENEFIT EVALUATION

17.1. Important Baseline Efficacy and Effectiveness Information

There have been no significant changes in the benefit or risk profile of *Infanrix hexa* in the reporting interval. A summary of epidemiology and natural history of the disease; and the baseline efficacy and effectiveness information is presented below.

17.1.1. Diphtheria

Disease overview

Diphtheria is an acute, toxin-mediated, potentially life-threatening disease that is caused by the Gram-positive bacterium *Corynebacterium diphtheriae* [Bethell, 2010; CDC, 2012a]. Humans are the only known reservoir of *C. diphtheriae*, with the bacterium being transmitted from person-to-person predominantly via the respiratory tract, although it can also occur through direct contact with exudates from infected skin lesions [CDC, 2012a].

It is the toxin-producing strains of *C. diphtheriae*, which have been infected by a bacteriophage carrying the toxin gene, that cause serious disease [CDC, 2012a]. Most complications are a result of the effects of the toxin, which, when absorbed into the bloodstream, can be distributed to tissues distant from the site of infection. Diphtheria usually affects the pharynx, tonsils and larynx, although the skin may also be affected [Bethell, 2010; Vitek, 2008]. The symptoms that develop during the clinical phase of the disease are dependent on the site of infection.

Pharyngeal and tonsillar diphtheria: The pharynx and the tonsils are the most common sites of diphtheria infection. Symptoms are initially non-specific and mild; early symptoms include malaise, sore throat, anorexia and low-grade fever [CDC, 2012a; Vitek, 2008]. Approximately 1 day after the onset of symptoms, small patches of exudate appear in the pharynx [Vitek, 2008]. After 2–3 days, the exudate spreads and may form an adherent membrane that can potentially cover the entire pharynx, including the tonsils. Respiratory obstruction can occur if membrane formation is extensive [CDC, 2012a]. The patient may recover at this point; however, if enough of the toxin has been absorbed they may develop severe prostration, a striking pallor, a rapid pulse, stupor and coma, and potentially die within 6–10 days [CDC, 2012a]. In some patients with severe disease, swelling of the lymph nodes and oedema of the surrounding soft tissues results in a characteristic 'bullneck' appearance.

Laryngeal diphtheria: A quarter of diphtheria cases involve the larynx, which can be an extension of the pharyngeal form of the disease or involve only the larynx [CDC, 2012a; Vitek, 2008]. Laryngeal diphtheria is associated with greater morbidity and mortality, due to greater toxin absorption from the membrane and the potential for airway obstruction.

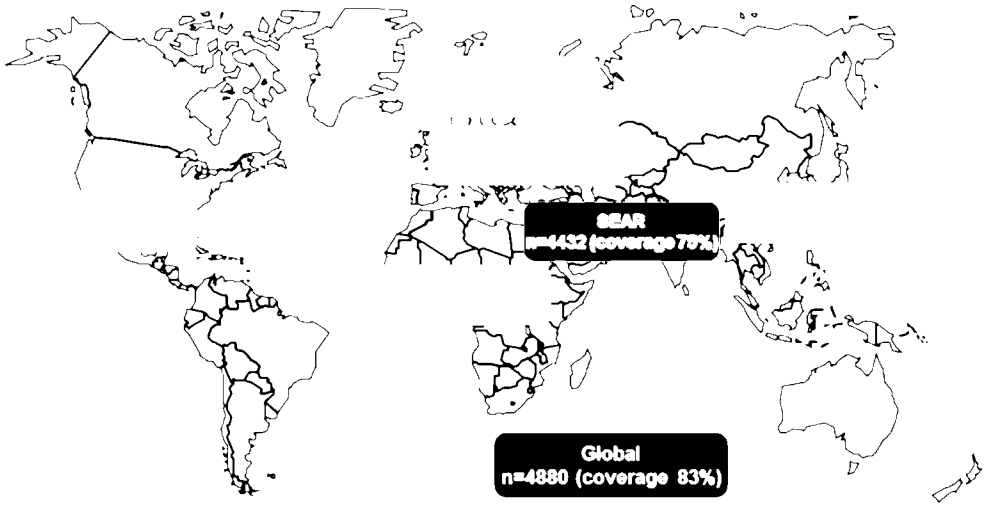
Cutaneous diphtheria: Cutaneous, aural, vaginal and conjunctival diphtheria account for about 2% of cases [Vitek, 2008]. They are generally mild, but serve as an important route of infection [Bethell, 2010; Vitek, 2008]. Cutaneous diphtheria is associated with tropical climates and conditions of overcrowding and poor sanitation [Bethell, 2010; CDC, 2012a; Vitek, 2008].

Systemic complications, including myocarditis and neuritis, can occur due to the effects of the toxin [CDC, 2012a]. Approximately 15–20% of cases result in neurological complications, which present 2–8 weeks after the onset of illness [Vitek, 2008]. Death occurs in 5–10% of cases, with rates higher (>2%) among those younger than 5 and older than 40 years of age [CDC, 2012a].

Epidemiology and impact of vaccination

Diphtheria still has a worldwide distribution, with 4880 cases reported globally in 2011 (Figure 3) [WHO, 2012a]. The highest proportion of cases was reported in South-East Asia (4432), particularly India (3485).

Figure 3 WHO [2012a]-reported cases (n) of diphtheria and WHO/UNICEF [2012] estimates of vaccination coverage (%) in 2011



Orange box represents the highest reported number of cases. AFR, African region; AMR, Americas region; EMR, Eastern Mediterranean region; EUR, European region; SEAR, South-East Asian region; UNICEF, United Nations Children's Fund; WHO, World Health Organization; WPR, Western Pacific region

Between 1980 and 2011, India has had persistent diphtheria, with little decline over the last 10 years [WHO, 2012a]. It has been established that the majority of cases are in children who are partially- or un-immunised against the disease, and that disease persistence is largely due to low primary and booster vaccination coverage [Murhekar, 2011]. Although the current (as of September 2012) WHO/United Nations Children's Fund (UNICEF) vaccination estimates are moderate for India (72%), actual vaccination coverage is thought to be lower [Murhekar, 2011; WHO/UNICEF, 2012].

Vaccination programmes have been successful in helping to control diphtheria. Between 1980 and 2000, the total number of reported diphtheria cases worldwide fell by >80%,

from 97 511 cases in 1980 to 11 625 cases in 2000 [WHO, 2012a]. However, there remains a need for maintaining diphtheria vaccination programmes, including boosters for adolescents and adults, as highlighted by a major diphtheria endemic that occurred in the Newly Independent States (NIS) of the former Soviet Union during most of the 1990s [Golaz, 2000; Markina, 2000]. The primary causes of the resurgence were the accumulation of susceptible individuals with low levels of immunity (due to incomplete childhood vaccinations and a lack of booster doses), the appearance of a new strain of C. diphtheriae, and poor social conditions (including increased numbers of migrants, crowded living conditions and deterioration of the health infrastructure) [Golaz, 2000; Markina, 2000].

Routine booster vaccination against diphtheria is recommended in many countries in response to waning immunity [CDC, 2012a; WHO, 2012b]. A number of countries, including Argentina, Canada, Germany and Portugal, recommend a dT booster dose every 10 years [WHO, 2012b].

17.1.2. Tetanus

Tetanus is an acute, and often fatal, disease that is caused by the Gram-positive, anaerobic, spore-forming bacterium *Clostridium tetani* [CDC, 2012b; Thwaites, 2010]. It is unique among vaccine-preventable diseases in that it is not communicable, but is acquired through environmental exposure to spores found in soil and animal faeces [CDC, 2012b; Wassilak, 2008].

The bacterial spores typically enter the body through a wound where, under favourable anaerobic conditions, such as in dirty wounds, they germinate and produce toxins [CDC, 2012b; WHO, 2006a]. The typical clinical manifestations of tetanus, unopposed muscle contraction and spasm, are a result of the toxin tetanospasmin interfering with the release of neurotransmitters, which blocks inhibitor impulses and prevents muscle relaxation [CDC, 2012b; WHO, 2006a].

The incubation period for tetanus is usually 8 days (ranging 3–21 days) [CDC, 2012b]. Generally, the further the injury site is from the central nervous system (CNS), the longer the incubation period. Based on clinical findings, tetanus can be divided into three different forms: local, cephalic and generalised (including neonatal tetanus).

Local tetanus: Patients have persistent contraction of muscles in the same area as the injury [Bleck, 2005; CDC, 2012b]. Contractions can persist for many weeks, but symptoms are generally milder than generalised tetanus (which can follow). This is an uncommon form of the disease, with about 1% of cases being fatal.

Cephalic tetanus: A rare form of the disease that affects the cranial nerve muscles [Bleck, 2005; CDC, 2012b]. It can occasionally occur following a head injury or with otitis media, where *C. tetani* is present in the flora of the middle ear.

Generalised tetanus: The most common form of tetanus, accounting for ~80% of cases [CDC, 2012b]. Symptoms appear in a descending pattern: trismus or 'lockjaw', stiffness of the neck, difficulty swallowing and muscle rigidity or spasm in the abdomen, back,

neck, thorax and extremities [CDC, 2012b; Wassilak, 2008]. Spasms can continue for 3–4 weeks and complete recovery may take months.

Neonatal tetanus is the most common form of the disease in developing countries [Wassilak, 2008]. It affects infants who do not have protective passive immunity, due to a lack of immunity in the mother [CDC, 2012b]. The most common cause of infection is through the unhealed umbilical stump, particularly if non-sterile instruments were used to cut the umbilical cord. Neonatal tetanus is associated with a mortality rate of >90% and remains a common cause of death in developing countries [Bleck, 2005; WHO, 2012c].

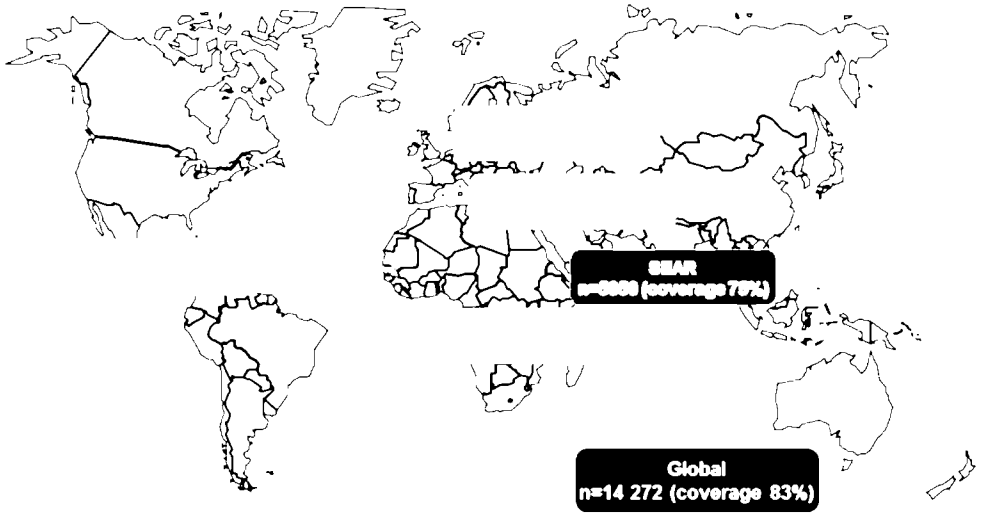
Sustained contractions and convulsions can result in fractures of the spine or long bones [CDC, 2012b]. In addition, spasm of the vocal cords and/or respiration muscles can lead to breathing problems, while hyperactivity of the autonomic nervous system can lead to hypertension and/or abnormal heart rhythm. Tetanus is fatal in 20–60% of adult cases; however, the introduction of critical care reduces the rate of complications and death [Udwadia, 2003].

Epidemiology and impact of vaccination

Tetanus occurs worldwide and is more common in agricultural regions and areas where contact with soil or animal excreta is more likely and immunisation is inadequate [CDC, 2012c].

In 2011, 14 272 cases of tetanus were reported worldwide (Figure 4) [WHO, 2012a]. The highest number of cases was reported in the African and South-East Asian WHO regions, areas with the lowest vaccination coverage [WHO, 2012a; WHO/UNICEF, 2012].

Figure 4 WHO [2012a]-reported cases (n) of tetanus and WHO/UNICEF [2012] estimates of vaccination coverage (%) in 2011



Orange box represents the highest reported number of cases. AFR, African region; AMR, Americas region; EMR, Eastern Mediterranean region; EUR, European region; SEAR, South-East Asian region; UNICEF, United Nations Children's Fund; WHO, World Health Organization; WPR, Western Pacific region

The widespread use of tetanus toxoid-containing vaccines in pregnant women has resulted in a dramatic reduction in the incidence of neonatal tetanus. Indeed, in countries with effective vaccination programmes and good standards of hygiene, cases of maternal and neonatal tetanus are <1 per 1000 live births [WHO, 2006a]. Furthermore, in 2011, only 4,213 cases of neonatal tetanus were reported, compared with 25,293 cases in 1990 [WHO, 2012a].

Vaccination has been used very successfully to protect against the disease, but it does not induce lifelong protection; therefore, booster vaccinations are important to maintain levels of immunity. A number of countries, including Argentina, Canada, Germany and Portugal, recommend a dT booster dose every 10 years [WHO, 2012b]. In addition, tetanus infection does not lead to subsequent immunity, requiring the vaccination of all survivors of the disease [Thwaites, 2010].

17.1.3. Pertussis

Disease overview

Pertussis, also known as whooping cough, is an acute respiratory infection caused by the Gram-negative bacillus *Bordetella pertussis* [CDC, 2012d; Edwards, 2008]. Pertussis is highly contagious, with a reproductive number of 12–17 (the number of people infected per original index case) [Fine, 1993], explaining the outbreak character of the disease. Humans are the only known natural host of *B. pertussis*, which is transmitted by inhaling airborne respiratory droplets or through direct contact with nasopharyngeal discharges from an infected person [CDC, 2012d; WHO, 2010a].

The bacteria attach to the cilia of epithelial cells in the upper respiratory tract, where they release a toxin that leads to local paralysis of the cilia and inflammation, interfering with the clearance of pulmonary secretions [CDC, 2012d].

The clinical course of the illness is divided into three sequential stages: catarrhal, paroxysmal and convalescent [CDC, 2012d; WHO, 2010a].

Catarrhal stage: This is the initial stage of the infection, where symptoms are similar to a common cold and include runny nose, sneezing, low-grade fever and a mild cough [CDC, 2012d]. The cough gradually worsens and the paroxysmal stage begins after 1–2 weeks.

Paroxysmal stage: During this stage, the patient experiences bursts of rapid uninterrupted coughing as they try to expel mucous [CDC, 2012d]. At the end of the attack, a long inspiratory effort is accompanied by a characteristic high-pitched 'whoop'. This stage, often very exhausting for the younger patients, usually lasts 1–6 weeks but can persist for up to 10 weeks.

Convalescent stage: Patients gradually recover; however, the coughing fits can recur with subsequent respiratory infections for many months after disease onset [CDC, 2012d].

Pertussis can be severe in infants and children, but in adults the symptoms tend to be mild and indistinguishable from those of other respiratory infections [CDC, 2012d]. However, infected adults can still transmit the disease to susceptible individuals, including infants who have not completed the full vaccination course. It has been established that siblings and adolescent or adult family members with unrecognised pertussis represent the primary source of infection to infants [Bisgard, 2004; Jardine, 2010].

The majority of patients with pertussis will gradually recover; however, some develop potentially life-threatening complications, including pneumonia, neurological complications, otitis media, anorexia and dehydration [CDC, 2012d]. Young infants are most at risk of complications; CDC data from 1997 to 2000 found that pneumonia occurred in 5.2% of pertussis cases, but in infants younger than 6 months of age it occurred in 11.8% of cases [CDC, 2012d].

Epidemiology and impact of vaccination

During the pre-vaccination era, pertussis was one of the most common childhood diseases and a major cause of infant mortality [CDC, 2012d]. In 2011, the burden of pertussis remained high, with 162 047 pertussis cases reported worldwide (Figure 5) [WHO, 2012a]. However, the true incidence of pertussis is likely to be much higher than reported in both developed and developing countries, as a result of under diagnosing and underreporting [Guiso, 2011; Tan, 2005]. Indeed, it has been estimated that 20–40 million cases of pertussis occur globally each year, 90% of which are in developing countries [Tan, 2005].

Figure 5 WHO [2012a]-reported cases (n) of pertussis and WHO/UNICEF [2012] estimates of vaccination coverage (%) in 2011

Orange box represents the highest reported number of cases. AFR, African region; AMR, Americas region; EMR, Eastern Mediterranean region; EUR, European region; SEAR, South-East Asian region; UNICEF, United Nations Children's Fund; WHO, World Health Organization; WPR, Western Pacific region

Following the introduction of vaccines (whole-cell followed by acellular pertussis vaccines), the number of cases fell dramatically. For example, in the USA, the annual number of reported cases of pertussis decreased from an average of 175,000 per year between 1940 and 1945, to 2,900 per year between 1980 and 1990 [CDC, 2012d]. However, the number of cases has been gradually increasing since the 1990s [WHO, 2012a]. The reproductive number of pertussis warrants high vaccination coverage of at least 92–94% to control pertussis transmission and keep disease at a low incidence [Anderson, 1990; Fine, 1993].

Despite high vaccination coverage, outbreaks have been reported in numerous countries since 2004. These outbreaks are an indication of the continued circulation of *B. pertussis* and highlight the importance of sustaining high level prevention programmes. Waning immunity in adolescents and adults is thought to be a large contributing factor for these outbreaks [Zepp, 2011], highlighting the need for continued protection through the use of booster vaccination. In addition, improved diagnostic testing, active surveillance, changes in disease susceptibility and increased awareness may have contributed to more cases being identified.

Pertussis outbreaks have also occurred in a number of European countries, including Belgium, Germany, Ireland, Slovenia, Spain and the UK during the last 10 years, [Barrét, 2010; Grgic-Vitek, 2008; HPA, 2012a; HPSC, 2012; Sin, 2009; Vincent, 2011]. These countries have high diphtheria-tetanus-pertussis (DTP3) vaccination coverage, with all achieving a national coverage rate of ≥95% in 2011 [WHO/UNICEF, 2012]. As of December 2012, the outbreak in the UK was still ongoing, with 8819 cases of laboratory confirmed whooping cough reported to the Health Protection Agency [HPA, 2012a]. In response to the current outbreak, in September 2012, the Department of Health introduced a temporary pertussis vaccination programme for pregnant women [HPA, 2012b]. The objective of the programme was to boost the short-term immunity that is passed on by women to their babies while they are still in the womb.

Like in European countries, vaccination coverage with DTP3 is high in the Americas (92% in 2011), and pertussis continues to be a public health problem in several countries in the region [PAHO, 2012; WHO/UNICEF, 2012]. Several Latin American countries, including Argentina, Brazil, Chile, Colombia, Guatemala, Mexico, Paraguay and Venezuela, have experienced recent outbreaks or a higher reported incidence of pertussis [PAHO, 2012]. As of 2012, acellular pertussis vaccines have not been introduced in any of these Latin American countries in generalized immunization programmes [WHO, 2012b], demonstrating that outbreaks and higher incidence rates are not just occurring in countries that use the acellular vaccine.

In recent years, adolescents and adults have accounted for a large proportion of cases of pertussis. In Europe, between 1998 and 2002, disease incidence remained steady among infants <1 year of age; whereas the rate doubled in adolescents and adults, from 16% to

35% [Celentano, 2005]. Between 2008 and 2010, adolescents and adults accounted for more than 50% of all cases in Europe (European surveillance network for vaccine-preventable diseases [EUVAC.NET, 2010; EUVAC.NET, 2011a; EUVAC.NET, 2011b]. A similar shift has been reported in the USA [Murphy, 2008].

Consequently, adults and adolescents with pertussis are a potential source of infection for infants too young to have been fully vaccinated [von König, 2002]. Routine booster vaccination is now recommended in many countries in response to waning immunity [WHO, 2010]. The Consensus on Pertussis Booster Vaccination in Europe (COPE) group recommends reduced-antigen diphtheria-tetanus-acellular pertussis (dTpa) booster vaccination for all adolescents 10–17 years of age and adults ≥18 years of age, whose last dT dose was ≥10 years ago [Zepp, 2011]. The group also recommends using the 'cocoon strategy'; vaccination of family members and close contacts of newborns, in order to protect infants from acquiring pertussis.

17.1.4. Hepatitis B

Disease overview

Hepatitis B (HepB) is a highly contagious infection of the liver that can cause both acute and chronic disease [CDC, 2012e; WHO, 2012d]. It is caused by the hepatitis B virus (HBV), a DNA virus of the *Hepadnaviridae* family that is 50–100 times more infectious than HIV [CDC, 2012e; WHO, 2012d] Humans are the only known host of HBV, which is transmitted via contact with infected blood or serous fluids (e.g. vaginal fluid) [CDC,2012e].

Risk factors for HepB include having unprotected sexual contact or sharing needles with an infected person, visiting endemic regions, frequently receiving blood or blood products, occupations involving contact with blood, household contacts of HBV carriers and perinatal transmission [CDC, 2012e; WHO, 2012d].

The clinical course of acute HepB is indistinguishable from other hepatitis infections, with an incubation period averaging 120 days, but ranging from 45 to 160 days [CDC, 2012e].

Pre-icteric/prodromal phase: This initial phase usually lasts 3–10 days. Characteristic symptoms include malaise, anorexia, nausea, vomiting, abdominal pain, fever, headache, myalgia, skin rashes, arthralgia and arthritis, and dark urine [CDC, 2012e].

Icteric phase: Usually lasts 1–3 weeks and is characterised by jaundice, light or grey faeces, hepatic tenderness and hepatomegaly; although malaise and fatigue can persist for weeks or months [CDC, 2012e].

While the majority of adults with acute HepB infection make a full recovery, resulting in the elimination of hepatitis B surface antigen (HBsAg) from the blood and production of anti-HBsAg antibodies, approximately 1% of cases are fatal [CDC, 2012e; CDC, 2012f].

Acute HepB progresses to a chronic state in 30–90% of people infected during childhood and in less than 5% of people infected during adolescence or adulthood [CDC, 2012e].

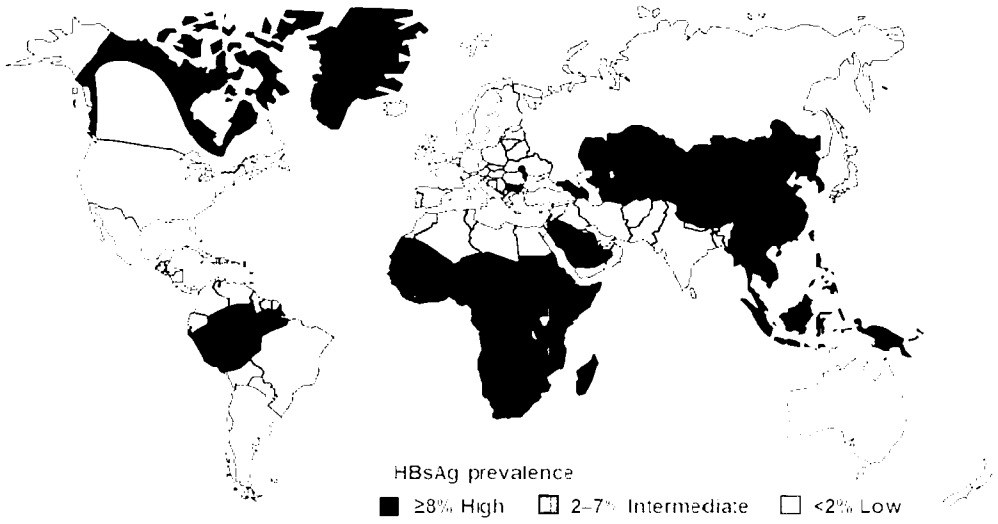
Chronic HepB infection is often asymptomatic, therefore, individuals may not be aware that they have been infected, although they are still able to infect others. Furthermore, chronic carriers are at an increased risk of developing cirrhosis of the liver or hepatocellular carcinoma, which can lead to premature death in ~25% of cases [CDC, 2012e].

Epidemiology and impact of vaccination

Hepatitis B remains a major global health problem and the most serious type of viral hepatitis [WHO, 2012a]. It has been estimated that >2 billion people worldwide have serologic evidence of past or present HepB infection; approximately 360 million are chronic carriers of the virus [WHO, 2009].

There is a variable prevalence of chronic HepB infection in the world, which can be divided into areas of high (≥8%), intermediate (2–7%) and low (<2%) endemicity, according to the HBsAg carrier rate in the population (Figure 6) [CDC, 2012f]. Approximately 45% of the world's population live in areas with a high prevalence of chronic Hep B infection, 43% live in areas with a moderate prevalence and 12% in areas with a low prevalence [CDC, 2012e].

Figure 6 Geographical prevalence of chronic infection with Hepatitis B (HBsAg) virus in 2006 [CDC, 2012f]



HBsAg, hepatits B surface antigen. High-endemicity areas: most of Africa, China and other parts of South-East Asia, the Amazon Basin and parts of the Middle East; Intermediate-endemicity areas: North Africa, Japan, Eastern and Southern Europe, Russia and Latin America; Low-endemicity areas: Australia, New Zealand, North America, Northern and Western Europe

The control and prevention of HepB infection have been recognized as important public health objectives due to the worldwide distribution of the virus. In 1991, the Global

Advisory Group of the Expanded Programme on Immunization recommended inclusion of HBV vaccination into national immunization programmes. This recommendation was further endorsed by the World Health Assembly of the WHO in 1992 [WHO, 2002]. Hepatitis B vaccination strategies encompass infant vaccination, with recommendations to provide: a birth dose to those at high risk of infection; catch-up vaccination in children and adolescents; and vaccination of adults who have not been vaccinated earlier in life [Van Herck, 2008].

In highly endemic countries, perinatal (from mother to baby at birth) and early childhood infections (interpersonal contact with infected household contacts) are common modes of transmission [WHO, 2009] and the risk of developing chronic infection is greatest [CDC, 2012e]. In these areas the lifetime risk of HepB infection is >60%, therefore, the best strategy to prevent HepB infection in areas of intermediate and high prevalence of HBV, is to provide universal vaccination of neonates, infants, children and adolescents, as well as adults belonging to groups at increased risk of infection.

The majority of infections in developed countries (i.e. areas with low endemicity) are transmitted during young adulthood by sexual activity and injecting-drug use [WHO, 2012b]. In contrast to countries with an intermediate or high prevalence of HBV, in low prevalence areas, the lifetime risk of HepB infection is <20%. Despite WHO recommendations, two different vaccination approaches are used in countries with a low prevalence of HBV: either universal mass vaccination of infants or adolescents; or vaccination of risk groups [Rots, 2010].

As of 2008, 177 countries had incorporated HBV vaccine into their national infant vaccination programmes. Since the introduction of universal mass vaccination with HBV vaccines, marked reductions in the incidence of HepB infection, including decreases in chronic carriage and HepB-related complications, have been observed [Cassidy, 2011].

17.1.5. Poliomyelitis

Disease overview

Poliomyelitis (commonly known as polio) is caused by poliovirus, a highly infectious RNA enterovirus, and member of the *Picornaviridae* family [CDC, 2012g]. There are three serotypes of poliovirus (1, 2 and 3); however, immunity to one serotype does not produce significant immunity to the other serotypes [CDC, 2012g; Minor, 2012]. In its most severe form, polio can result in paralysis and death.

Humans are the only known host of poliovirus, which is spread by direct or indirect contact with infected individuals, usually via the faecal–oral route [CDC, 2012g; Nathanson, 2010]. The virus enters the body via the mouth and replicates at the site of implantation in the pharynx and gastrointestinal tract, before invading local lymphoid tissue and entering the bloodstream [CDC, 2012g]. Poliovirus may infect cells of the CNS, resulting in the destruction of motor neurons and major neurological illness.

The clinical manifestations of polio vary (from mild illness to paralysis) and are usually categorised according to severity [CDC, 2012g; Modlin, 2005].

Asymptomatic polio: Up to 95% of all polio infections are asymptomatic. Infected individuals with no symptoms are still able to transmit the virus to others.

Abortive polio: Approximately 4–8% of infections are minor, with no evidence of CNS involvement. Symptoms are non-specific and include sore throat, fever, gastrointestinal disturbances and influenza-like illness. Patients usually completely recover in less than a week.

Non-paralytic polio: Characterised by typical symptoms of meningitis (i.e. stiff neck, back or legs) and is observed in 1–2% of infections. Symptoms last 2–10 days and are followed by complete recovery.

Paralytic polio: Less than 1% of infections result in flaccid paralysis, occurring 1–10 days after prodromal symptoms and progressing for 2–3 days. Many patients make a full recovery, but any weakness and paralysis still present 12 months after onset is usually permanent. The mortality rate is around 15–30% in adults and 2–5% in children, and increases to 25–75% with bulbar involvement.

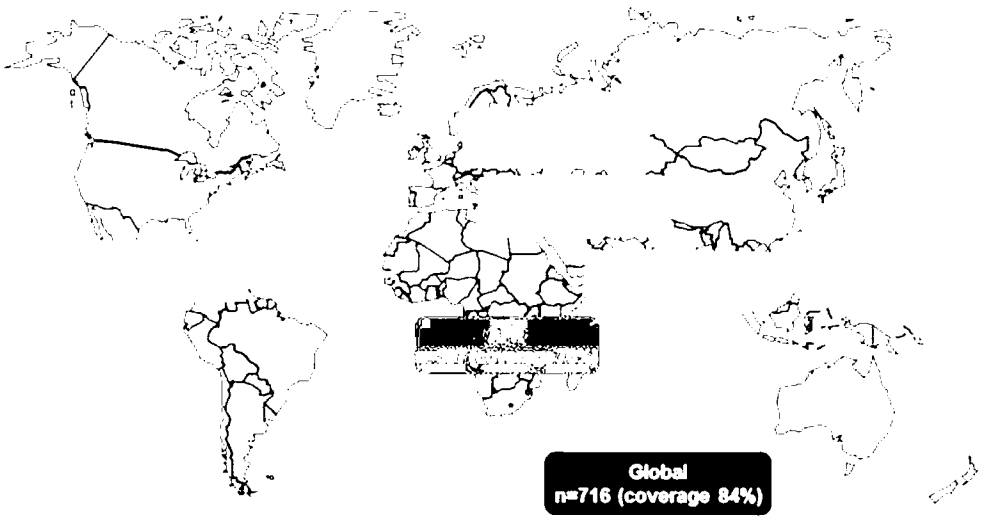
Epidemiology and impact of vaccination

Following the introduction of the inactivated poliovirus vaccine (IPV) and the oral poliovirus vaccine (OPV) in the 1950s and the 1960s, respectively, the incidence of polio fell dramatically [CDC, 2012g; Nathanson, 2010; WHO, 2010b]. Despite this, the number of reported cases was still high in 1980, with more than 52,000 cases reported to the WHO [WHO, 2012b].

In 1988, the Global Polio Eradication Initiative (GPEI) was launched with the aim of global eradication of polio by 2000 [GPEI, 2010; Markina, 2000]. Following the implementation of this initiative, the number of reported cases fell from more than 52 000 in 1980, to ~23 000 in 1990, to only 716 in 2011 (with the majority reported in the WHO African and Eastern Mediterranean regions) (Figure 7) [WHO, 2012b].

Although the goal of the GPEI was not met, all of the Pacific region, the Americas and most of the South-East Asian region had eradicated the disease by the end of 2000 [Minor, 2012]. The decline in the number of polio cases corresponded with the increase in vaccination coverage. In 1980, vaccination coverage was only 22%, but by 1990 it had increased to 75%, and to 84% by 2011 [WHO, 2010c].

Figure 7 WHO [2012a]-reported cases (n) of poliomyelitis and WHO/UNICEF [2012] estimates of vaccination coverage (%) in 2011



Orange box represents the highest reported number of cases. AFR, African region; AMR, Americas region; EMR, Eastern Mediterranean region; EUR, European region; SEAR, South-East Asian region; UNICEF, United Nations Children's Fund; WHO, World Health Organization; WPR, Western Pacific region

As of August 2013, polio remains endemic in Afghanistan, Nigeria and Pakistan [GPEI, 2012]. Furthermore, during 2011, polio outbreaks occurred in several countries, including Niger, Guinea, Cote d'Ivoire, Mali, Gabon and the Republic of Congo. This demonstrates that until global eradication of polio is achieved, it will be essential to maintain adequate vaccination programmes, even in those areas where eradication is considered achieved.

Vaccine-Associated Paralytic Poliomyelitis (VAPP) is a rare adverse event that can occur following vaccination with OPV. IPV does not cause VAPP. To reduce the risk of VAPP, the US changed from an all OPV schedule to a sequential IPV/OPV schedule in 1997, and then to an all IPV schedule in 2000 [CDC, 1997; CDC, 2000]. Before the use of OPV was discontinued in 2000, approximately 8 cases of VAPP occurred in the United States each year [Alexander, 2004]. Since 2000, only two cases of VAPP have been reported in the US, one in 2005 in a traveller to countries using OPV and a second who had common-variable immunodeficiency (CVID) [CDC, 2006; DeVries, 2008].

17.1.6. *Haemophilus influenzae* type b

Disease overview

Haemophilus influenzae, a Gram-negative bacterium indigenous to humans, causes significant morbidity and mortality worldwide, particularly among young infants (Centres for Disease Control and Prevention [CDC, 2012h; Chandran, 2008].

The bacteria can exist as encapsulated and non-capsulated strains, with the encapsulated form having six serologically defined types (a–f) (Centres for Disease Control and Prevention CDC, 2012h; Chandran, 2008]. The polysaccharide capsule is a major virulence factor (Chandran, 2008]. Prior to the introduction of vaccines, *H. influenzae* type b (Hib) was responsible for 95% of serious diseases caused by *H. influenzae.*

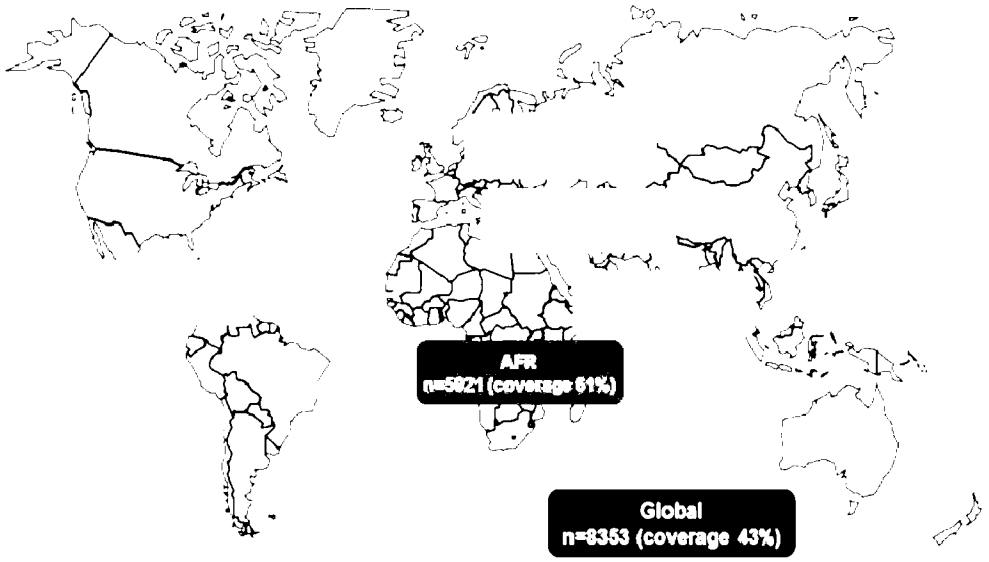
Transmission of Hib occurs primarily via respiratory droplets or contact with secretions from infected individuals (Centres for Disease Control and Prevention [CDC, 2012h]. The bacterium enters and colonises the nasopharynx, where it can remain for several months with no evidence of symptoms. Colonisation can lead to mucosal infections in the respiratory tract, including bronchitis, sinusitis and otitis media [Chandran, 2008].

Haemophilus influenzae type b may also invade the bloodstream and spread to many different sites, causing invasive infections, such as arthritis, cellulitis, epiglottitis, meningitis and pneumonia (Centres for Disease Control and Prevention [CDC, 2012h]. In the pre-vaccination era, meningitis accounted for 50–65% of these cases. Long-term neurological sequelae (including hearing impairment) occur in 15–30% of those recovering from the disease and the case-fatality rate is 2–5% despite appropriate antimicrobial therapy.

Epidemiology and impact of vaccination

Cases of Hib disease are still reported worldwide with 8353 global cases in 2011 and the highest number of cases reported in Africa (Figure 8) (World Health Organization [WHO, 2012a].

Figure 8 WHO [2012a]-reported cases (n) of *Haemophilus influenzae* type b meningitis and WHO/UNICEF [2012] estimates of vaccination coverage (%) in 2011



Orange box represents the highest reported number of cases AFR, African region; AMR, Americas region; EMR, Eastern Mediterranean region; EUR, European region; SEAR, South-East Asian region; UNICEF, United Nations Children's Fund; WHO, World Health Organization; WPR, Western Pacific region.

It is suggested that Hib conjugate vaccines, and particularly their ability to reduce asymptomatic carriage of serotype b, may affect the epidemiology of *H. influenzae* more widely and potentially lead to serotype replacement (i.e. where non-type b serotypes or non-typeable [NTHi] strains emerge as causes of invasive disease) [Agrawal, 2011]. A number of studies have investigated the phenomenon for potential serotype replacement. Several studies suggest an increased incidence of invasive NTHi strains [Bruce, 2008; Gessner, 2009; Ladhani, 2010]. However, the observed increase in NTHi invasive disease is only marginal compared to the reduction in Hib disease due to vaccination programmes. Currently, there is insufficient evidence to support any serotype replacement as a specific consequence of widespread vaccination with Hib conjugate vaccines [Agrawal, 2011]. However, continued surveillance and monitoring for potential serotype replacement remains important [Agrawal, 2011].

In the pre-vaccination era, almost all cases of invasive Hib disease occurred in children under 5 years of age, and two-thirds occurred in children younger than 18 months of age (Centres for Disease Control and Prevention [CDC, 2012h]. Invasive Hib disease was a major cause of morbidity and mortality among preschool children, with higher rates of disease observed among some indigenous populations [Agrawal, 2011; Chandran, 2008].

Infants younger than 6 months of age may be protected from invasive Hib infection due to maternal antibodies and breastfeeding.

Vaccination against Hib began in the 1970s with the development of polysaccharide vaccines, and evolved in the late 1980s with the advent of conjugate vaccines [Ladhani, 2008; Plotkin, 2008]. These conjugate vaccines were found to have the additional advantage of reducing asymptomatic carriage in the nasopharynx, offering the potential to generate herd immunity [Bröker, 2009; Morris, 2008]. A dramatic reduction in Hib disease incidence has subsequently been observed in both developed and developing countries where Hib conjugate vaccines are now routinely used, with Hib disease changing from being a major cause of childhood illness to a now rare disease [Gessner 2009; Ladhani, 2010; MacNeil, 2011; Morris, 2008].

However, although vaccination against Hib has been introduced in many countries, there is still a large proportion of the world's children who are not being fully vaccinated. In 2009, 82% of the WHO member states used the Hib vaccine in their infant vaccination schedules, but only 45% of the world's children were fully vaccinated with it [Ojo, 2010]. This was mainly due to a few countries with large birth cohorts, such as India and China, who had yet to introduce the vaccine. Hib, therefore, remains a significant cause of disease due to suboptimal use of vaccine and each year it is estimated to be responsible for ~3 million serious illnesses and an estimated 386 000 deaths, mainly due to meningitis and pneumonia (World Health Organization [WHO, 2005]. Furthermore, despite high rates of vaccination, the incidence of Hib disease remains higher among indigenous populations than in non-native populations [Agrawal, 2011].

The majority of countries using Hib conjugate vaccines recommend three routine doses for infants [Morris, 2008]. A routine booster vaccine in the second year of life has been demonstrated to maximise control of Hib disease, particularly in the longer term (Centres for Disease Control and Prevention [CDC, 2012h; WHO, 2005]. In addition to improving direct protection in this age group, this approach exploits the ability of Hib conjugate vaccines to reduce asymptomatic carriage, the highest levels of which are found in toddlers, thereby generating herd immunity by reducing transmission of Hib across all age groups [Heath, 2002; Ladhani, 2008]. A routine toddler booster is now included by a number of countries, including the USA (Centres for Disease Control and Prevention [CDC, 2012h; WHO, 2005].

The introduction of the Hib vaccine has resulted in a substantial decline in Hib invasive disease in Africa; however, a number of issues remain that may affect vaccine use, including cost, differing vaccination schedules and the HIV epidemic [Gessner, 2009]. There is evidence to suggest that the Hib vaccine may lead to a poorer immune response and lower vaccine effectiveness among HIV-positive populations in Africa.

17.1.7. Efficacy

Efficacy after a primary course of Infanrix (DTPa) has been extensively documented following administration of more than 100 000 doses in clinical trials. In a household contact study of vaccine efficacy, conducted in Germany, Infanrix was shown to have a protective efficacy of 88.7% (95% CI: 76.6%.94.6%) against typical pertussis as defined by the WHO (spasmodic cough 21 days duration, with laboratory confirmation) when administered as a three-dose primary vaccination course at 3, 4 and 5 months of age [Schmitt, 1996a; Schmitt, 1996b]. The protective efficacy of Infanrix as a three-dose primary vaccination at 2, 4 and 6 months of age has also been evaluated in a large placebo-controlled prospective cohort study conducted in Italy under the auspices of the US National Institute of Allergy and Infectious Diseases. In this study, Infanrix was shown to have an efficacy of 83.9% (95% CI: 75.8.89.4) against WHO-defined pertussis [Greco, 1996], a finding which correlates with that of the German household contact study. Follow-up of subjects included in this Italian study for up to 60 months after vaccination has shown no decrease in vaccine efficacy over this period despite the absence of a booster dose in the second year of life [Salmaso, 2001].

Protective immunogenicity was demonstrated in clinical trials against the diphtheria, tetanus, and each of the three polio antigens.

Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are highly efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months of age. However, data indicate that protection against pertussis may be waning at 7-8 years of age. This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.

Protective immunity against hepatitis B has been shown to persist for at least 3.5 years in more than 90% of children administered four doses of *Infanrix hexa*. Antibody levels

were not different from what was observed in a parallel cohort administered monovalent hepatitis B vaccine.

The effectiveness of the Hib component of *Infanrix hexa* was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a seven year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was *Infanrix hexa*, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

17.2. Newly Identified Information on Efficacy and Effectiveness

In the past years there have been outbreaks of pertussis in different countries where the coverage of Tdap and DTaP was considered high and the burden of disease of this '*well controlled disease in the past*' began to affect the most vulnerable individuals: children less than one year of age, who are at highest risk of mortality and sequelae. In the past adolescents and adults rarely presented pertussis disease whereas nowadays there is an epidemiological shift in these older ages. Teens and adults presented in recent years a higher burden of disease, especially in the United States, Europe and Australia [ACIP, 2013, CDC 2013a].

The United States did have an outbreak of pertussis in 2010 in California, with more than 9000 reported cases and 10 reported infant deaths. The highest incidence of pertussis disease was observed in children less than one year of age as well as in children between 7 and 10 years old. As of June 2014, the total number of cases reported exceeded the cases reported in 2013, indicating another epidemic. In April 2012, the Center for Disease Control and Prevention (CDC) declared an epidemic of pertussis in Washington State, which extended throughout all the country. According to the CDC 2013 Provisional Pertussis Surveillance Report, in 2012 and 2013, there were 48,277 and 24,231 cases reported nationwide, respectively [Jakinovich, 2014].

In 2009, 20,591 cases of pertussis have been notified in Europe (4.9/100,000 inhabitants); the highest incidence rates were observed in Norway, Estonia, The Netherlands and Poland. Data were distributed between age groups as follows: 6%, 7%, 10%, 25%, 15%, 4%, 3% and 31% in subjects aged <1 year, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29 and >30 years, respectively. Incidence was highest among infants (22/100,000) and among children aged 10–14 years. (20/100,000) [Gabutti ,2012].

In Australia between 2000 and 2010, multiple epidemics of pertussis occurred; however, the timing and frequency of these varied by geographical location. More than 139,000 cases were reported over this 11-year period, with the highest annual incidence of notifications (156 cases per 100 000 population) reported in 2010 [AGDH,2014]. Australia remained on epidemic period since 2009, and the removal of the toddler's booster in 2003, did influence in the increase of disease shown in this age cohort. Like the United States, Australia reported a higher increased in teens and adults since 2009.

These epidemics demonstrated a new pattern, with particularly high rates of disease among pre-adolescents and early adolescents. These high rates of pertussis coincided with the first cohorts vaccinated with purely acellular pertussis vaccine, which replaced whole-cell pertussis (wP) vaccine in the later 1990s in the USA and Australia [Sheridan,

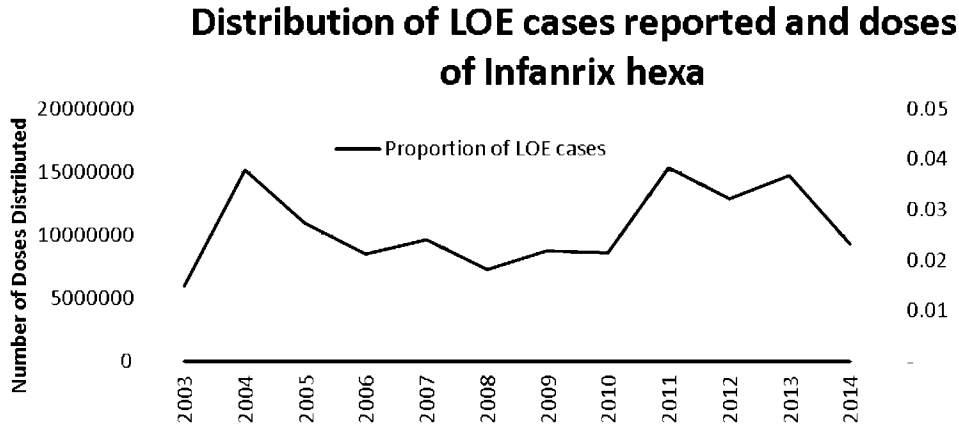
2014]. Studies undertaken during these epidemics provide new evidence of more rapid waning of acellular pertussis-containing vaccines and longer-term protection from effective wP-containing vaccines. There is evidence that receiving wP as at least the first dose of pertussis-containing vaccine provides greater and more long-lived protection, irrespective of the nature of subsequent doses [Sheridan, 2014].

Many explanations have been advanced for the dramatic resurgence of pertussis. These include improved reporting of cases secondary to increased awareness, use of polymerase chain reaction (PCR) as a diagnostic tool, waning of immunity of acellular vaccines compared with the previous whole-cell vaccines, genetic changes in the organism, pockets of populations with high rates of vaccine refusal, infant susceptibility, and lack of cocooning. As would be expected, the problem is multifactorial [Jakinovich, 2014; Smallridge, 2014].

Tdap (reduced pertussis content) waning of immunity was presented in the ACIP of June 2013, following preliminary results of the CDC study on Tdap Vaccine Effectiveness. Until now this study is not yet published, only the abstract is available, where their conclusion is that Tdap VE and duration of protection among adolescents who would have been vaccinated solely with acellular pertussis vaccines is modest and wanes substantially with time. Although current Tdap vaccines may not fully control pertussis in the United States, vaccination remains the best way to protect individuals against disease [Acosta, 2013].

GSK has followed these signals closely, and identify waning of immunity as an important identified risk in all DTaP and Tdap vaccines. Extensive epidemiological literature reviews were done in order to make a proper in depth assessment. After review of spontaneous reports of lack of efficacy since launch with DTaP vaccines, there is a higher reporting of this event in 2010-2011 for *Infanrix hexa*, but not to concerning values. In conclusion, there is no extensive reporting of LOE (Lack of efficacy) cases with DTaP vaccines combos. **Figure 9** shows the distribution of LOE cases and the number of doses distributed of *Infanrix hexa*. An evaluation of LOE is also presented in APPENDIX 7B.1.

Figure 9 Distribution of LOE cases and the number of doses distributed of *Infanrix hexa*



Confirmed vaccination failure is defined as the occurrence of specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization. This definition requires clinical and laboratory confirmation that the actual disease is vaccine preventable, i.e. that the pathogen and clinical manifestations are specifically targeted by the vaccine.

17.3. Characterisation of Benefits

The baseline efficacy and effectiveness information is presented in Section 17.1 Important baseline efficacy/effectiveness information.

New vaccine (pertussis) effectiveness data have become available during this reporting period described in Section 17.2 Newly identified information on efficacy/effectiveness: the immune response to pertussis boosting at pre-school age wanes, and may not be sufficient to maintain adequate protection until the next pertussis booster dose in adolescence.

Nevertheless, the overall benefit profile for *Infanrix hexa* remains favourable.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR APPROVED INDICATIONS

18.1. Benefit :Risk Context: Medical Need and Important Alternatives

Medical need

Infectious diseases are a leading cause of morbidity and mortality in young children worldwide. The World Health Organization (WHO) estimates that at least 2 million deaths could be prevented annually among children under 5 years of age by administering existing vaccines [WHO, 1998; Prymula, 2008].

See also Sections on burden of diseases above (Section 17.1) for more specific information on medical need for vaccination against diphtheria, tetanus, pertussis, hepatis B, poliomyelitis and Hib.

Concerns during the 70's raised among the public about the possible risk of whole cell pertussis vaccine-induced childhood encephalopathy led to a decline in pertussis vaccine use in the United Kingdom. This decrease in vaccine acceptance was quickly followed by outbreaks of disease in 1977–1979 and 1982. Similar events took place in Japan and Sweden in the late 1970s [Ray, 2006]. As a result of general concerns about the safety of the whole cell pertussis vaccine, the United States and many other countries stopped using the whole-cell vaccine and adopted the use of acellular pertussis vaccines that have similar effectiveness and lower reactogenicity than the whole cell pertussis vaccine.

Important alternatives
One **DTPa-HBV-IPV/Hib** alternative to *Infanrix hexa* (three component pertussis - PT, FHA and PRN) is obtainable from Sanofi Pasteur MSD: Hexacima™/Hexyon™ (two component pertussis: PT and FHA). Alternative vaccines also include combined use of monovalent vaccines, such as:

- for **DTPa**: Infanrix™ (GSK) or Daptacel™/Tripacel™ (Sanofi).
- for **HepB**: Engerix™ (GSK), Recombivax HB™ (Sanofi Pasteur MSD), HBVAX™ Pro (Sanofi Pasteur MSD), Gen Hevac™ B (Sanofi Pasteur) or Hepavax™-Gene (Crucell), EuvaxB™ (20mcg HBsAg from LG Chemicals, with Sanofi Pasteur MSD as license holder in some countries in Central-Eastern Europe).
- for **IPV**: Poliorix™ (GSK) or IPOL™/Immovax™ Polio (Sanofi Pasteur MSD).
- for **Hib**: Hiberix™ (GSK - Tetanus toxoid conjugate), ActiHib™ (Sanofi Pasteur MSD - Tetanus toxoid conjugate) or PedvaxHIB™ (Merck - Meningococcal Protein Conjugate).

Some of these monovalent vaccines are also available as combination vaccines:

- for **DTPa-IPV**: Infanrix™-IPV/Kinrix™ (GSK), Tetravac™/ Tetraxim™ (Sanofi Pasteur MSD, two component pertussis: PT and FHA) or Quadracel (Sanofi Pasteur, five-component pertussis: PT, FHA, PRN, FIM2 and FIM3).
- for **DTPa-IPV/Hib**: Infanrix-IPV/Hib (called Infanrix Quinta in France, GSK) or Pentacel™ (Sanofi Pasteur, five-component pertussis: PT, FHA, PRN, FIM2 and FIM3) or Pediacel and Pentaxim, or Pentavac (Sanofi for Pasteur MSD, two-component pertussis).
- for **DTPa-HBV-IPV**: Infanrix™ Penta/Pediarix™ (GSK).

Actual use of these alternative vaccines depends on the approval status of each of these vaccines in a given country.

18.2. Benefit:Risk Analysis Evaluation

GSK has extensive clinical and post-marketing experience with *Infanrix hexa*. Since launch over 119 million doses have been distributed worldwide. *Infanrix hexa* is currently licensed in over 100 countries and has not been withdrawn from any country due to regulatory action or safety concern. *Infanrix hexa* has a long-established safety and efficacy profile which has not altered after many years on the market.

Vaccination has greatly reduced the burden of infectious diseases. Diphtheria, tetanus, pertussis, hepatitis B, polio and diseases caused by *Haemophilus influenza* type b are a common cause of disease in children worldwide, with significant morbidity and mortality. A dramatic decline in the incidence of diphtheria, tetanus, pertussis, hepatitis B, polio and diseases caused by *Haemophilus influenza* type b have been evidenced in countries in which infants are routinely immunised against these diseases.

According to peer reviewed literature, a risk of waning of acellular pertussis vaccine-induced immunity was identified for pertussis containing vaccines. Review of recent available US CDC California effectiveness data for DTaP [Misegades, 2012] suggests that the immune response to pertussis boosting at pre-school age wanes, and may not be sufficient to maintain adequate protection until the next pertussis booster dose in adolescence (decrease from 98.1% VE in the first year since receipt of the fifth dose to 71.2% by 5 years or more after vaccination). The data currently available to GSK suggest that there is a higher incidence of pertussis after acellular pertussis boosting in cohorts primed with acellular pertussis than in those primed with whole cell vaccines [CDC, 2012d; Sheridan, 2012].

The relatively rapid waning of acellular pertussis vaccine immunity according to time since vaccination contributed to the outbreaks in the US, as shown by the clusters of cases in specific birth cohorts, with an impact of the primary schedule (in particular the first dose) on pertussis incidence. The use of acellular vaccines in the primary schedule and in particular for the first dose led to a higher incidence later in life (in >= 10 years old) both in Australia and in the US. However, whether or not similar outbreaks as seen in the US and Australia can be predicted in the future in other countries is difficult to understand, for the following reasons: a) in the US there was a sub-optimal coverage and timeliness of vaccination (including primary schedule), b) acellular vaccines used in 1998-2002 included vaccines that were not used after 2002, c) the progressive implementation of Tdap since 2006 involved at the beginning cohorts primed with whole cell vaccines, and then, cohorts primed with acellular vaccines. This means that due to a different duration of protection depending on the type of vaccine used in the primary schedule several cohorts lost their vaccine protection at about the same moment, which may facilitate outbreaks.

The current *Infanrix hexa* RSI appropriately reflects the product's safety profile. No new safety concerns that would impact the benefit-risk ratio have been identified during the current reporting period.

Although the under-reporting inherent to any spontaneous reporting setting is a limitation of this integrated assessment, it is concluded, at population level, that (potentially) severe infectious diseases are prevented by the use of *Infanrix hexa* compared to the relatively low risk of side effects.

19. CONCLUSIONS AND ACTIONS

Data relating to the benefit: risk profile of *Infanrix hexa* received in the reporting period 23 October 2011 to 22 October 2014 has been reviewed and placed in a cumulative context.

According to peer reviewed literature, a risk of waning of acellular pertussis vaccine induced immunity was identified for acellular pertussis containing vaccines. GSK concludes that it is critical to maintain strong acellular pertussis immunization programs (i.e. high vaccine coverage and timeliness of vaccination) to control pertussis in this period of increased circulation of disease. GSK will continue close monitoring waning of acellular pertussis vaccine induced immunity and post-marketing lack of efficacy cases through routine pharmacovigilance.

The potential increase of HHE and convulsions with or without fever after co-administration of *Infanrix hexa* with Prevenar™ 13 vaccine found after review of post-marketing data, does not represent a change of the frequencies of these 'very rare' events.

The benefit: risk profile of *Infanrix hexa* for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b continues to be favourable.

The company continues to monitor cases of anaemia haemolytic autoimmune,thrombocytopenia, thrombocytopenic purpura, autoimmune thrombocytopenia, idiopathic thrombocytopenic purpura, haemolytic anemia, Kawasaki's disease, important neurological events (including encephalitis and encephalopathy), Henoch-Schonlein purpura, petechiae, purpura, haematochezia, allergic reactions (including anaphylactic and anaphylactoid reactions), extensive swelling of vaccinated limb, cases of lack of effectiveness as well as fatal cases.

The company ended close monitoring of Cyanosis, Gaze palsy, Haematochezia, Injection site nodule, abscess and injection site abscess.

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APPENDIX 1A : REFERENCE INFORMATION

GLOBAL PRESCRIBER INFORMATION version 014 dated 13 March 2014

TITLE

Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine.

SCOPE

Trade Name(s)

Infanrix hexa

Formulation and Strength

Powder and suspension for suspension for injection.

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International Units (IU)
Tetanus toxoid[1]	not less than 40 International Units (IU)
Bordetella pertussis antigens	
Pertussis toxoid[1]	25 micrograms
Filamentous Haemagglutinin[1]	25 micrograms
Pertactin[1]	8 micrograms
Hepatitis B surface antigen[2,3]	10 micrograms
Poliovirus (inactivated)	
type 1 (Mahoney strain)[4]	40 D-antigen unit
type 2 (MEF-1 strain)[4]	8 D-antigen unit
type 3 (Saukett strain)[4]	32 D-antigen unit
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate)[3] conjugated to tetanus toxoid as carrier protein	10 micrograms approximately 25 micrograms

[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 milligrams Al^{3+}
[2]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[3]adsorbed on aluminium phosphate ($AlPO_4$) 0.32 milligrams Al^{3+}
[4]propagated in VERO cells

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed. This is a normal observation.

The Hib component is presented as a white powder.

Excipients

It is mandatory for country product information to include both the complete list of excipients for all locally marketed presentations, and any locally imposed excipient warning statements.

Lactose

Sodium chloride (NaCl)

Medium 199 (as stabilizer including amino acids, mineral salts and vitamins)

Water for injections

Residues

Potassium chloride

Disodium phosphate

Monopotassium phosphate

Polysorbate 20 and 80

Glycine

Formaldehyde

Neomycin sulphate

Polymyxin B sulphate

CLINICAL INFORMATION

Indications

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b.

Dosage and Administration

Posology

- **Primary vaccination**

The primary vaccination schedule consists of three doses of 0.5 ml (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) or two doses (e.g. 3, 5 months). There should be an interval of at least 1 month between doses. The Expanded Program on Immunisation schedule (at 6, 10, 14 weeks of age) may only be used if a dose of hepatitis B vaccine has been given at birth.

Locally established immunoprophylactic measures against hepatitis B should be maintained. Where a dose of hepatitis B vaccine is given at birth, Infanrix hexa can be used as a replacement for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

- **Booster vaccination**

After a vaccination with 2 doses (e.g. 3, 5 months) of Infanrix hexa a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age.

After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) of Infanrix hexa a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

Booster doses should be given in accordance with the official recommendations.

Infanrix hexa can be considered for the booster if the composition is in accordance with the official recommendations.

Other combinations of antigens have been studied in clinical trials following primary vaccination with Infanrix hexa and may be used for a booster dose: diphtheria, tetanus, acellular pertussis (DTPa), diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b (DTPa+Hib), diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-IPV+Hib) and diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-HBV-IPV+Hib).

Method of administration

Infanrix hexa is for deep intramuscular injection.

Contraindications

Hypersensitivity to the active substances or to any of the excipients or residues (see *Formulation and Strength*, *Excipients* and *Residues*).

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

Infanrix hexa is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

Warnings and Precautions

As with other vaccines, administration of Infanrix hexa should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:

- Temperature of ≥ 40.0°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours of vaccination.

- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Infanrix hexa should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Infanrix hexa should under no circumstances be administered intravascularly or intradermally.

Infanrix hexa contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Infanrix hexa will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

A protective immune response may not be elicited in all vaccinees (see *Pharmacodynamic Effects*).

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of Infanrix hexa. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the Hib capsular polysaccharide antigen is excreted in the urine a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Limited data in 169 premature infants indicate that Infanrix hexa can be given to premature children. However, a lower immune response may be observed and the level of clinical protection remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of

respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

High incidence of fever (> 39.5°C) was reported in infants receiving Infanrix hexa and Prevenar compared to infants receiving the hexavalent vaccine alone.

Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of Infanrix hexa and Prevenar 13 (see *Adverse Reactions*).

Antipyretic treatment should be initiated according to local treatment guidelines.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Interactions

There are insufficient data with regard to the efficacy and safety of simultaneous administration of Infanrix hexa and Measles-Mumps-Rubella vaccine to allow any recommendation to be made.

Data on concomitant administration of Infanrix hexa with Prevenar (pneumococcal saccharide conjugated vaccine, adsorbed) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a 3 dose primary vaccination. However, high incidence of fever (> 39.5°C) was reported in infants receiving Infanrix hexa and Prevenar compared to infants receiving the hexavalent vaccine alone (see *Warnings and Precautions* for guidance on Prevenar and Prevenar 13).

As with other vaccines, it may be expected that in patients receiving immunosuppressive therapy, an adequate response may not be achieved.

Pregnancy and Lactation

Pregnancy

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during pregnancy is not available.

Lactation

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during lactation is not available.

Ability to perform tasks that require judgement, motor or cognitive skills

Not relevant.

Adverse Reactions

Clinical Trial Data

The safety profile presented below is based on data from more than 16,000 subjects.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with Infanrix hexa with respect to the primary course.

Adverse reactions reported are listed according to the following frequency:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100
Rare: ≥ 1/10000 to < 1/1000
Very rare: < 1/10000

Infections and infestations

Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders

Very common: appetite lost

Psychiatric disorders

Very common: irritability, crying abnormal, restlessness
Common: nervousness

Nervous system disorders

Uncommon: somnolence
Very rare: convulsions (with or without fever)***

Respiratory, thoracic and mediastinal disorders

Uncommon: cough*
Rare: bronchitis

Gastrointestinal disorders

Common: vomiting, diarrhoea

Skin and subcutaneous tissue disorders

Common: pruritus*
Rare: rash
Very rare: dermatitis, urticaria*

General disorders and administration site conditions

Very common: pain, redness, local swelling at the injection site (≤ 50 mm), fever ≥ 38°C, fatigue
Common: local swelling at the injection site (> 50 mm)**, fever >39.5°C, injection site reactions, including induration
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint**

Post Marketing Data

Blood and lymphatic system disorders

Lymphadenopathy, thrombocytopenia

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders

Collapse or shock-like state (hypotonic hyporesponsive episode)***

Respiratory, thoracic and mediastinal disorders

Apnoea* *[see Warnings and Precautions for apnoea in very premature infants (≤ 28 weeks of gestation)]*

Skin and subcutaneous tissue disorders

Angioneurotic oedema*

General disorders and administration site conditions

Extensive swelling reactions, swelling of the entire injected limb**, vesicles at the injection site

* observed with other GSK DTPa-containing vaccines

** Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

*** Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of Infanrix hexa with Prevenar 13 to those which reported use of Infanrix hexa alone.

Experience with hepatitis B vaccine:

Meningitis, allergic reactions mimicking serum sickness, paralysis, encephalitis, encephalopathy, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis, muscular weakness have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants < 2 years old. The causal relationship to the vaccine has not been established.

Overdosage

Insufficient data are available.

Clinical Pharmacology

Pharmacodynamics

ATC Code

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA09

Pharmacodynamic Effects

Immunogenicity

Result obtained in the clinical studies for each of the components are summarised in the tables below:

Percentage of subjects with antibody titres ≥ assay cut-off one month after primary vaccination with Infanrix hexa

Antibody (cut-off)	**Two doses**	**Three doses**			
	3-5 months N= 530 (4 studies)	**2-3-4 months N= 196 (2 studies)**	**2-4-6 months N= 1693 (6 studies)**	**3-4-5 months N= 1055 (6 studies)**	**6-10-14 weeks N= 265 (1 study)**
	%	**%**	**%**	**%**	**%**
Anti-diphtheria (0.1 IU/ml) †	98.0	100.0	99.8	99.7	99.2
Anti-tetanus (0.1 IU/ml) †	100.0	100.0	100.0	100.0	99.6
Anti-PT (5 EL.U/ml)	99.5	100.0	100.0	99.8	99.6
Anti-FHA (5 EL.U/ml)	99.7	100.0	100.0	100.0	100.0
Anti-PRN (5 EL.U/ml)	99.0	100.0	100.0	99.7	98.9
Anti-HBs (10 mIU/ml) †	96.8	99.5	98.9	98.0	98.5*
Anti-Polio type 1 (1/8 dilution) †	99.4	100.0	99.9	99.7	99.6
Anti-Polio type 2 (1/8 dilution) †	96.3	97.8	99.3	98.9	95.7
Anti-Polio type 3 (1/8 dilution) †	98.8	100.0	99.7	99.7	99.6
Anti-PRP (0.15 μg/ml) †	91.7	96.4	96.6	96.8	97.4

N=number of subjects

* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres ≥ 10 mIU/ml

† cut-off accepted as indicative of protection

Percentage of subjects with antibody titres ≥ assay cut-off one month after booster vaccination with Infanrix hexa

Antibody (cut-off)	**Booster vaccination at 11 months of age following a 3-5 month primary course N=532 (3 studies)**	**Booster vaccination during the second year of life following a three dose primary course N= 2009 (12 studies)**
	%	**%**
Anti-diphtheria (0.1 IU/ml) †	100.0	99.9
Anti-tetanus (0.1 IU/ml) †	100.0	99.9
Anti-PT (5 EL.U/ml)	100.0	99.9
Anti-FHA (5 EL.U/ml)	100.0	99.9
Anti-PRN (5 EL.U/ml)	99.2	99.5
Anti-HBs (10 mIU/ml) †	98.9	98.4
Anti-Polio type 1 (1/8 dilution) †	99.8	99.9
Anti-Polio type 2 (1/8 dilution) †	99.4	99.9
Anti-Polio type 3 (1/8 dilution) †	99.2	99.9
Anti-PRP (0.15 μg/ml) †	99.6	99.7

N= Number of subjects
† cut-off accepted as indicative of protection

As the immune response to pertussis antigens following Infanrix hexa administration is equivalent to that of Infanrix, the protective efficacy of the two vaccines is expected to be equivalent.

Efficacy in protecting against pertussis

The protective efficacy of the pertussis component of Infanrix against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated after 3-dose primary immunisation in the studies tabulated below:

Study	**Country**	**Schedule**	**Vaccine efficacy**	**Considerations**
Household contact study	Germany	3,4,5 months	88.7%	Based on data collected from secondary contacts in households where there was

(prospective blinded)				an index case with typical pertussis
Efficacy study (NIH sponsored)	Italy	2,4,6 months	84%	In a follow-up of the same cohort, the efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.

Persistence of the immune response

Protective immunity against hepatitis B has been shown to persist for at least 3.5 years in more than 90% of children administered four doses of Infanrix hexa. Antibody levels were not different from what was observed in a parallel cohort administered monovalent hepatitis B vaccine.

Post marketing experience

Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months. However, data indicate that protection against pertussis may be waning at 7-8 years of age. This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.

The effectiveness of the Hib component of Infanrix hexa was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a seven year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was Infanrix hexa, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

Infanrix hexa has been the only Hib vaccine available in Italy since 2006. The vaccine is administered at 3, 5 and 11 months of age and coverage has exceeded 95%. Hib disease has continued to be well controlled, with no more than three confirmed Hib cases reported annually between 2006 and 2011 in Italian children aged less than 5 years.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See *Pharmacodynamic Effects*.

NON-CLINICAL INFORMATION

Preclinical data reveal no special hazard for humans based on conventional studies of safety, specific toxicity, repeated dose toxicity and compatibility of ingredients.

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date of the vaccine is indicated on the label and packaging. The expiry date refers to the last day of the month mentioned.

The shelf-life is 3 years.

Storage

Infanrix hexa should be stored at +2°C to +8°C.

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Protect from light.

During transport, recommended conditions of storage must be respected.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Nature and Contents of Container

The DTPa-HBV-IPV component is presented in a pre-filled syringe or vial.

The Hib component is presented as a white pellet in a glass vial.

The vials and pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Vial and pre-filled syringe presentations (with or without needles) are available in packs of 1, 10, 20 and 50.
Vial and vial presentation is available in pack sizes of 1 and 50.

Incompatibilities

Infanrix hexa should not be mixed with other vaccines in the same syringe.

Use and Handling

1. Wording for vial and pre-filled syringe presentation

The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The DTPa-HBV-IPV suspension and the Hib powder should be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

Infanrix hexa must be reconstituted by adding the entire content of the pre-filled syringe to the vial containing the Hib powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room

temperature (25 ± 3 °C) for at least five minutes before connecting the pre-filled syringe and reconstituting the vaccine.

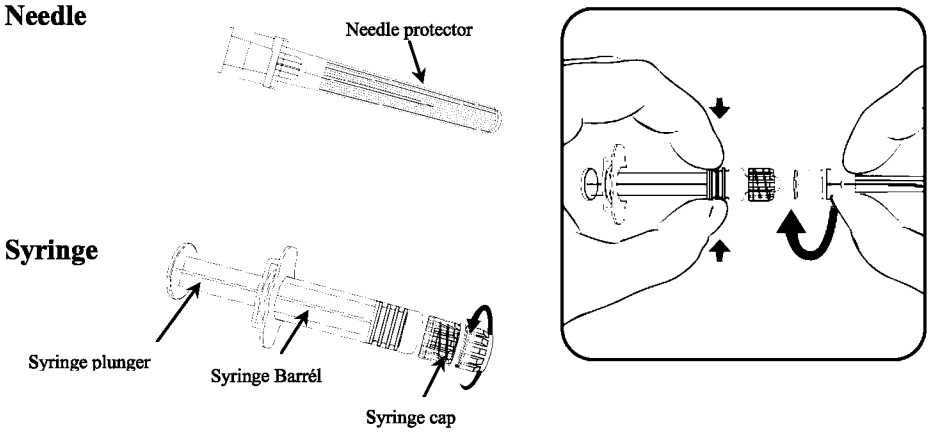
The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be injected immediately. However the vaccine may be kept for up to 8 hours at room temperature (21°C).

Withdraw the entire contents of the vial.

- ***Specific instructions for the pre-filled syringe with a luer lock adaptor (PRTC)***



1. Holding the syringe **Barrél** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

2. Wording for vial and vial presentation

Infanrix hexa must be reconstituted by adding the entire content of the vial containing the DTPa-HBV-IPV suspension to the vial containing the Hib powder. To do so, draw up the

suspension with a syringe and add the suspension to the powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

A new needle should be used to administer the vaccine.

After reconstitution, the vaccine should be used immediately.

Withdraw the entire contents of the vial.

Any unused product or waste material should be disposed of in accordance with local requirements.

APPENDIX 1B : REFERENCE INFORMATION REFLECTING CHANGES DURING THE REPORTING PERIOD (GPI VERSION 011 DATED 17 OCTOBER 2012)

GLOBAL PRESCRIBER INFORMATION

TITLE

Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine.

SCOPE

Trade Name(s)

Infanrix hexa

Formulation and Strength

Powder and suspension for suspension for injection.

1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International units
Tetanus toxoid[1]	not less than 40 International units
Bordetella pertussis antigens	
Pertussis toxoid[1]	25 micrograms
Filamentous Haemagglutinin[1]	25 micrograms
Pertactin[1]	8 micrograms
Hepatitis B surface antigen[2,3]	10 micrograms
Poliovirus (inactivated)	
type 1 (Mahoney strain)[4]	40 D-antigen unit
type 2 (MEF-1 strain)[4]	8 D-antigen unit
type 3 (Saukett strain)[4]	32 D-antigen unit
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate)[3] conjugated to tetanus toxoid as carrier protein	10 micrograms 20 - 40 micrograms

[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 milligrams Al^{3+}
[2]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[3]adsorbed on aluminium phosphate ($AlPO_4$) 0.32 milligrams Al^{3+}
[4]propagated in VERO cells

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed.

The Hib component is presented as a white powder.

Excipients

It is mandatory for country product information to include both the complete list of excipients for all locally marketed presentations, and any locally imposed excipient warning statements.

Lactose

Sodium chloride (NaCl)

Medium 199 (as stabilizer including amino acids, mineral salts and vitamins)

Water for injections

Residues

Potassium chloride

Disodium phosphate

Monopotassium phosphate

Polysorbate 20 and 80

Glycine

Formaldehyde

Neomycin sulphate

Polymyxin B sulphate

CLINICAL INFORMATION

Indications

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenza* type b.

Dosage and Administration

Posology

- **Primary vaccination**

The primary vaccination schedule consists of three doses of 0.5 ml (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) or two doses (e.g. 3, 5 months). There should be an interval of at least 1 month between doses. The Expanded Program on Immunisation schedule (at 6, 10, 14 weeks of age) may only be used if a dose of hepatitis B vaccine has been given at birth.

Locally established immunoprophylactic measures against hepatitis B should be maintained. Where a dose of hepatitis B vaccine is given at birth, Infanrix hexa can be used as a replacement for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

- **Booster vaccination**

After a vaccination with 2 doses (e.g. 3, 5 months) of Infanrix hexa a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age.

After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) of Infanrix hexa a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

Booster doses should be given in accordance with the official recommendations.

Infanrix hexa can be considered for the booster if the composition is in accordance with the official recommendations.

Other combinations of antigens have been studied in clinical trials following primary vaccination with Infanrix hexa and may be used for a booster dose: diphtheria, tetanus, acellular pertussis (DTPa), diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b (DTPa+Hib), diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-IPV+Hib) and diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-HBV-IPV+Hib).

Method of administration

Infanrix hexa is for deep intramuscular injection.

Contraindications

Hypersensitivity to the active substances or to any of the excipients or residues (see *Formulation and Strength*, *Excipients* and *Residues*).

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

Infanrix hexa is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

Warnings and Precautions

As with other vaccines, administration of Infanrix hexa should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:

- Temperature of ≥ 40.0°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsiveness episode) within 48 hours of vaccination.

- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Infanrix hexa should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Infanrix hexa should under no circumstances be administered intravascularly or intradermally.

Infanrix hexa contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Infanrix hexa will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

A protective immune response may not be elicited in all vaccinees (see *Pharmacodynamic Effects*).

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of Infanrix hexa. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the Hib capsular polysaccharide antigen is excreted in the urine a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Limited data in 169 premature infants indicate that Infanrix hexa can be given to premature children. However, a lower immune response may be observed and the level of clinical protection remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of

respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Interactions

There are insufficient data with regard to the efficacy and safety of simultaneous administration of Infanrix hexa and Measles-Mumps-Rubella vaccine to allow any recommendation to be made.

Data on concomitant administration of Infanrix hexa with Prevenar (pneumococcal saccharide conjugated vaccine, adsorbed) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a 3 dose primary vaccination.

However, high incidence of fever (> 39.5°C) was reported in infants receiving Infanrix hexa and Prevenar compared to infants receiving the hexavalent vaccine alone.

Antipyretic treatment should be initiated according to local treatment guidelines.

As with other vaccines, it may be expected that in patients receiving immunosuppressive therapy, an adequate response may not be achieved.

Pregnancy and Lactation

Pregnancy

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during pregnancy is not available.

Lactation

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during lactation is not available.

Ability to perform tasks that require judgement, motor or cognitive skills

Not relevant.

Adverse Reactions

Clinical Trial Data

The safety profile presented below is based on data from more than 16,000 subjects.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with Infanrix hexa with respect to the primary course.

Adverse reactions reported are listed according to the following frequency:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100

Rare: ≥ 1/10000 to < 1/1000
Very rare: < 1/10000

Infections and infestations

Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders

Very common: appetite lost

Psychiatric disorders

Very common: irritability, crying abnormal, restlessness
Common: nervousness

Nervous system disorders

Uncommon: somnolence
Very rare: convulsions (with or without fever)

Respiratory, thoracic and mediastinal disorders

Uncommon: cough*
Rare: bronchitis

Gastrointestinal disorders

Common: vomiting, diarrhoea

Skin and subcutaneous tissue disorders

Common: pruritus*
Rare: rash
Very rare: dermatitis, urticaria*

General disorders and administration site conditions

Very common: pain, redness, local swelling at the injection site (≤ 50 mm), fever ≥ 38°C, fatigue
Common: local swelling at the injection site (> 50 mm)**, fever >39.5°C, injection site reactions, including induration
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint**

Post Marketing Data

Blood and lymphatic system disorders

Lymphadenopathy, thrombocytopenia

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders

Collapse or shock-like state (hypotonic-hyporesponsiveness episode)

Respiratory, thoracic and mediastinal disorders

Apnoea* *[see Warnings and Precautions for apnoea in very premature infants (≤ 28 weeks of gestation)]*

Skin and subcutaneous tissue disorders

Angioneurotic oedema*

General disorders and administration site conditions

Extensive swelling reactions, swelling of the entire injected limb**, vesicles at the injection site

* observed with other GSK DTPa-containing vaccines

** Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

Experience with hepatitis B vaccine:

Meningitis, ***allergic reactions*** mimicking serum sickness, paralysis, encephalitis, encephalopathy, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis, muscular weakness have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants < 2 years old. The causal relationship to the vaccine has not been established.

Overdosage

Insufficient data are available.

Clinical Pharmacology

Pharmacodynamics

ATC Code

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA09

Pharmacodynamic Effects

Result obtained in the clinical studies for each of the components are summarised in the tables below:

Percentage of subjects with antibody titres ≥ assay cut-off one month after primary vaccination with Infanrix hexa

Antibody (cut-off)	**Two doses**	**Three doses**			
	3-5 months N= 530 (4 studies)	**2-3-4 months N= 196 (2 studies)**	**2-4-6 months N= 1693 (6 studies)**	**3-4-5 months N= 1055 (6 studies)**	**6-10-14 weeks N= 265 (1 study)**
	%	**%**	**%**	**%**	**%**
Anti-diphtheria (0.1 IU/ml) †	98.0	100.0	99.8	99.7	99.2
Anti-tetanus (0.1 IU/ml) †	100.0	100.0	100.0	100.0	99.6
Anti-PT (5 EL.U/ml)	99.5	100.0	100.0	99.8	99.6
Anti-FHA (5 EL.U/ml)	99.7	100.0	100.0	100.0	100.0
Anti-PRN (5 EL.U/ml)	99.0	100.0	100.0	99.7	98.9
Anti-HBs (10 mIU/ml) †	96.8	99.5	98.9	98.0	98.5*
Anti-Polio type 1 (1/8 dilution) †	99.4	100.0	99.9	99.7	99.6
Anti-Polio type 2 (1/8 dilution) †	96.3	97.8	99.3	98.9	95.7
Anti-Polio type 3 (1/8 dilution) †	98.8	100.0	99.7	99.7	99.6
Anti-PRP (0.15 μg/ml) †	91.7	96.4	96.6	96.8	97.4

N=number of subjects

* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres ≥ 10 mIU/ml

† cut-off accepted as indicative of protection

Percentage of subjects with antibody titres ≥ assay cut-off one month after booster vaccination with Infanrix hexa

Antibody (cut-off)	**Booster vaccination at 11 months of age following a 3-5 month primary course N=532 (3 studies)**	**Booster vaccination during the second year of life following a three dose primary course N= 2009 (12 studies)**
	%	**%**
Anti-diphtheria (0.1 IU/ml) †	100.0	99.9
Anti-tetanus (0.1 IU/ml) †	100.0	99.9
Anti-PT (5 EL.U/ml)	100.0	99.9
Anti-FHA (5 EL.U/ml)	100.0	99.9
Anti-PRN (5 EL.U/ml)	99.2	99.5
Anti-HBs (10 mIU/ml) †	98.9	98.4
Anti-Polio type 1 (1/8 dilution) †	99.8	99.9
Anti-Polio type 2 (1/8 dilution) †	99.4	99.9
Anti-Polio type 3 (1/8 dilution) †	99.2	99.9
Anti-PRP (0.15 μg/ml) †	99.6	99.7

N= Number of subjects
† cut-off accepted as indicative of protection

As the immune response to pertussis antigens following Infanrix hexa administration is equivalent to that of Infanrix, the protective efficacy of the two vaccines is expected to be equivalent.

The protective efficacy of the pertussis component of Infanrix against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated in:

- a prospective blinded household contact study performed in Germany (3, 4, 5 months schedule). Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was 88.7%.

- a NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule). The vaccine efficacy was found to be 84%. In a follow-up of the same cohort, the efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.

Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are highly efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months. However, data indicate that protection against pertussis may be waning at 7-8 years of age.

This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.

~~**Protective immunity against hepatitis B has been shown to persist for at least 3.5 years in more than 90% of children administered four doses of Infanrix hexa. Antibody levels were not different from what was observed in a parallel cohort administered monovalent hepatitis B vaccine.**~~

HBV persistence

Four different clinical studies were performed to assess the percentages of subjects who maintained seroprotective antibody concentration (i.e. anti-HBs ≥ 10mIU/ml) after vaccination with Infanrix hexa. These cohorts had received primary vaccination in a clinical trial setting, according to 2 different vaccination schedules, and were assessed at 3 different ages (4-5, 7-8 and 11-12 years). In three of these studies, subjects received a monovalent hepatitis B vaccine challenge dose to assess the anamnestic response.

Circulating antibodies to hepatitis B wane over time as illustrated by the progressive reduction of subjects maintaining seroprotective antibody concentration. However, one month after a challenge dose, at least 95% of subjects mounted an anamnestic response, demonstrating immune memory in all tested age groups. Results are presented in the table below. Antibody levels were in the same range as those observed in a parallel cohort administered with monovalent hepatitis B vaccine in primary vaccination.

Study number	*Age (years)*	*HBV Seroprotection rate*		*HBV Anamnestic response*	
		N	*%*	*N*	*%*
Schedule 3+1					
DTPa-HBV-IPV-096	*4-5*	*89*	*91.0*	*NA*	*NA*
DTPa-HBV-IPV-111	*4-5*	*198*	*86.4*	*186*	*95.7*
DTPa-HBV-IPV-110	*7-8*	*193*	*77.2*	*186*	*98.9*
Schedule 2+1					
DTPa-HBV-IPV-126	*11-12*	*95*	*53.7*	*95*	*95.8*

N = Number of subjects
NA = Not Applicable: These subjects did not receive a challenge dose

Two additional studies in 2 different age groups (4-5 and 7-8 years) assessed the persistence of anti-HBs antibodies in subjects not primed in a clinical study but who received 4 doses of Infanrix hexa during infancy. In these studies, subjects received a monovalent hepatitis B vaccine challenge dose to assess the anamnestic response.

One month after the challenge dose, at least 96% of subjects mounted an anamnestic response demonstrating immune memory in both studies. Results are presented in the following table:

Study number	*Age (years)*	*HBV Seroprotection rate*		*HBV Anamnestic response*	
		N	*%*	*N*	*%*
Schedule 3+1					
DTPa-HBV-IPV-112	*4-5*	*293*	*85.3*	*285*	*96.8*
DTPa-HBV-IPV-113	*7-8*	*287*	*80.5*	*284*	*97.2*

N = Number of subjects

Hib effectiveness

The effectiveness of the Hib component of Infanrix hexa was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a seven year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was Infanrix hexa, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See *Pharmacodynamic Effects*.

NON-CLINICAL INFORMATION

Preclinical data reveal no special hazard for humans based on conventional studies of safety, specific toxicity, repeated dose toxicity and compatibility of ingredients.

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date of the vaccine is indicated on the label and packaging. The expiry date refers to the last day of the month mentioned.

The shelf-life is 3 years.

Storage

Infanrix hexa should be stored at +2°C to +8°C. Protect from light.

During transport, recommended conditions of storage must be respected.

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Nature and Contents of Container

The DTPa-HBV-IPV component is presented in a pre-filled syringe or vial.

The Hib component is presented as a white pellet in a glass vial.

The vials and pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Vial and pre-filled syringe presentations (with or without needles) are available in packs of 1, 10, 20 and 50.
Vial and vial presentation is available in pack sizes of 1 and 50.

Incompatibilities

Infanrix hexa should not be mixed with other vaccines in the same syringe.

Use and Handling

1. Wording for vial and pre-filled syringe presentation

The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The DTPa-HBV-IPV suspension and the Hib powder should be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

Infanrix hexa must be reconstituted by adding the entire content of the pre-filled syringe to the vial containing the Hib powder. ***The mixture should be well shaken until the powder is completely dissolved in the suspension.***

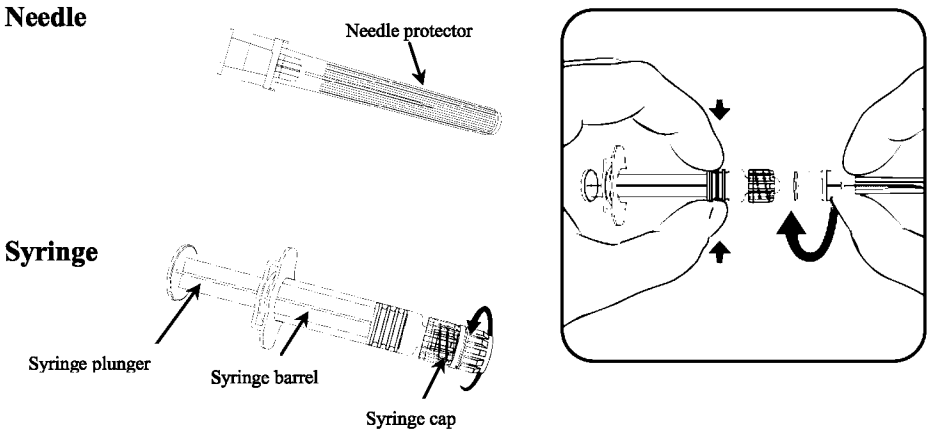
It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room temperature (25 ± 3 °C) for at least five minutes before connecting the pre-filled syringe and reconstituting the vaccine.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine. In the event of other variation being observed, discard the vaccine.

After reconstitution, the vaccine should be injected immediately. However the vaccine may be kept for up to 8 hours at room temperature (21°C).

Withdraw the entire contents of the vial.

- ***Specific instructions for the pre-filled syringe with a luer lock adaptor (PRTC)***



1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.

2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

2. Wording for vial and vial presentation

Upon storage, a white deposit and clear supernatant may be observed in the vial containing the DTPa-HBV-IPV suspension. This does not constitute a sign of deterioration.

Infanrix hexa must be reconstituted by adding the entire content of the vial containing the DTPa-HBV-IPV suspension to the vial containing the Hib powder. To do so, draw up the suspension with a syringe and add the suspension to the powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

A new needle should be used to administer the vaccine.

After reconstitution, the vaccine should be used immediately.

Withdraw the entire contents of the vial.

Any unused product or waste material should be disposed of in accordance with local requirements.

APPENDIX 1C : REFERENCE INFORMATION REFLECTING CHANGES DURING THE REPORTING PERIOD (GPI VERSION 012 DATED 16 APRIL 2013)

GLOBAL PRESCRIBER INFORMATION

TITLE

Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine.

SCOPE

Trade Name(s)

Infanrix hexa

Formulation and Strength

Powder and suspension for suspension for injection.

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International ***U~~u~~nits (IU)***
Tetanus toxoid[1]	not less than 40 International ***U~~u~~nits (IU)***
Bordetella pertussis antigens	
Pertussis toxoid[1]	25 micrograms
Filamentous Haemagglutinin[1]	25 micrograms
Pertactin[1]	8 micrograms
Hepatitis B surface antigen[2,3]	10 micrograms
Poliovirus (inactivated)	
type 1 (Mahoney strain)[4]	40 D-antigen unit
type 2 (MEF-1 strain)[4]	8 D-antigen unit
type 3 (Saukett strain)[4]	32 D-antigen unit
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate)[3] conjugated to tetanus toxoid as carrier protein	10 micrograms ***approximately 2520~~–40~~*** micrograms

[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 milligrams Al^{3+}
[2]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[3]adsorbed on aluminium phosphate ($AlPO_4$) 0.32 milligrams Al^{3+}
[4]propagated in VERO cells

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed. ***This is a normal observation.***

The Hib component is presented as a white powder.

Excipients

It is mandatory for country product information to include both the complete list of excipients for all locally marketed presentations, and any locally imposed excipient warning statements.

Lactose

Sodium chloride (NaCl)

Medium 199 (as stabilizer including amino acids, mineral salts and vitamins)

Water for injections

Residues

Potassium chloride

Disodium phosphate

Monopotassium phosphate

Polysorbate 20 and 80

Glycine

Formaldehyde

Neomycin sulphate

Polymyxin B sulphate

CLINICAL INFORMATION

Indications

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b.

Dosage and Administration

Posology

- **Primary vaccination**

The primary vaccination schedule consists of three doses of 0.5 ml (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) or two doses (e.g. 3, 5 months). There should be an interval of at least 1 month between doses. The Expanded Program on Immunisation schedule (at 6, 10, 14 weeks of age) may only be used if a dose of hepatitis B vaccine has been given at birth.

Locally established immunoprophylactic measures against hepatitis B should be maintained. Where a dose of hepatitis B vaccine is given at birth, Infanrix hexa can be used as a replacement for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

- **Booster vaccination**

After a vaccination with 2 doses (e.g. 3, 5 months) of Infanrix hexa a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age.

After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) of Infanrix hexa a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

Booster doses should be given in accordance with the official recommendations.

Infanrix hexa can be considered for the booster if the composition is in accordance with the official recommendations.

Other combinations of antigens have been studied in clinical trials following primary vaccination with Infanrix hexa and may be used for a booster dose: diphtheria, tetanus, acellular pertussis (DTPa), diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b (DTPa+Hib), diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-IPV+Hib) and diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-HBV-IPV+Hib).

Method of administration

Infanrix hexa is for deep intramuscular injection.

Contraindications

Hypersensitivity to the active substances or to any of the excipients or residues (see *Formulation and Strength*, *Excipients* and *Residues*).

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

Infanrix hexa is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

Warnings and Precautions

As with other vaccines, administration of Infanrix hexa should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:

- Temperature of ≥ 40.0°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsiveness episode) within 48 hours of vaccination.

- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Infanrix hexa should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Infanrix hexa should under no circumstances be administered intravascularly or intradermally.

Infanrix hexa contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Infanrix hexa will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

A protective immune response may not be elicited in all vaccinees (see *Pharmacodynamic Effects*).

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of Infanrix hexa. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the Hib capsular polysaccharide antigen is excreted in the urine a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Limited data in 169 premature infants indicate that Infanrix hexa can be given to premature children. However, a lower immune response may be observed and the level of clinical protection remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of

respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Interactions

There are insufficient data with regard to the efficacy and safety of simultaneous administration of Infanrix hexa and Measles-Mumps-Rubella vaccine to allow any recommendation to be made.

Data on concomitant administration of Infanrix hexa with Prevenar (pneumococcal saccharide conjugated vaccine, adsorbed) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a 3 dose primary vaccination.

However, high incidence of fever (> 39.5°C) was reported in infants receiving Infanrix hexa and Prevenar compared to infants receiving the hexavalent vaccine alone.

Antipyretic treatment should be initiated according to local treatment guidelines.

As with other vaccines, it may be expected that in patients receiving immunosuppressive therapy, an adequate response may not be achieved.

Pregnancy and Lactation

Pregnancy

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during pregnancy is not available.

Lactation

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during lactation is not available.

Ability to perform tasks that require judgement, motor or cognitive skills

Not relevant.

Adverse Reactions

Clinical Trial Data

The safety profile presented below is based on data from more than 16,000 subjects.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with Infanrix hexa with respect to the primary course.

Adverse reactions reported are listed according to the following frequency:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100

Rare: ≥ 1/10000 to < 1/1000
Very rare: < 1/10000

Infections and infestations

Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders

Very common: appetite lost

Psychiatric disorders

Very common: irritability, crying abnormal, restlessness
Common: nervousness

Nervous system disorders

Uncommon: somnolence
Very rare: convulsions (with or without fever)

Respiratory, thoracic and mediastinal disorders

Uncommon: cough*
Rare: bronchitis

Gastrointestinal disorders

Common: vomiting, diarrhoea

Skin and subcutaneous tissue disorders

Common: pruritus*
Rare: rash
Very rare: dermatitis, urticaria*

General disorders and administration site conditions

Very common: pain, redness, local swelling at the injection site (≤ 50 mm), fever ≥ 38°C, fatigue
Common: local swelling at the injection site (> 50 mm)**, fever >39.5°C, injection site reactions, including induration
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint**

Post Marketing Data

Blood and lymphatic system disorders

Lymphadenopathy, thrombocytopenia

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders

Collapse or shock-like state (hypotonic-hyporesponsiveness episode)

Respiratory, thoracic and mediastinal disorders

Apnoea* *[see Warnings and Precautions for apnoea in very premature infants (≤ 28 weeks of gestation)]*

Skin and subcutaneous tissue disorders

Angioneurotic oedema*

General disorders and administration site conditions

Extensive swelling reactions, swelling of the entire injected limb**, vesicles at the injection site

* observed with other GSK DTPa-containing vaccines

** Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

Experience with hepatitis B vaccine:

Meningitis, allergic reactions mimicking serum sickness, paralysis, encephalitis, encephalopathy, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis, muscular weakness have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants < 2 years old. The causal relationship to the vaccine has not been established.

Overdosage

Insufficient data are available.

Clinical Pharmacology

Pharmacodynamics

ATC Code

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA09

Pharmacodynamic Effects

Result obtained in the clinical studies for each of the components are summarised in the tables below:

Percentage of subjects with antibody titres ≥ assay cut-off one month after primary vaccination with Infanrix hexa

Antibody (cut-off)	**Two doses**	**Three doses**			
	3-5 months N= 530 (4 studies)	**2-3-4 months N= 196 (2 studies)**	**2-4-6 months N= 1693 (6 studies)**	**3-4-5 months N= 1055 (6 studies)**	**6-10-14 weeks N= 265 (1 study)**
	%	**%**	**%**	**%**	**%**
Anti-diphtheria (0.1 IU/ml) †	98.0	100.0	99.8	99.7	99.2
Anti-tetanus (0.1 IU/ml) †	100.0	100.0	100.0	100.0	99.6
Anti-PT (5 EL.U/ml)	99.5	100.0	100.0	99.8	99.6
Anti-FHA (5 EL.U/ml)	99.7	100.0	100.0	100.0	100.0
Anti-PRN (5 EL.U/ml)	99.0	100.0	100.0	99.7	98.9
Anti-HBs (10 mIU/ml) †	96.8	99.5	98.9	98.0	98.5*
Anti-Polio type 1 (1/8 dilution) †	99.4	100.0	99.9	99.7	99.6
Anti-Polio type 2 (1/8 dilution) †	96.3	97.8	99.3	98.9	95.7
Anti-Polio type 3 (1/8 dilution) †	98.8	100.0	99.7	99.7	99.6
Anti-PRP (0.15 μg/ml) †	91.7	96.4	96.6	96.8	97.4

N=number of subjects

* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres ≥ 10 mIU/ml

† cut-off accepted as indicative of protection

Percentage of subjects with antibody titres ≥ assay cut-off one month after booster vaccination with Infanrix hexa

Antibody (cut-off)	**Booster vaccination at 11 months of age following a 3-5 month primary course N=532 (3 studies)**	**Booster vaccination during the second year of life following a three dose primary course N= 2009 (12 studies)**
	%	**%**
Anti-diphtheria (0.1 IU/ml) †	100.0	99.9
Anti-tetanus (0.1 IU/ml) †	100.0	99.9
Anti-PT (5 EL.U/ml)	100.0	99.9
Anti-FHA (5 EL.U/ml)	100.0	99.9
Anti-PRN (5 EL.U/ml)	99.2	99.5
Anti-HBs (10 mIU/ml) †	98.9	98.4
Anti-Polio type 1 (1/8 dilution) †	99.8	99.9
Anti-Polio type 2 (1/8 dilution) †	99.4	99.9
Anti-Polio type 3 (1/8 dilution) †	99.2	99.9
Anti-PRP (0.15 μg/ml) †	99.6	99.7

N= Number of subjects
† cut-off accepted as indicative of protection

As the immune response to pertussis antigens following Infanrix hexa administration is equivalent to that of Infanrix, the protective efficacy of the two vaccines is expected to be equivalent.

The protective efficacy of the pertussis component of Infanrix against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated in:

- a prospective blinded household contact study performed in Germany (3, 4, 5 months schedule). Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was 88.7%.

- a NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule). The vaccine efficacy was found to be 84%. In a follow-up of the same cohort, the efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.

Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are highly efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months. However, data indicate that protection against pertussis may be waning at 7-8 years of age.

This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.

Protective immunity against hepatitis B has been shown to persist for at least 3.5 years in more than 90% of children administered four doses of Infanrix hexa. Antibody levels were not different from what was observed in a parallel cohort administered monovalent hepatitis B vaccine.

HBV persistence

Four different clinical studies were performed to assess the percentages of subjects who maintained seroprotective antibody concentration (i.e. anti-HBs ≥ 10mIU/ml) after vaccination with Infanrix hexa. These cohorts had received primary vaccination in a clinical trial setting, according to 2 different vaccination schedules, and were assessed at 3 different ages (4-5, 7-8 and 11-12 years). In three of these studies, subjects received a monovalent hepatitis B vaccine challenge dose to assess the anamnestic response.

Circulating antibodies to hepatitis B wane over time as illustrated by the progressive reduction of subjects maintaining seroprotective antibody concentration. However, one month after a challenge dose, at least 95% of subjects mounted an anamnestic response, demonstrating immune memory in all tested age groups. Results are presented in the table below. Antibody levels were in the same range as those observed in a parallel cohort administered with monovalent hepatitis B vaccine in primary vaccination.

Study number	Age (years)	HBV Seroprotection rate		HBV Anamnestic response	
		N	%	N	%
Schedule 3+1					
DTPa-HBV-IPV-096	4-5	89	91.0	NA	NA
DTPa-HBV-IPV-111	4-5	198	86.4	186	95.7
DTPa-HBV-IPV-110	7-8	193	77.2	186	98.9
Schedule 2+1					
DTPa-HBV-IPV-126	11-12	95	53.7	95	95.8

N = Number of subjects
NA = Not Applicable: These subjects did not receive a challenge dose

Two additional studies in 2 different age groups (4-5 and 7-8 years) assessed the persistence of anti-HBs antibodies in subjects not primed in a clinical study but who received 4 doses of Infanrix hexa during infancy. In these studies, subjects received a monovalent hepatitis B vaccine challenge dose to assess the anamnestic response.

One month after the challenge dose, at least 96% of subjects mounted an anamnestic response demonstrating immune memory in both studies. Results are presented in the following table:

Study number	Age (years)	HBV Seroprotection rate		HBV Anamnestic response	
		N	%	N	%
Schedule 3+1					
DTPa-HBV-IPV-112	4-5	293	85.3	285	96.8
DTPa-HBV-IPV-113	7-8	287	80.5	284	97.2

~~N = Number of subjects~~

~~Hib effectiveness~~

The effectiveness of the Hib component of Infanrix hexa was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a seven year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was Infanrix hexa, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See *Pharmacodynamic Effects*.

NON-CLINICAL INFORMATION

Preclinical data reveal no special hazard for humans based on conventional studies of safety, specific toxicity, repeated dose toxicity and compatibility of ingredients.

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date of the vaccine is indicated on the label and packaging. The expiry date refers to the last day of the month mentioned.

The shelf-life is 3 years.

Storage

Infanrix hexa should be stored at +2°C to +8°C. ~~**Protect from light.**~~

~~**During transport, recommended conditions of storage must be respected.**~~

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Protect from light.

During transport, recommended conditions of storage must be respected.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Nature and Contents of Container

The DTPa-HBV-IPV component is presented in a pre-filled syringe or vial.

The Hib component is presented as a white pellet in a glass vial.

The vials and pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Vial and pre-filled syringe presentations (with or without needles) are available in packs of 1, 10, 20 and 50.
Vial and vial presentation is available in pack sizes of 1 and 50.

Incompatibilities

Infanrix hexa should not be mixed with other vaccines in the same syringe.

Use and Handling

1. Wording for vial and pre-filled syringe presentation

The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension. ~~**The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension.**~~ The DTPa-HBV-IPV suspension and the Hib powder should be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

-Infanrix hexa must be reconstituted by adding the entire content of the pre-filled syringe to the vial containing the Hib powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room temperature (25 ± 3 °C) for at least five minutes before connecting the pre-filled syringe and reconstituting the vaccine. ~~**It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room temperature (25 ± 3 °C) for at least five minutes before connecting the pre-filled syringe and reconstituting the vaccine.**~~

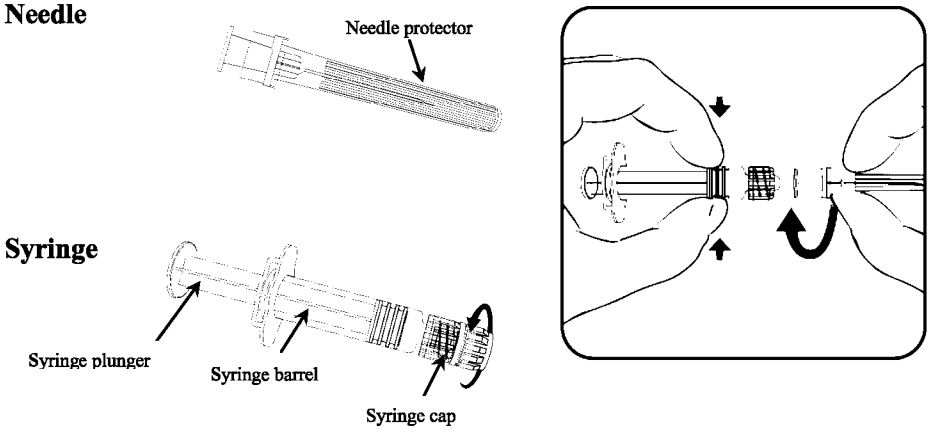
The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is ***a*** normal ***observation*** ~~**and does not impair the performance of the vaccine**~~. ~~**The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine.**~~

~~**In the event of other variation being observed, discard the vaccine.**~~***The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.***

After reconstitution, the vaccine should be injected immediately. ***However the vaccine may be kept for up to 8 hours at room temperature (21°C).*** ~~**However the vaccine may be kept for up to 8 hours at room temperature (21°C).**~~

Withdraw the entire contents of the vial.

- ***Specific instructions for the pre-filled syringe with a luer lock adaptor (PRTC)***



1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

2. Wording for vial and vial presentation

~~**Upon storage, a white deposit and clear supernatant may be observed in the vial containing the DTPa-HBV-IPV suspension. This does not constitute a sign of deterioration.**~~

Infanrix hexa must be reconstituted by adding the entire content of the vial containing the DTPa-HBV-IPV suspension to the vial containing the Hib powder. ***To do so, draw up the suspension with a syringe and add the suspension to the powder.*** ~~**To do so, draw up the suspension with a syringe and add the suspension to the powder.**~~ The mixture should be well shaken until the powder is completely dissolved in the suspension.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine. ~~**The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine.**~~

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

A new needle should be used to administer the vaccine. ~~**A new needle should be used to administer the vaccine.**~~

After reconstitution, the vaccine should be used immediately.

Withdraw the entire contents of the vial.

Any unused product or waste material should be disposed of in accordance with local requirements. ~~**Any unused product or waste material should be disposed of in accordance with local requirements.**~~

APPENDIX 1D : REFERENCE INFORMATION REFLECTING CHANGES DURING THE REPORTING PERIOD (GPI VERSION 013 DATED 26 AUGUST 2013)

GLOBAL PRESCRIBER INFORMATION

TITLE

Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine.

SCOPE

Trade Name(s)

Infanrix hexa

Formulation and Strength

Powder and suspension for suspension for injection.

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International Units (IU)
Tetanus toxoid[1]	not less than 40 International Units (IU)
Bordetella pertussis antigens	
Pertussis toxoid[1]	25 micrograms
Filamentous Haemagglutinin[1]	25 micrograms
Pertactin[1]	8 micrograms
Hepatitis B surface antigen[2,3]	10 micrograms
Poliovirus (inactivated)	
type 1 (Mahoney strain)[4]	40 D-antigen unit
type 2 (MEF-1 strain)[4]	8 D-antigen unit
type 3 (Saukett strain)[4]	32 D-antigen unit
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate)[3] conjugated to tetanus toxoid as carrier protein	10 micrograms approximately 25 micrograms

[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 milligrams Al^{3+}
[2]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[3]adsorbed on aluminium phosphate ($AlPO_4$) 0.32 milligrams Al^{3+}
[4]propagated in VERO cells

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed. This is a normal observation.

The Hib component is presented as a white powder.

Excipients

It is mandatory for country product information to include both the complete list of excipients for all locally marketed presentations, and any locally imposed excipient warning statements.

Lactose

Sodium chloride (NaCl)

Medium 199 (as stabilizer including amino acids, mineral salts and vitamins)

Water for injections

Residues

Potassium chloride

Disodium phosphate

Monopotassium phosphate

Polysorbate 20 and 80

Glycine

Formaldehyde

Neomycin sulphate

Polymyxin B sulphate

CLINICAL INFORMATION

Indications

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b.

Dosage and Administration

Posology

- **Primary vaccination**

The primary vaccination schedule consists of three doses of 0.5 ml (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) or two doses (e.g. 3, 5 months). There should be an interval of at least 1 month between doses. The Expanded Program on Immunisation schedule (at 6, 10, 14 weeks of age) may only be used if a dose of hepatitis B vaccine has been given at birth.

Locally established immunoprophylactic measures against hepatitis B should be maintained. Where a dose of hepatitis B vaccine is given at birth, Infanrix hexa can be used as a replacement for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

- **Booster vaccination**

After a vaccination with 2 doses (e.g. 3, 5 months) of Infanrix hexa a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age.

After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) of Infanrix hexa a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

Booster doses should be given in accordance with the official recommendations.

Infanrix hexa can be considered for the booster if the composition is in accordance with the official recommendations.

Other combinations of antigens have been studied in clinical trials following primary vaccination with Infanrix hexa and may be used for a booster dose: diphtheria, tetanus, acellular pertussis (DTPa), diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b (DTPa+Hib), diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-IPV+Hib) and diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-HBV-IPV+Hib).

Method of administration

Infanrix hexa is for deep intramuscular injection.

Contraindications

Hypersensitivity to the active substances or to any of the excipients or residues (see *Formulation and Strength*, *Excipients* and *Residues*).

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

Infanrix hexa is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

Warnings and Precautions

As with other vaccines, administration of Infanrix hexa should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:

- Temperature of ≥ 40.0°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic-hyporesponsiveness episode) within 48 hours of vaccination.

- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Infanrix hexa should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Infanrix hexa should under no circumstances be administered intravascularly or intradermally.

Infanrix hexa contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Infanrix hexa will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

A protective immune response may not be elicited in all vaccinees (see *Pharmacodynamic Effects*).

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of Infanrix hexa. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the Hib capsular polysaccharide antigen is excreted in the urine a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Limited data in 169 premature infants indicate that Infanrix hexa can be given to premature children. However, a lower immune response may be observed and the level of clinical protection remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of

respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Interactions

There are insufficient data with regard to the efficacy and safety of simultaneous administration of Infanrix hexa and Measles-Mumps-Rubella vaccine to allow any recommendation to be made.

Data on concomitant administration of Infanrix hexa with Prevenar (pneumococcal saccharide conjugated vaccine, adsorbed) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a 3 dose primary vaccination.

However, high incidence of fever (> 39.5°C) was reported in infants receiving Infanrix hexa and Prevenar compared to infants receiving the hexavalent vaccine alone.

Antipyretic treatment should be initiated according to local treatment guidelines.

As with other vaccines, it may be expected that in patients receiving immunosuppressive therapy, an adequate response may not be achieved.

Pregnancy and Lactation

Pregnancy

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during pregnancy is not available.

Lactation

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during lactation is not available.

Ability to perform tasks that require judgement, motor or cognitive skills

Not relevant.

Adverse Reactions

Clinical Trial Data

The safety profile presented below is based on data from more than 16,000 subjects.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with Infanrix hexa with respect to the primary course.

Adverse reactions reported are listed according to the following frequency:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100

Rare: ≥ 1/10000 to < 1/1000
Very rare: < 1/10000

Infections and infestations

Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders

Very common: appetite lost

Psychiatric disorders

Very common: irritability, crying abnormal, restlessness
Common: nervousness

Nervous system disorders

Uncommon: somnolence
Very rare: convulsions (with or without fever)

Respiratory, thoracic and mediastinal disorders

Uncommon: cough*
Rare: bronchitis

Gastrointestinal disorders

Common: vomiting, diarrhoea

Skin and subcutaneous tissue disorders

Common: pruritus*
Rare: rash
Very rare: dermatitis, urticaria*

General disorders and administration site conditions

Very common: pain, redness, local swelling at the injection site (≤ 50 mm), fever ≥ 38°C, fatigue
Common: local swelling at the injection site (> 50 mm)**, fever >39.5°C, injection site reactions, including induration
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint**

Post Marketing Data

Blood and lymphatic system disorders

Lymphadenopathy, thrombocytopenia

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders

Collapse or shock-like state (hypotonic-hyporesponsiveness episode)

Respiratory, thoracic and mediastinal disorders

Apnoea* *[see Warnings and Precautions for apnoea in very premature infants (≤ 28 weeks of gestation)]*

Skin and subcutaneous tissue disorders

Angioneurotic oedema*

General disorders and administration site conditions

Extensive swelling reactions, swelling of the entire injected limb**, vesicles at the injection site

* observed with other GSK DTPa-containing vaccines

** Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

Experience with hepatitis B vaccine:

Meningitis, allergic reactions mimicking serum sickness, paralysis, encephalitis, encephalopathy, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis, muscular weakness have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants < 2 years old. The causal relationship to the vaccine has not been established.

Overdosage

Insufficient data are available.

Clinical Pharmacology

Pharmacodynamics

ATC Code

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA09

Pharmacodynamic Effects

Immunogenicity

Result obtained in the clinical studies for each of the components are summarised in the tables below:

Percentage of subjects with antibody titres ≥ assay cut-off one month after primary vaccination with Infanrix hexa

Antibody (cut-off)	**Two doses**	**Three doses**			
	3-5 months N= 530 (4 studies)	**2-3-4 months N= 196 (2 studies)**	**2-4-6 months N= 1693 (6 studies)**	**3-4-5 months N= 1055 (6 studies)**	**6-10-14 weeks N= 265 (1 study)**
	%	**%**	**%**	**%**	**%**
Anti-diphtheria (0.1 IU/ml) †	98.0	100.0	99.8	99.7	99.2
Anti-tetanus (0.1 IU/ml) †	100.0	100.0	100.0	100.0	99.6
Anti-PT (5 EL.U/ml)	99.5	100.0	100.0	99.8	99.6
Anti-FHA (5 EL.U/ml)	99.7	100.0	100.0	100.0	100.0
Anti-PRN (5 EL.U/ml)	99.0	100.0	100.0	99.7	98.9
Anti-HBs (10 mIU/ml) †	96.8	99.5	98.9	98.0	98.5*
Anti-Polio type 1 (1/8 dilution) †	99.4	100.0	99.9	99.7	99.6
Anti-Polio type 2 (1/8 dilution) †	96.3	97.8	99.3	98.9	95.7
Anti-Polio type 3 (1/8 dilution) †	98.8	100.0	99.7	99.7	99.6
Anti-PRP (0.15 μg/ml) †	91.7	96.4	96.6	96.8	97.4

N=number of subjects

* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres ≥ 10 mIU/ml

† cut-off accepted as indicative of protection

Percentage of subjects with antibody titres ≥ assay cut-off one month after booster vaccination with Infanrix hexa

Antibody (cut-off)	**Booster vaccination at 11 months of age following a 3-5 month primary course N=532 (3 studies)**	**Booster vaccination during the second year of life following a three dose primary course N= 2009 (12 studies)**
	%	**%**
Anti-diphtheria (0.1 IU/ml) †	100.0	99.9
Anti-tetanus (0.1 IU/ml) †	100.0	99.9
Anti-PT (5 EL.U/ml)	100.0	99.9
Anti-FHA (5 EL.U/ml)	100.0	99.9
Anti-PRN (5 EL.U/ml)	99.2	99.5
Anti-HBs (10 mIU/ml) †	98.9	98.4
Anti-Polio type 1 (1/8 dilution) †	99.8	99.9
Anti-Polio type 2 (1/8 dilution) †	99.4	99.9
Anti-Polio type 3 (1/8 dilution) †	99.2	99.9
Anti-PRP (0.15 μg/ml) †	99.6	99.7

N= Number of subjects
† cut-off accepted as indicative of protection

As the immune response to pertussis antigens following Infanrix hexa administration is equivalent to that of Infanrix, the protective efficacy of the two vaccines is expected to be equivalent.

Efficacy in protecting against pertussis

The protective efficacy of the pertussis component of Infanrix against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated ***after 3-dose primary immunisation in the studies tabulated belowin***:

Study	***Country***	***Schedule***	***Vaccine efficacy***	***Considerations***
Household contact study (prospective blinded)	***Germany***	***3,4,5 months***	***88.7%***	***Based on data collected from secondary contacts in households where there was an index case with typical pertussis***
Efficacy study (NIH sponsored)	***Italy***	***2,4,6 months***	***84%***	***In a follow-up of the same cohort, the efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose***

				of pertussis.

~~– a prospective blinded household contact study performed in Germany (3, 4, 5 months schedule). Based on data collected from secondary contacts in households where there was an index case with typical pertussis, the protective efficacy of the vaccine was 88.7%.~~

~~– a NIH sponsored efficacy study performed in Italy (2, 4, 6 months schedule). The vaccine efficacy was found to be 84%. In a follow-up of the same cohort, the efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.~~

~~Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are highly efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months. However, data indicate that protection against pertussis may be waning at 7-8 years of age. This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.~~

Persistence of the immune response

Protective immunity against hepatitis B has been shown to persist for at least 3.5 years in more than 90% of children administered four doses of Infanrix hexa. Antibody levels were not different from what was observed in a parallel cohort administered monovalent hepatitis B vaccine.

Post marketing experience

Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months. However, data indicate that protection against pertussis may be waning at 7-8 years of age. This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.

The effectiveness of the Hib component of Infanrix hexa was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a seven year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was Infanrix hexa, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

Infanrix hexa has been the only Hib vaccine available in Italy since 2006. The vaccine is administered at 3, 5 and 11 months of age and coverage has exceeded 95%. Hib disease has continued to be well controlled, with no more than three confirmed Hib cases reported annually between 2006 and 2011 in Italian children aged less than 5 years.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See *Pharmacodynamic Effects*.

NON-CLINICAL INFORMATION

Preclinical data reveal no special hazard for humans based on conventional studies of safety, specific toxicity, repeated dose toxicity and compatibility of ingredients.

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date of the vaccine is indicated on the label and packaging. The expiry date refers to the last day of the month mentioned.

The shelf-life is 3 years.

Storage

Infanrix hexa should be stored at +2°C to +8°C.

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Protect from light.

During transport, recommended conditions of storage must be respected.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Nature and Contents of Container

The DTPa-HBV-IPV component is presented in a pre-filled syringe or vial.

The Hib component is presented as a white pellet in a glass vial.

The vials and pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Vial and pre-filled syringe presentations (with or without needles) are available in packs of 1, 10, 20 and 50.
Vial and vial presentation is available in pack sizes of 1 and 50.

Incompatibilities

Infanrix hexa should not be mixed with other vaccines in the same syringe.

Use and Handling

1. Wording for vial and pre-filled syringe presentation

The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The DTPa-HBV-IPV suspension and the Hib powder should be

inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

Infanrix hexa must be reconstituted by adding the entire content of the pre-filled syringe to the vial containing the Hib powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room temperature (25 ± 3 °C) for at least five minutes before connecting the pre-filled syringe and reconstituting the vaccine.

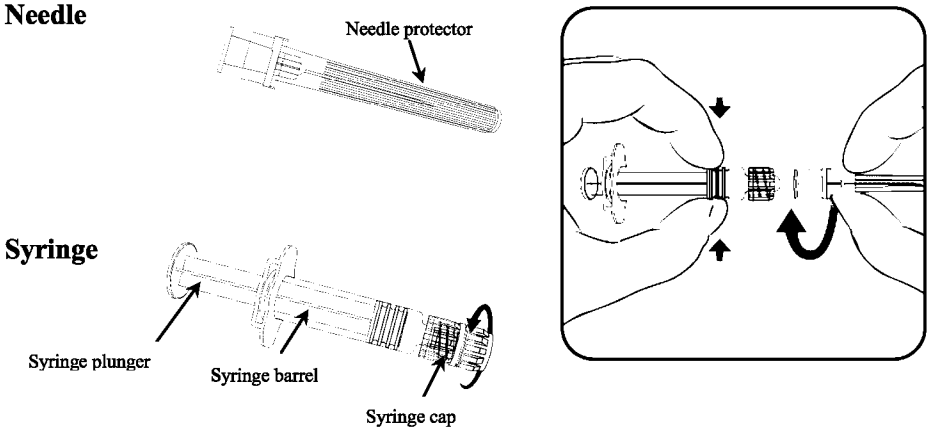
The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be injected immediately. However the vaccine may be kept for up to 8 hours at room temperature (21°C).

Withdraw the entire contents of the vial.

- ***Specific instructions for the pre-filled syringe with a luer lock adaptor (PRTC)***



1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

2. Wording for vial and vial presentation

Infanrix hexa must be reconstituted by adding the entire content of the vial containing the DTPa-HBV-IPV suspension to the vial containing the Hib powder. To do so, draw up the suspension with a syringe and add the suspension to the powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

A new needle should be used to administer the vaccine.

After reconstitution, the vaccine should be used immediately.

Withdraw the entire contents of the vial.

Any unused product or waste material should be disposed of in accordance with local requirements.

APPENDIX 1E : REFERENCE INFORMATION REFLECTING CHANGES DURING THE REPORTING PERIOD (GPI VERSION 014 DATED 13 MARCH 2014)

GLOBAL PRESCRIBER INFORMATION

TITLE

Combined diphtheria-tetanus-acellular pertussis, hepatitis B, enhanced inactivated polio vaccine and *Haemophilus influenzae* type b vaccine.

SCOPE

Trade Name(s)

Infanrix hexa

Formulation and Strength

Powder and suspension for suspension for injection.

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International Units (IU)
Tetanus toxoid[1]	not less than 40 International Units (IU)
Bordetella pertussis antigens	
Pertussis toxoid[1]	25 micrograms
Filamentous Haemagglutinin[1]	25 micrograms
Pertactin[1]	8 micrograms
Hepatitis B surface antigen[2,3]	10 micrograms
Poliovirus (inactivated)	
type 1 (Mahoney strain)[4]	40 D-antigen unit
type 2 (MEF-1 strain)[4]	8 D-antigen unit
type 3 (Saukett strain)[4]	32 D-antigen unit
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate)[3] conjugated to tetanus toxoid as carrier protein	10 micrograms approximately 25 micrograms

[1]adsorbed on aluminium hydroxide, hydrated ($Al(OH)_3$) 0.5 milligrams Al^{3+}
[2]produced in yeast cells (*Saccharomyces cerevisiae*) by recombinant DNA technology
[3]adsorbed on aluminium phosphate ($AlPO_4$) 0.32 milligrams Al^{3+}
[4]propagated in VERO cells

The DTPa-HBV-IPV component is presented as a turbid white suspension. Upon storage, a white deposit and clear supernatant can be observed. This is a normal observation.

The Hib component is presented as a white powder.

Excipients

It is mandatory for country product information to include both the complete list of excipients for all locally marketed presentations, and any locally imposed excipient warning statements.

Lactose

Sodium chloride (NaCl)

Medium 199 (as stabilizer including amino acids, mineral salts and vitamins)

Water for injections

Residues

Potassium chloride

Disodium phosphate

Monopotassium phosphate

Polysorbate 20 and 80

Glycine

Formaldehyde

Neomycin sulphate

Polymyxin B sulphate

CLINICAL INFORMATION

Indications

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b.

Dosage and Administration

Posology

- **Primary vaccination**

The primary vaccination schedule consists of three doses of 0.5 ml (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) or two doses (e.g. 3, 5 months). There should be an interval of at least 1 month between doses. The Expanded Program on Immunisation schedule (at 6, 10, 14 weeks of age) may only be used if a dose of hepatitis B vaccine has been given at birth.

Locally established immunoprophylactic measures against hepatitis B should be maintained. Where a dose of hepatitis B vaccine is given at birth, Infanrix hexa can be used as a replacement for supplementary doses of hepatitis B vaccine from the age of 6 weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

- **Booster vaccination**

After a vaccination with 2 doses (e.g. 3, 5 months) of Infanrix hexa a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age.

After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) of Infanrix hexa a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

Booster doses should be given in accordance with the official recommendations.

Infanrix hexa can be considered for the booster if the composition is in accordance with the official recommendations.

Other combinations of antigens have been studied in clinical trials following primary vaccination with Infanrix hexa and may be used for a booster dose: diphtheria, tetanus, acellular pertussis (DTPa), diphtheria, tetanus, acellular pertussis, *Haemophilus influenzae* type b (DTPa+Hib), diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-IPV+Hib) and diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis, *Haemophilus influenzae* type b (DTPa-HBV-IPV+Hib).

Method of administration

Infanrix hexa is for deep intramuscular injection.

Contraindications

Hypersensitivity to the active substances or to any of the excipients or residues (see *Formulation and Strength*, *Excipients* and *Residues*).

Hypersensitivity after previous administration of diphtheria, tetanus, pertussis, hepatitis B, polio or Hib vaccines.

Infanrix hexa is contraindicated if the child has experienced an encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine. In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria-tetanus, hepatitis B, inactivated polio and Hib vaccines.

Warnings and Precautions

As with other vaccines, administration of Infanrix hexa should be postponed in subjects suffering from acute severe febrile illness. The presence of a minor infection is not a contra-indication.

Vaccination should be preceded by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccines should be carefully considered:

- Temperature of ≥ 40.0°C within 48 hours, not due to another identifiable cause.
- Collapse or shock-like state (hypotonic -hyporesponsive~~ness~~ episode) within 48 hours of vaccination.

- Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination.
- Convulsions with or without fever, occurring within 3 days of vaccination.

There may be circumstances, such as a high incidence of pertussis, when the potential benefits outweigh possible risks.

In children with progressive neurological disorders, including infantile spasms, uncontrolled epilepsy or progressive encephalopathy, it is better to defer pertussis (Pa or Pw) immunization until the condition is corrected or stable. However, the decision to give pertussis vaccine must be made on an individual basis after careful consideration of the risks and benefits.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event following the administration of the vaccine.

Infanrix hexa should be administered with caution to subjects with thrombocytopenia or a bleeding disorder since bleeding may occur following an intramuscular administration to these subjects.

Infanrix hexa should under no circumstances be administered intravascularly or intradermally.

Infanrix hexa contains traces of neomycin and polymyxin. The vaccine should be used with caution in patients with known hypersensitivity to one of these antibiotics.

Infanrix hexa will not prevent disease caused by pathogens other than *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, hepatitis B virus, poliovirus or *Haemophilus influenzae* type b. However, it can be expected that hepatitis D will be prevented by immunisation as hepatitis D (caused by the delta agent) does not occur in the absence of hepatitis B infection.

A protective immune response may not be elicited in all vaccinees (see *Pharmacodynamic Effects*).

A history of febrile convulsions, a family history of convulsions or Sudden Infant Death Syndrome (SIDS) do not constitute contraindications for the use of Infanrix hexa. Vaccinees with a history of febrile convulsions should be closely followed up as such adverse events may occur within 2 to 3 days post vaccination.

Human Immunodeficiency Virus (HIV) infection is not considered as a contra-indication. The expected immunological response may not be obtained after vaccination of immunosuppressed patients.

Since the Hib capsular polysaccharide antigen is excreted in the urine a positive urine test can be observed within 1-2 weeks following vaccination. Other tests should be performed in order to confirm Hib infection during this period.

Limited data in 169 premature infants indicate that Infanrix hexa can be given to premature children. However, a lower immune response may be observed and the level of clinical protection remains unknown.

The potential risk of apnoea and the need for respiratory monitoring for 48-72h should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of

respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

High incidence of fever (> 39.5°C) was reported in infants receiving Infanrix hexa and Prevenar compared to infants receiving the hexavalent vaccine alone.

Increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) were observed with concomitant administration of Infanrix hexa and Prevenar 13 (see Adverse Reactions).

Antipyretic treatment should be initiated according to local treatment guidelines.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. It is important that procedures are in place to avoid injury from faints.

Interactions

There are insufficient data with regard to the efficacy and safety of simultaneous administration of Infanrix hexa and Measles-Mumps-Rubella vaccine to allow any recommendation to be made.

Data on concomitant administration of Infanrix hexa with Prevenar (pneumococcal saccharide conjugated vaccine, adsorbed) have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a 3 dose primary vaccination. However, high incidence of fever (> 39.5°C) was reported in infants receiving Infanrix hexa and Prevenar compared to infants receiving the hexavalent vaccine alone. ***(see Warnings and Precautions for guidance on Prevenar and Prevenar 13).***

~~**Antipyretic treatment should be initiated according to local treatment guidelines.**~~

As with other vaccines, it may be expected that in patients receiving immunosuppressive therapy, an adequate response may not be achieved.

Pregnancy and Lactation

Pregnancy

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during pregnancy is not available.

Lactation

As Infanrix hexa is not intended for use in adults, information on the safety of the vaccine when used during lactation is not available.

Ability to perform tasks that require judgement, motor or cognitive skills

Not relevant.

Adverse Reactions

Clinical Trial Data

The safety profile presented below is based on data from more than 16,000 subjects.

As has been observed for DTPa and DTPa-containing combinations, an increase in local reactogenicity and fever was reported after booster vaccination with Infanrix hexa with respect to the primary course.

Adverse reactions reported are listed according to the following frequency:

Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100
Rare: ≥ 1/10000 to < 1/1000
Very rare: < 1/10000

Infections and infestations

Uncommon: upper respiratory tract infection

Metabolism and nutrition disorders

Very common: appetite lost

Psychiatric disorders

Very common: irritability, crying abnormal, restlessness
Common: nervousness

Nervous system disorders

Uncommon: somnolence
Very rare: convulsions (with or without fever)***

Respiratory, thoracic and mediastinal disorders

Uncommon: cough*
Rare: bronchitis

Gastrointestinal disorders

Common: vomiting, diarrhoea

Skin and subcutaneous tissue disorders

Common: pruritus*
Rare: rash
Very rare: dermatitis, urticaria*

General disorders and administration site conditions

Very common: pain, redness, local swelling at the injection site (≤ 50 mm), fever ≥ 38°C, fatigue
Common: local swelling at the injection site (> 50 mm)**, fever >39.5°C, injection site reactions, including induration
Uncommon: diffuse swelling of the injected limb, sometimes involving the adjacent joint**

Post Marketing Data

Blood and lymphatic system disorders

Lymphadenopathy, thrombocytopenia

Immune system disorders

Allergic reactions (including anaphylactic and anaphylactoid reactions)

Nervous system disorders

Collapse or shock-like state (hypotonic -hyporesponsiveness episode)***

Respiratory, thoracic and mediastinal disorders

Apnoea* *[see Warnings and Precautions for apnoea in very premature infants (≤ 28 weeks of gestation)]*

Skin and subcutaneous tissue disorders

Angioneurotic oedema*

General disorders and administration site conditions

Extensive swelling reactions, swelling of the entire injected limb**, vesicles at the injection site

* observed with other GSK DTPa-containing vaccines

** Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

****** Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of Infanrix hexa with Prevenar 13 to those which reported use of Infanrix hexa alone.***

Experience with hepatitis B vaccine:

Meningitis, allergic reactions mimicking serum sickness, paralysis, encephalitis, encephalopathy, neuropathy, neuritis, hypotension, vasculitis, lichen planus, erythema multiforme, arthritis, muscular weakness have been reported during post-marketing surveillance following GlaxoSmithKline Biologicals' hepatitis B vaccine in infants < 2 years old. The causal relationship to the vaccine has not been established.

Overdosage

Insufficient data are available.

Clinical Pharmacology

Pharmacodynamics

ATC Code

Pharmaco-therapeutic group: Bacterial and viral vaccines combined, ATC code J07CA09

Pharmacodynamic Effects

Immunogenicity

Result obtained in the clinical studies for each of the components are summarised in the tables below:

Percentage of subjects with antibody titres ≥ assay cut-off one month after primary vaccination with Infanrix hexa

Antibody (cut-off)	**Two doses**	**Three doses**			
	3-5 months N= 530 (4 studies)	**2-3-4 months N= 196 (2 studies)**	**2-4-6 months N= 1693 (6 studies)**	**3-4-5 months N= 1055 (6 studies)**	**6-10-14 weeks N= 265 (1 study)**
	%	**%**	**%**	**%**	**%**
Anti-diphtheria (0.1 IU/ml) †	98.0	100.0	99.8	99.7	99.2
Anti-tetanus (0.1 IU/ml) †	100.0	100.0	100.0	100.0	99.6
Anti-PT (5 EL.U/ml)	99.5	100.0	100.0	99.8	99.6
Anti-FHA (5 EL.U/ml)	99.7	100.0	100.0	100.0	100.0
Anti-PRN (5 EL.U/ml)	99.0	100.0	100.0	99.7	98.9
Anti-HBs (10 mIU/ml) †	96.8	99.5	98.9	98.0	98.5*
Anti-Polio type 1 (1/8 dilution) †	99.4	100.0	99.9	99.7	99.6
Anti-Polio type 2 (1/8 dilution) †	96.3	97.8	99.3	98.9	95.7
Anti-Polio type 3 (1/8 dilution) †	98.8	100.0	99.7	99.7	99.6
Anti-PRP (0.15 μg/ml) †	91.7	96.4	96.6	96.8	97.4

N=number of subjects

* in a subgroup of infants not administered hepatitis B vaccine at birth, 77.7% of subjects had anti-HBs titres ≥ 10 mIU/ml

† cut-off accepted as indicative of protection

Percentage of subjects with antibody titres ≥ assay cut-off one month after booster vaccination with Infanrix hexa

Antibody (cut-off)	**Booster vaccination at 11 months of age following a 3-5 month primary course N=532 (3 studies)**	**Booster vaccination during the second year of life following a three dose primary course N= 2009 (12 studies)**
	%	**%**
Anti-diphtheria (0.1 IU/ml) †	100.0	99.9
Anti-tetanus (0.1 IU/ml) †	100.0	99.9
Anti-PT (5 EL.U/ml)	100.0	99.9
Anti-FHA (5 EL.U/ml)	100.0	99.9
Anti-PRN (5 EL.U/ml)	99.2	99.5
Anti-HBs (10 mIU/ml) †	98.9	98.4
Anti-Polio type 1 (1/8 dilution) †	99.8	99.9
Anti-Polio type 2 (1/8 dilution) †	99.4	99.9
Anti-Polio type 3 (1/8 dilution) †	99.2	99.9
Anti-PRP (0.15 μg/ml) †	99.6	99.7

N= Number of subjects
† cut-off accepted as indicative of protection

As the immune response to pertussis antigens following Infanrix hexa administration is equivalent to that of Infanrix, the protective efficacy of the two vaccines is expected to be equivalent.

Efficacy in protecting against pertussis

The protective efficacy of the pertussis component of Infanrix against WHO-defined typical pertussis (≥ 21 days of paroxysmal cough) was demonstrated after 3-dose primary immunisation in the studies tabulated below:

Study	**Country**	**Schedule**	**Vaccine efficacy**	**Considerations**
Household contact study	Germany	3,4,5 months	88.7%	Based on data collected from secondary contacts in households where there was

(prospective blinded)				an index case with typical pertussis
Efficacy study (NIH sponsored)	Italy	2,4,6 months	84%	In a follow-up of the same cohort, the efficacy was confirmed up to 60 months after completion of primary vaccination without administration of a booster dose of pertussis.

Persistence of the immune response

Protective immunity against hepatitis B has been shown to persist for at least 3.5 years in more than 90% of children administered four doses of Infanrix hexa. Antibody levels were not different from what was observed in a parallel cohort administered monovalent hepatitis B vaccine.

Post marketing experience

Results of long term follow-up in Sweden demonstrate that acellular pertussis vaccines are efficacious in infants when administered according to the 3 and 5 months primary vaccination schedule, with a booster dose administered at approximately 12 months. However, data indicate that protection against pertussis may be waning at 7-8 years of age. This suggests that a second booster dose of pertussis vaccine is warranted in children aged 5-7 years who have previously been vaccinated following this schedule.

The effectiveness of the Hib component of Infanrix hexa was investigated via an extensive post-marketing surveillance study conducted in Germany. Over a seven year follow-up period, the effectiveness of the Hib components of two hexavalent vaccines, of which one was Infanrix hexa, was 89.6% for a full primary series and 100% for a full primary series plus booster dose (irrespective of the Hib vaccine used for priming).

Infanrix hexa has been the only Hib vaccine available in Italy since 2006. The vaccine is administered at 3, 5 and 11 months of age and coverage has exceeded 95%. Hib disease has continued to be well controlled, with no more than three confirmed Hib cases reported annually between 2006 and 2011 in Italian children aged less than 5 years.

Pharmacokinetics

Evaluation of pharmacokinetic properties is not required for vaccines.

Clinical Studies

See *Pharmacodynamic Effects*.

NON-CLINICAL INFORMATION

Preclinical data reveal no special hazard for humans based on conventional studies of safety, specific toxicity, repeated dose toxicity and compatibility of ingredients.

PHARMACEUTICAL INFORMATION

Shelf-Life

The expiry date of the vaccine is indicated on the label and packaging. The expiry date refers to the last day of the month mentioned.

The shelf-life is 3 years.

Storage

Infanrix hexa should be stored at +2°C to +8°C.

The DTPa-HBV-IPV suspension and the reconstituted vaccine must not be frozen. Discard if it has been frozen.

Protect from light.

During transport, recommended conditions of storage must be respected.

Stability data indicate that the vaccine components are stable at temperatures up to 25°C for 72 hours. These data are intended to guide healthcare professionals in case of temporary temperature excursion only.

Nature and Contents of Container

The DTPa-HBV-IPV component is presented in a pre-filled syringe or vial.

The Hib component is presented as a white pellet in a glass vial.

The vials and pre-filled syringes are made of neutral glass type I, which conforms to European Pharmacopoeia Requirements.

Vial and pre-filled syringe presentations (with or without needles) are available in packs of 1, 10, 20 and 50.
Vial and vial presentation is available in pack sizes of 1 and 50.

Incompatibilities

Infanrix hexa should not be mixed with other vaccines in the same syringe.

Use and Handling

1. Wording for vial and pre-filled syringe presentation

The DTPa-HBV-IPV suspension should be well shaken in order to obtain a homogeneous turbid white suspension. The DTPa-HBV-IPV suspension and the Hib powder should be inspected visually for any foreign particulate matter and/or variation of physical aspect. In the event of either being observed, discard the vaccine.

Infanrix hexa must be reconstituted by adding the entire content of the pre-filled syringe to the vial containing the Hib powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

It is good clinical practice to only inject a vaccine when it has reached room temperature. In addition, a vial at room temperature ensures sufficient elasticity of the rubber closure to minimise any coring of rubber particles. To achieve this, the vial should be kept at room

temperature (25 ± 3 °C) for at least five minutes before connecting the pre-filled syringe and reconstituting the vaccine.

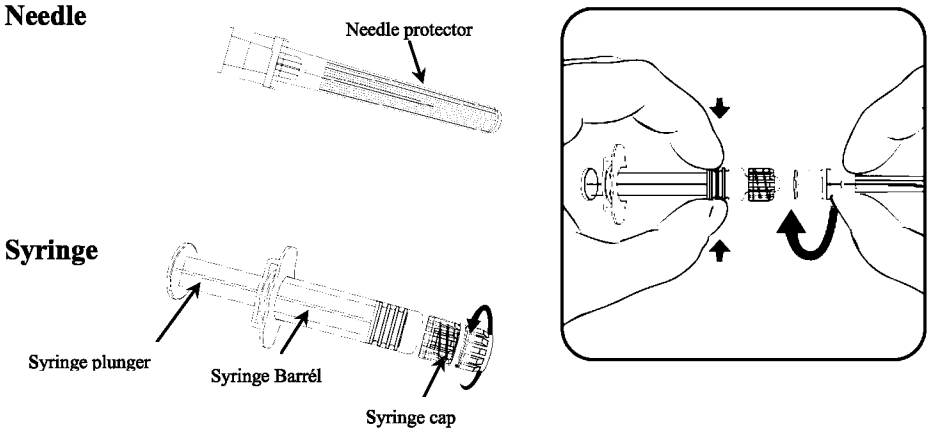
The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is a normal observation.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

After reconstitution, the vaccine should be injected immediately. However the vaccine may be kept for up to 8 hours at room temperature (21°C).

Withdraw the entire contents of the vial.

- ***Specific instructions for the pre-filled syringe with a luer lock adaptor (PRTC)***



1. Holding the syringe **Barrél** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock (see picture).
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

2. Wording for vial and vial presentation

Infanrix hexa must be reconstituted by adding the entire content of the vial containing the DTPa-HBV-IPV suspension to the vial containing the Hib powder. To do so, draw up the

suspension with a syringe and add the suspension to the powder. The mixture should be well shaken until the powder is completely dissolved in the suspension.

The reconstituted vaccine presents as a slightly more cloudy suspension than the liquid component alone. This is normal and does not impair the performance of the vaccine.

The reconstituted vaccine should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vaccine.

A new needle should be used to administer the vaccine.

After reconstitution, the vaccine should be used immediately.

Withdraw the entire contents of the vial.

Any unused product or waste material should be disposed of in accordance with local requirements.

APPENDIX 2A : CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS FROM CLINICAL TRIALS

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Infections and infestations						
Abdominal wall abscess	1	0	1	0	0	0
Abscess	16	0	11	0	0	0
Abscess limb	11	0	16	0	0	0
Abscess neck	5	0	9	0	0	0
Abscess of eyelid	1	0	1	0	0	0
Acarodermatitis	4	0	1	0	0	0
Acquired immunodeficiency syndrome	1	0	0	0	0	0
Acute sinusitis	2	0	3	0	0	0
Acute tonsillitis	8	0	2	0	0	0
Adenoiditis	2	0	4	0	0	0
Adenoviral hepatitis	1	0	0	0	0	0
Adenovirus infection	4	0	2	0	0	0
Amoebiasis	1	0	2	0	0	0
Amoebic dysentery	0	0	3	0	0	0
Anal abscess	6	0	5	0	0	0
Appendicitis	4	0	3	0	0	0
Appendicitis perforated	1	0	0	0	0	0
Arthritis bacterial	3	0	2	0	0	0

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Ascariasis	0	0	1	0	0	0
Atypical pneumonia	15	0	15	0	0	0
Bacteraemia	9	0	6	0	0	0
Bacterial diarrhoea	2	0	2	0	0	0
Bacterial infection	4	2	3	0	0	0
Bacterial pyelonephritis	2	0	0	0	0	0
Bacteriuria	2	0	0	0	0	0
Beta haemolytic streptococcal infection	0	0	1	0	0	0
Botulism	0	0	1	0	0	0
Breast abscess	1	0	1	0	0	0
Bronchiolitis	675	0	585	0	0	0
Bronchitis	499	7	227	2	0	0
Bronchitis viral	1	0	0	0	0	0
Bronchopneumonia	227	2	130	0	0	0
Bullous impetigo	1	0	0	0	0	0
Burn infection	2	0	1	0	0	0
Campylobacter gastroenteritis	0	1	0	0	0	0
Candida infection	2	0	1	0	0	0
Cat scratch disease	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Cellulitis	52	0	48	0	0	0
Cellulitis of male external genital organ	1	0	1	0	0	0
Cellulitis orbital	2	0	2	0	0	0
CNS ventriculitis	1	0	0	0	0	0
Colostomy infection	1	0	0	0	0	0
Conjunctivitis	17	1	3	0	0	0
Conjunctivitis bacterial	1	0	1	0	0	0
Conjunctivitis chlamydial	0	0	1	0	0	0
Coxsackie viral infection	1	0	0	0	0	0
Croup infectious	13	0	10	0	0	0
Cystitis	2	0	1	0	0	0
Cytomegalovirus hepatitis	1	0	1	0	0	0
Dengue fever	18	0	15	0	0	0
Diarrhoea infectious	3	0	0	0	0	0
Diverticulitis	0	0	1	0	0	0
Dysentery	0	0	1	0	0	0
Ear infection	21	0	6	0	0	0
Eczema impetiginous	1	0	0	0	0	0
Empyema	3	0	2	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Encephalitis	2	0	0	0	0	0
Encephalitis cytomegalovirus	1	0	0	0	0	0
Encephalitis viral	2	0	1	0	0	0
Enteritis infectious	1	0	0	0	0	0
Enterococcal sepsis	1	0	0	0	0	0
Enterovirus infection	3	0	2	0	0	0
Epididymitis	3	0	1	0	0	0
Epstein-Barr virus infection	1	0	0	0	0	0
Erysipelas	2	0	0	0	0	0
Erythema infectiosum	0	0	1	0	0	0
Erythema migrans	1	0	0	0	0	0
Escherichia infection	1	0	0	0	0	0
Escherichia pyelonephritis	3	0	0	0	0	0
Escherichia sepsis	1	0	1	0	0	0
Escherichia urinary tract infection	14	0	2	0	0	0
Exanthema subitum	27	1	6	0	0	0
External ear cellulitis	2	0	0	0	0	0
Febrile infection	5	0	6	0	0	0
Fungal skin infection	1	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Gastritis viral	0	0	1	0	0	0
Gastroenteritis	920	5	653	1	0	0
Gastroenteritis adenovirus	5	0	5	0	0	0
Gastroenteritis bacterial	11	0	9	0	0	0
Gastroenteritis Escherichia coli	2	1	0	0	0	0
Gastroenteritis norovirus	4	0	2	1	0	0
Gastroenteritis rotavirus	124	3	81	0	0	0
Gastroenteritis salmonella	15	0	6	0	0	0
Gastroenteritis shigella	9	0	8	0	0	0
Gastroenteritis viral	19	1	15	0	0	0
Gastrointestinal infection	3	0	0	0	0	0
Genital candidiasis	1	0	1	0	0	0
Genital herpes	1	0	0	0	0	0
Gianotti-Crosti syndrome	1	0	0	0	0	0
Giardiasis	1	0	3	0	0	0
Gingivitis	1	0	1	0	0	0
H1N1 influenza	1	0	0	0	0	0
Haemophilus infection	0	0	1	0	0	0
Hand-foot-and-mouth disease	1	1	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Hantaviral infection	1	0	0	0	0	0
Hepatitis infectious	1	0	0	0	0	0
Herpangina	9	0	0	0	0	0
Herpes simplex	2	0	1	0	0	0
Herpes virus infection	0	0	1	0	0	0
Herpes zoster	1	0	0	0	0	0
Impetigo	12	0	4	0	0	0
Infected bites	0	0	1	0	0	0
Infected cyst	2	0	0	0	0	0
Infected fistula	0	0	1	0	0	0
Infection	1	0	4	0	0	0
Infectious mononucleosis	9	0	5	0	0	0
Infective pulmonary exacerbation of cystic fibrosis	3	0	0	0	0	0
Influenza	7	0	5	0	0	0
Intervertebral discitis	2	0	1	0	0	0
Klebsiella bacteraemia	1	0	0	0	0	0
Klebsiella infection	0	0	1	0	0	0
Klebsiella sepsis	1	0	0	0	0	0
Laryngitis	236	3	23	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Lobar pneumonia	4	0	1	0	0	0
Lower respiratory tract infection	6	0	2	0	0	0
Lower respiratory tract infection viral	1	0	1	0	0	0
Lung infection	2	0	0	0	0	0
Lymph node abscess	2	0	1	0	0	0
Mastoiditis	7	0	2	0	0	0
Measles	1	0	0	0	0	0
Meningitis	6	0	4	0	0	0
Meningitis aseptic	8	0	2	0	0	0
Meningitis bacterial	0	0	1	0	0	0
Meningitis meningococcal	2	0	1	0	0	0
Meningitis pneumococcal	0	0	3	0	0	0
Meningitis streptococcal	1	0	0	0	0	0
Meningitis tuberculous	1	0	0	0	0	0
Meningitis viral	3	0	4	0	0	0
Meningococcal sepsis	1	0	0	0	0	0
Molluscum contagiosum	1	0	0	0	0	0
Myiasis	1	0	4	0	0	0
Nasal abscess	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Nasopharyngitis	64	1	3	0	0	0
Necrotising fasciitis	0	0	1	0	0	0
Nosocomial infection	1	0	5	0	0	0
Ophthalmia neonatorum	0	0	2	0	0	0
Oral candidiasis	5	0	1	0	0	0
Oral herpes	15	0	4	0	0	0
Osteomyelitis	2	0	0	0	0	0
Otitis externa	1	0	0	0	0	0
Otitis media	92	3	29	1	0	0
Otitis media acute	50	0	23	0	0	0
Otitis media chronic	2	0	0	0	0	0
Parainfluenzae virus infection	2	0	2	0	0	0
Paronychia	5	0	1	0	0	0
Parotitis	1	0	0	0	0	0
Periorbital cellulitis	14	0	16	0	0	0
Perirectal abscess	1	0	0	0	0	0
Peritonitis	4	0	4	0	0	0
Peritonsillar abscess	1	0	0	0	0	0
Pertussis	28	0	17	0	0	0

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Pharyngeal abscess	1	0	0	0	0	0
Pharyngitis	55	0	21	0	0	0
Pharyngitis bacterial	1	0	0	0	0	0
Pharyngotonsillitis	10	0	3	0	0	0
Pneumococcal bacteraemia	1	0	0	0	0	0
Pneumococcal sepsis	3	0	3	0	0	0
Pneumocystis jirovecii infection	1	0	0	0	0	0
Pneumonia	668	2	659	0	0	0
Pneumonia adenoviral	2	0	1	0	0	0
Pneumonia bacterial	3	0	1	0	0	0
Pneumonia influenzal	1	0	1	0	0	0
Pneumonia parainfluenzae viral	1	0	0	0	0	0
Pneumonia pneumococcal	0	0	1	0	0	0
Pneumonia respiratory syncytial viral	12	0	6	0	0	0
Pneumonia viral	11	0	9	0	0	0
Postoperative wound infection	2	0	1	0	0	0
Pseudocroup	3	0	4	0	0	0
Pseudomembranous colitis	1	0	0	0	0	0
Pseudomonal sepsis	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Pulmonary sepsis	1	0	0	0	0	0
Pyelocystitis	1	0	0	0	0	0
Pyelonephritis	74	1	17	0	0	0
Pyelonephritis acute	40	2	7	0	0	0
Pyoderma	4	0	8	0	0	0
Pyomyositis	2	0	0	0	0	0
Respiratory syncytial virus bronchiolitis	72	0	23	0	0	0
Respiratory syncytial virus bronchitis	10	0	9	0	0	0
Respiratory syncytial virus infection	13	0	6	0	0	0
Respiratory tract infection	14	2	3	0	0	0
Respiratory tract infection viral	1	0	1	0	0	0
Rhinitis	19	1	9	0	0	0
Roseola	1	0	0	0	0	0
Rotavirus infection	9	0	7	0	0	0
Salmonellosis	26	0	5	0	0	0
Scarlet fever	2	0	3	0	0	0
Sepsis	23	0	14	0	0	0
Sepsis neonatal	0	0	2	0	0	0
Sepsis syndrome	1	0	0	0	0	0

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Septic shock	4	0	7	0	0	0
Shigella infection	1	0	1	0	0	0
Sinusitis	10	0	5	0	0	0
Skin candida	1	0	2	0	0	0
Skin infection	3	0	1	0	0	0
Staphylococcal bacteraemia	2	0	1	0	0	0
Staphylococcal scalded skin syndrome	3	0	0	0	0	0
Staphylococcal sepsis	2	0	1	0	0	0
Staphylococcal skin infection	1	0	0	0	0	0
Streptococcal sepsis	2	0	0	0	0	0
Subcutaneous abscess	8	0	15	0	0	0
Superinfection bacterial	0	0	1	0	0	0
Superinfection fungal	3	0	0	0	0	0
Systemic candida	2	0	1	0	0	0
Thyroglossal cyst infection	1	0	0	0	0	0
Tonsillitis	19	0	6	0	0	0
Tonsillitis bacterial	1	0	0	0	0	0
Tooth abscess	2	0	0	0	0	0
Tooth infection	1	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Toxoplasmosis	1	0	0	0	0	0
Tracheitis	25	0	9	0	0	0
Tracheobronchitis	3	0	1	0	0	0
Tuberculosis	1	0	0	0	0	0
Typhoid fever	1	0	1	0	0	0
Upper respiratory tract infection	81	0	36	0	0	0
Upper respiratory tract infection bacterial	0	0	1	0	0	0
Urinary tract infection	153	2	120	0	0	0
Urinary tract infection bacterial	1	0	0	0	0	0
Urosepsis	1	0	0	0	0	0
Vaginal infection	1	0	0	0	0	0
Varicella	13	0	20	0	0	0
Varicella post vaccine	0	0	1	0	0	0
Viral diarrhoea	2	0	1	0	0	0
Viral infection	95	1	26	0	0	0
Viral pharyngitis	9	0	7	0	0	0
Viral rash	8	0	4	0	0	0
Viral sepsis	0	0	1	0	0	0
Viral tonsillitis	2	0	1	0	0	0

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Viral upper respiratory tract infection	1	0	2	0	0	0
Vulvitis	1	0	0	0	0	0
Vulvovaginitis	0	0	1	0	0	0
Wound infection	0	0	3	0	0	0
SOC Sub Total	**5,018**	**43**	**3,222**	**5**	**0**	**0**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Acute leukaemia	1	0	0	0	0	0
Acute lymphocytic leukaemia	1	0	2	0	0	0
Acute myeloid leukaemia	1	0	1	0	0	0
Astrocytoma, low grade	0	0	1	0	0	0
Brain neoplasm	2	0	0	0	0	0
Cerebral haemangioma	1	0	0	0	0	0
Haemangioma	2	0	1	0	0	0
Haemangioma of liver	1	0	0	0	0	0
Haemangioma of skin	1	0	0	0	0	0
Hepatoblastoma	1	0	0	0	0	0
Langerhans' cell histiocytosis	0	0	1	0	0	0
Lymphangioma	0	0	1	0	0	0
Lymphocytic leukaemia	1	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Melanocytic naevus	1	0	0	0	0	0
Nephroblastoma	0	0	1	0	0	0
Neuroblastoma	1	0	2	0	0	0
Oral neoplasm	1	0	0	0	0	0
Retinoblastoma	2	0	0	0	0	0
Skin papilloma	1	0	0	0	0	0
Teratoma benign	1	0	0	0	0	0
Testis cancer	1	0	1	0	0	0
Tongue neoplasm	1	0	0	0	0	0
SOC Sub Total	**21**	**0**	**11**	**0**	**0**	**0**
Blood and lymphatic system disorders						
Anaemia	27	0	13	1	0	0
Anaemia neonatal	1	0	0	0	0	0
Aplasia pure red cell	1	0	0	0	0	0
Coagulopathy	2	0	0	0	0	0
Disseminated intravascular coagulation	1	0	0	0	0	0
Febrile neutropenia	5	0	6	0	0	0
Granulocytopenia	0	0	1	0	0	0
Haemolysis	1	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Haemolytic anaemia	1	0	1	0	0	0
Haemolytic uraemic syndrome	2	0	2	0	0	0
Haemorrhagic anaemia	1	0	0	0	0	0
Haemorrhagic disorder	1	0	0	0	0	0
Histiocytosis haematophagic	0	0	1	0	0	0
Hypersplenism	2	0	0	0	0	0
Hypochromic anaemia	2	0	0	0	0	0
Immune thrombocytopenic purpura	6	0	3	0	0	0
Iron deficiency anaemia	1	0	2	0	0	0
Leukaemoid reaction	0	0	1	0	0	0
Leukocytosis	2	0	1	0	0	0
Lymphadenitis	25	0	21	0	0	0
Lymphadenopathy	5	0	3	0	0	0
Microcytic anaemia	1	0	0	0	0	0
Neutropenia	1	0	1	0	0	0
Pancytopenia	1	0	0	0	0	0
Sickle cell anaemia with crisis	0	0	8	0	0	0
Splenic lesion	0	0	1	0	0	0
Splenomegaly	1	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Thrombocytopenia	3	0	2	0	0	0
Thrombocytopenic purpura	1	0	2	0	0	0
Thrombocytosis	1	0	0	0	0	0
SOC Sub Total	**95**	**0**	**70**	**1**	**0**	**0**
Immune system disorders						
Allergy to arthropod sting	1	0	0	0	0	0
Drug hypersensitivity	3	0	0	0	0	0
Food allergy	1	0	1	0	0	0
Hypersensitivity	11	0	7	1	0	0
Immunisation reaction	1	0	0	0	0	0
Immunodeficiency	0	0	1	0	0	0
Milk allergy	6	0	1	0	0	0
Selective IgA immunodeficiency	1	0	0	0	0	0
SOC Sub Total	**24**	**0**	**10**	**1**	**0**	**0**
Endocrine disorders						
Hyperadrenalism	1	0	0	0	0	0
Hypothyroidism	1	0	0	0	0	0
Pituitary hypoplasia	1	0	0	0	0	0
SOC Sub Total	**3**	**0**	**0**	**0**	**0**	**0**

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Metabolism and nutrition disorders						
Acidosis	0	0	1	0	0	0
Amino acid metabolism disorder	1	0	0	0	0	0
Cow's milk intolerance	4	0	2	0	0	0
Decreased appetite	14	1	2	0	0	0
Dehydration	541	0	510	0	0	0
Diabetes mellitus	1	0	0	0	0	0
Diabetic ketoacidosis	1	0	0	0	0	0
Electrolyte imbalance	8	0	5	0	0	0
Failure to thrive	4	0	0	0	0	0
Feeding disorder	1	0	0	0	0	0
Feeding disorder neonatal	0	0	2	0	0	0
Feeding disorder of infancy or early childhood	1	0	0	0	0	0
Fluid intake reduced	0	0	1	0	0	0
Food intolerance	0	0	3	0	0	0
Hypercalcaemia	1	0	0	0	0	0
Hypercarotinaemia	1	0	0	0	0	0
Hyperglycaemia	0	0	1	0	0	0
Hypoglycaemia	5	2	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Hypokalaemia	4	0	5	0	0	0
Hyponatraemia	1	0	0	0	0	0
Hypoproteinaemia	1	0	0	0	0	0
Iron deficiency	0	0	0	1	0	0
Lactose intolerance	0	0	1	0	0	0
Malnutrition	5	0	5	0	0	0
Metabolic acidosis	1	0	1	0	0	0
Type 1 diabetes mellitus	0	1	1	0	0	0
Vitamin B complex deficiency	1	0	0	0	0	0
Weight gain poor	8	0	1	0	0	0
SOC Sub Total	**604**	**4**	**541**	**1**	**0**	**0**
Psychiatric disorders						
Agitation	1	0	1	0	0	0
Binge eating	1	0	0	0	0	0
Breath holding	20	1	9	0	0	0
Eating disorder	5	0	0	0	0	0
Food aversion	1	0	0	0	0	0
Irritability	4	0	0	0	0	0
Listless	1	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Nightmare	1	0	0	0	0	0
Polydipsia psychogenic	1	0	0	0	0	0
Psychomotor retardation	4	2	1	0	0	0
Restlessness	2	0	0	0	0	0
Screaming	0	0	2	0	0	0
Sleep disorder	1	0	0	0	0	0
Staring	1	0	0	0	0	0
SOC Sub Total	**43**	**3**	**13**	**0**	**0**	**0**
Nervous system disorders						
Acquired epileptic aphasia	1	0	0	0	0	0
Altered state of consciousness	2	0	0	0	0	0
Ataxia	2	0	2	0	0	0
Brain hypoxia	0	0	1	0	0	0
Brain injury	3	0	1	0	0	0
Brain oedema	0	0	2	0	0	0
Burning sensation	2	1	0	0	0	0
Cerebral haemorrhage	0	0	1	0	0	0
Cerebral infarction	1	0	0	0	0	0
Cerebral ventricle dilatation	1	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Cerebrospinal fistula	1	0	0	0	0	0
Complex partial seizures	2	0	0	0	0	0
Convulsion	47	0	46	0	0	0
Coordination abnormal	2	0	0	0	0	0
Diplegia	0	0	1	0	0	0
Dystonia	0	0	1	0	0	0
Encephalopathy	0	0	1	0	0	0
Epilepsy	16	1	4	0	0	0
Extrapyramidal disorder	2	0	0	0	0	0
Febrile convulsion	215	2	177	0	0	0
Generalised tonic-clonic seizure	2	0	1	0	0	0
Guillain-Barre syndrome	0	0	1	0	0	0
Hemiparesis	0	0	1	0	0	0
Hydrocephalus	0	0	1	0	0	0
Hypersomnia	1	0	0	0	0	0
Hypertonia	1	0	1	0	0	0
Hypokinesia	1	0	0	0	0	0
Hypotonia	4	1	0	0	0	0
Hypotonic-hyporesponsive episode	3	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Hypoxic-ischaemic encephalopathy	1	0	0	0	0	0
Infantile spasms	4	0	2	0	0	0
Intracranial pressure increased	0	0	1	0	0	0
Lethargy	1	0	0	0	0	0
Loss of consciousness	3	0	0	0	0	0
Meningism	1	0	0	0	0	0
Myoclonic epilepsy	0	0	1	0	0	0
Myoclonus	3	0	0	0	0	0
Neurodegenerative disorder	1	0	0	0	0	0
Nystagmus	2	0	1	0	0	0
Paralysis	1	0	0	0	0	0
Partial seizures	1	0	0	0	0	0
Petit mal epilepsy	2	0	1	0	0	0
Post-traumatic epilepsy	1	0	0	0	0	0
Presyncope	0	0	1	0	0	0
Psychomotor skills impaired	0	0	1	0	0	0
Quadriparesis	1	0	0	0	0	0
Somnolence	3	0	0	0	0	0
Status epilepticus	1	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Subdural hygroma	1	0	0	0	0	0
Syncope	5	0	1	0	0	0
Tonic convulsion	1	0	0	0	0	0
Tremor	1	0	1	0	0	0
Tremor neonatal	0	0	1	0	0	0
VIIth nerve paralysis	0	0	1	0	0	0
VIth nerve paralysis	1	0	0	0	0	0
SOC Sub Total	**344**	**5**	**255**	**0**	**0**	**0**
Eye disorders						
Amaurosis	0	0	1	0	0	0
Conjunctivitis allergic	1	0	1	0	0	0
Dacryostenosis acquired	1	0	0	0	0	0
Eyelid oedema	1	0	0	0	0	0
Ulcerative keratitis	1	0	0	0	0	0
SOC Sub Total	**4**	**0**	**2**	**0**	**0**	**0**
Ear and labyrinth disorders						
Ear disorder	1	0	0	0	0	0
Otorrhoea	1	0	0	0	0	0
Tympanic membrane perforation	1	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
SOC Sub Total	**3**	**0**	**0**	**0**	**0**	**0**
Cardiac disorders						
Angina pectoris	0	0	1	0	0	0
Bradycardia	0	0	1	0	0	0
Cardiac arrest	0	0	3	0	0	0
Cardiac failure	2	0	1	0	0	0
Cardiac failure congestive	1	0	0	0	0	0
Cardio-respiratory arrest	2	0	1	0	0	0
Cardiomegaly	1	0	0	0	0	0
Cyanosis	4	0	6	0	0	0
Intracardiac mass	1	0	0	0	0	0
Mitral valve incompetence	1	0	0	0	0	0
Sinus tachycardia	1	0	0	0	0	0
Supraventricular tachycardia	3	0	0	0	0	0
Tachycardia	1	0	0	0	0	0
Ventricular arrhythmia	1	0	0	0	0	0
Wolff-Parkinson-White syndrome	1	0	0	0	0	0
SOC Sub Total	**19**	**0**	**13**	**0**	**0**	**0**
Vascular disorders						

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Angiopathy	1	0	0	0	0	0
Capillary fragility	1	0	0	0	0	0
Circulatory collapse	4	0	3	0	0	0
Extremity necrosis	0	0	1	0	0	0
Flushing	0	0	1	0	0	0
Haematoma	4	1	3	0	0	0
Haemorrhage	1	0	0	0	0	0
Hypertension	1	0	0	0	0	0
Hypovolaemic shock	3	0	3	0	0	0
Kawasaki's disease	18	0	4	0	0	0
Pallor	1	0	1	0	0	0
Phlebitis	1	0	1	0	0	0
Shock	2	0	5	0	0	0
Vasculitis	4	0	1	0	0	0
SOC Sub Total	**41**	**1**	**23**	**0**	**0**	**0**
Respiratory, thoracic and mediastinal disorders						
Acute lung injury	1	0	0	0	0	0
Acute pulmonary oedema	1	0	1	0	0	0
Acute respiratory failure	3	0	2	0	0	0

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Adenoidal hypertrophy	18	0	1	0	0	0
Allergic bronchitis	3	0	1	0	0	0
Apnoea	15	2	5	0	0	0
Apnoeic attack	2	0	1	0	0	0
Apparent life threatening event	12	0	7	0	0	0
Asphyxia	6	0	3	0	0	0
Aspiration	5	0	4	0	0	0
Asthma	122	0	100	0	0	0
Asthmatic crisis	267	0	268	0	0	0
Atelectasis	15	0	6	0	0	0
Bronchial hyperreactivity	23	0	20	0	0	0
Bronchial obstruction	168	0	179	0	0	0
Bronchiectasis	1	0	0	0	0	0
Bronchitis chronic	4	0	0	0	0	0
Bronchopneumopathy	1	0	1	0	0	0
Bronchospasm	20	0	12	1	0	0
Choking	3	0	0	0	0	0
Cough	0	0	1	0	0	0
Dyspnoea	4	0	2	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Epistaxis	1	0	1	0	0	0
Hypopnoea	0	0	1	0	0	0
Hypoventilation	1	0	0	0	0	0
Hypoxia	2	0	1	0	0	0
Infantile asthma	1	0	1	0	0	0
Interstitial lung disease	10	0	5	0	0	0
Laryngeal oedema	0	0	1	0	0	0
Laryngospasm	1	0	0	0	0	0
Lung disorder	3	0	1	0	0	0
Lung infiltration	1	0	0	0	0	0
Obstructive airways disorder	2	0	2	0	0	0
Pleural effusion	8	0	3	0	0	0
Pneumonia aspiration	7	0	3	0	0	0
Pneumonitis	9	0	4	0	0	0
Pneumothorax	1	0	2	0	0	0
Pneumothorax spontaneous	1	0	0	0	0	0
Pulmonary arterial hypertension	1	0	0	0	0	0
Pulmonary congestion	0	0	1	0	0	0
Pulmonary oedema	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Respiratory arrest	0	0	3	0	0	0
Respiratory disorder	5	0	2	0	0	0
Respiratory distress	7	0	7	0	0	0
Respiratory failure	1	0	3	0	0	0
Respiratory tract congestion	1	0	0	0	0	0
Rhinitis allergic	1	0	0	0	0	0
Rhinorrhoea	1	0	0	0	0	0
Sleep apnoea syndrome	1	0	2	0	0	0
Status asthmaticus	1	0	1	0	0	0
Suffocation feeling	1	0	0	0	0	0
Tachypnoea	2	0	0	0	0	0
Vocal cord polyp	1	0	0	0	0	0
Wheezing	63	0	52	0	0	0
SOC Sub Total	**828**	**2**	**711**	**1**	**0**	**0**
Gastrointestinal disorders						
Abdominal adhesions	0	0	1	0	0	0
Abdominal distension	2	0	2	0	0	0
Abdominal mass	1	0	0	0	0	0
Abdominal pain	14	0	8	0	0	0

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Acetonaemic vomiting	2	0	0	0	0	0
Acute abdomen	2	0	0	0	0	0
Anal fissure	2	0	1	0	0	0
Anal fistula	1	0	0	0	0	0
Aphthous stomatitis	10	1	3	0	0	0
Appendix disorder	2	0	0	0	0	0
Coeliac disease	1	0	1	0	0	0
Constipation	23	0	18	0	0	0
Diarrhoea	94	1	65	0	0	0
Diarrhoea haemorrhagic	1	0	2	0	0	0
Dyspepsia	32	1	9	0	0	0
Enteritis	66	0	31	0	0	0
Enterocolitis	21	0	0	0	0	0
Enterocolitis haemorrhagic	1	0	0	0	0	0
Epulis	1	0	0	0	0	0
Faecaloma	2	0	3	0	0	0
Food poisoning	5	0	1	0	0	0
Gastritis	20	0	4	0	0	0
Gastritis erosive	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Gastrointestinal disorder	1	0	1	0	0	0
Gastrointestinal haemorrhage	1	0	3	0	0	0
Gastrooesophageal reflux disease	23	0	9	0	0	0
Gingival bleeding	1	0	0	0	0	0
Haematemesis	2	0	0	0	0	0
Haematochezia	1	0	0	0	0	0
Ileus	4	0	3	0	0	0
Ileus paralytic	34	0	24	0	0	0
Incarcerated inguinal hernia	15	0	4	0	0	0
Infantile colic	0	0	1	0	0	0
Inguinal hernia	21	0	10	1	0	0
Intestinal haemorrhage	3	0	0	0	0	0
Intestinal obstruction	2	0	5	0	0	0
Intestinal perforation	1	0	0	0	0	0
Intestinal stenosis	0	0	1	0	0	0
Intussusception	20	0	17	0	0	0
Malabsorption	0	0	1	0	0	0
Mallory-Weiss syndrome	1	0	1	0	0	0
Oesophagitis	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Pancreatitis	1	0	0	0	0	0
Rectal fissure	0	1	0	0	0	0
Rectal haemorrhage	0	0	1	0	0	0
Rectal polyp	1	0	0	0	0	0
Rectal prolapse	1	0	0	0	0	0
Sandifer's syndrome	0	0	1	0	0	0
Stomatitis	7	0	6	0	0	0
Teething	1	0	0	0	0	0
Tooth development disorder	1	0	0	0	0	0
Umbilical hernia	0	1	0	0	0	0
Upper gastrointestinal haemorrhage	2	0	2	0	0	0
Vomiting	73	0	45	0	0	0
SOC Sub Total	**520**	**5**	**286**	**1**	**0**	**0**
Hepatobiliary disorders						
Cholangitis	1	0	0	0	0	0
Cholecystitis	0	0	1	0	0	0
Hepatic failure	1	0	1	0	0	0
Hepatitis	1	0	0	0	0	0
Hepatitis acute	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Hepatitis neonatal	1	0	0	0	0	0
Hepatosplenomegaly	3	0	0	0	0	0
Jaundice	0	0	1	0	0	0
SOC Sub Total	**7**	**0**	**4**	**0**	**0**	**0**
Skin and subcutaneous tissue disorders						
Acute haemorrhagic oedema of infancy	0	0	1	0	0	0
Angioedema	3	0	3	0	0	0
Cutaneous loxoscelism	1	0	0	0	0	0
Dermal cyst	1	0	0	0	0	0
Dermatitis	3	0	0	0	0	0
Dermatitis allergic	16	0	2	0	0	0
Dermatitis atopic	9	0	2	0	0	0
Dermatitis bullous	1	0	0	0	0	0
Dermatitis contact	1	0	0	0	0	0
Dermatitis diaper	3	0	0	0	0	0
Dermatitis exfoliative	1	0	0	0	0	0
Dermatosis	1	0	0	0	0	0
Drug eruption	1	0	0	0	0	0
Eczema	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Eczema infantile	1	0	0	0	0	0
Erythema	2	0	0	0	0	0
Erythema multiforme	0	0	2	0	0	0
Haemorrhagic urticaria	1	0	0	0	0	0
Henoch-Schonlein purpura	6	0	3	0	0	0
Hyperhidrosis	1	0	0	0	0	0
Ingrowing nail	2	0	0	0	0	0
Intertrigo	1	0	0	0	0	0
Miliaria	0	0	1	0	0	0
Neurodermatitis	1	0	1	0	0	0
Petechiae	4	0	1	0	0	0
Purpura	2	0	0	0	0	0
Rash	15	0	4	0	0	0
Rash erythematous	1	0	0	0	0	0
Rash maculo-papular	0	0	1	0	0	0
Rash scarlatiniform	0	0	1	0	0	0
Skin burning sensation	1	0	0	0	0	0
Skin discolouration	0	1	0	0	0	0
Skin exfoliation	1	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Skin oedema	1	0	0	0	0	0
Urticaria	20	1	17	0	0	0
SOC Sub Total	**101**	**2**	**40**	**0**	**0**	**0**
Musculoskeletal and connective tissue disorders						
Arthritis	2	0	3	0	0	0
Arthritis reactive	0	0	1	0	0	0
Back pain	1	0	0	0	0	0
Compartment syndrome	1	0	0	0	0	0
Connective tissue disorder	0	0	1	0	0	0
Dactylitis	0	0	2	0	0	0
Fistula	1	0	0	0	0	0
Mobility decreased	1	0	0	0	0	0
Muscle atrophy	1	0	0	0	0	0
Muscle rigidity	1	0	0	0	0	0
Muscle spasms	3	0	0	0	0	0
Muscular weakness	0	0	1	0	0	0
Myositis	0	0	1	0	0	0
Osteoarthritis	1	0	0	0	0	0
Periostitis	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Rickets	2	0	0	0	0	0
Sacroiliitis	1	0	1	0	0	0
Scoliosis	1	0	0	0	0	0
Spinal deformity	1	0	0	0	0	0
Synovitis	4	0	2	0	0	0
Tenosynovitis	0	0	1	0	0	0
Torticollis	2	0	1	0	0	0
Trigger finger	1	0	0	0	0	0
SOC Sub Total	**24**	**0**	**15**	**0**	**0**	**0**
Renal and urinary disorders						
Dysuria	1	0	0	0	0	0
Glomerulonephritis acute	2	0	0	0	0	0
Glycosuria	1	0	0	0	0	0
Haematuria	5	0	4	0	0	0
Hydronephrosis	3	0	1	0	0	0
Leukocyturia	2	0	0	0	0	0
Micturition disorder	1	0	0	0	0	0
Nephritis	1	0	0	0	0	0
Nephrolithiasis	0	1	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Nephropathy	1	0	0	0	0	0
Nephrotic syndrome	2	0	3	0	0	0
Oliguria	1	0	0	0	0	0
Polyuria	1	0	0	0	0	0
Prerenal failure	1	0	0	0	0	0
Pyelocaliectasis	1	0	0	0	0	0
Renal failure acute	0	0	1	0	0	0
Renal tubular acidosis	1	0	0	0	0	0
Tubulointerstitial nephritis	2	0	0	0	0	0
Vesicoureteric reflux	5	0	1	0	0	0
SOC Sub Total	**31**	**1**	**10**	**0**	**0**	**0**
Pregnancy, puerperium and perinatal conditions						
Cephalhaematoma	1	0	1	0	0	0
Jaundice neonatal	0	0	5	0	0	0
Poor weight gain neonatal	0	0	1	0	0	0
SOC Sub Total	**1**	**0**	**7**	**0**	**0**	**0**
Reproductive system and breast disorders						
Balanoposthitis	6	0	2	0	0	0
Genital labial adhesions	0	0	1	0	0	0

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Genital lesion	1	0	0	0	0	0
Testicular retraction	2	0	0	0	0	0
SOC Sub Total	**9**	**0**	**3**	**0**	**0**	**0**
Congenital, familial and genetic disorders						
Aorticopulmonary septal defect	0	0	1	0	0	0
Arteriovenous malformation	1	0	0	0	0	0
Cerebral palsy	2	0	1	0	0	0
Coarctation of the aorta	0	0	1	0	0	0
Congenital absence of bile ducts	1	0	0	0	0	0
Congenital anomaly	1	0	0	0	0	0
Congenital cyst	1	0	0	0	0	0
Congenital herpes simplex infection	0	0	1	0	0	0
Congenital labia pudendi adhesions	1	0	0	0	0	0
Congenital megaureter	2	0	0	0	0	0
Congenital oral malformation	0	0	1	0	0	0
Congenital osteodystrophy	1	0	0	0	0	0
Congenital retinoblastoma	0	0	1	0	0	0
Congenital syphilis	1	0	0	0	0	0
Cryptorchism	3	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Cystic fibrosis	5	0	0	0	0	0
Dacryostenosis congenital	1	0	0	0	0	0
Dermoid cyst	1	0	2	0	0	0
Factor VIII deficiency	1	0	0	0	0	0
Heart disease congenital	0	0	1	0	0	0
Hydrocele	5	0	1	0	0	0
Ichthyosis	0	0	1	0	0	0
Interruption of aortic arch	0	0	1	0	0	0
Laryngomalacia	3	0	1	0	0	0
Laurence-Moon-Bardet-Biedl syndrome	0	0	1	0	0	0
Meningomyelocele	1	0	0	0	0	0
Microcephaly	1	0	0	0	0	0
Muscular dystrophy	0	0	1	0	0	0
Phimosis	0	2	0	0	0	0
Plagiocephaly	1	0	0	0	0	0
Platybasia	1	0	0	0	0	0
Pyloric stenosis	1	0	2	0	0	1
Scaphocephaly	1	0	0	0	0	0
Schizencephaly	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Sickle cell anaemia	1	0	1	0	0	0
Spinal muscular atrophy	4	0	0	0	0	0
Thalassaemia sickle cell	0	0	1	0	0	0
Urinary tract malformation	1	0	1	0	0	0
Velo-cardio-facial syndrome	0	0	1	0	0	0
SOC Sub Total	**42**	**2**	**22**	**0**	**0**	**1**
General disorders and administration site conditions						
Accidental death	0	0	1	0	0	0
Adhesion	0	0	1	0	0	0
Adverse event	1	0	1	0	0	0
Chest pain	1	0	0	0	0	0
Chills	1	0	0	0	0	0
Crying	6	0	4	0	0	0
Cyst	1	0	0	0	0	0
Developmental delay	3	0	0	0	0	0
Drowning	3	0	0	0	0	0
Effusion	1	0	0	0	0	0
Electrocution	3	0	2	0	0	0
Fatigue	2	0	0	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Gait disturbance	1	0	0	0	0	0
Hernia	1	0	0	0	0	0
Hyperpyrexia	4	0	4	0	0	0
Hyperthermia	2	0	1	0	0	0
Hypothermia	1	0	1	0	0	0
Ill-defined disorder	2	0	2	0	0	0
Inflammation	1	0	0	0	0	0
Injection site erythema	1	0	0	0	0	0
Injection site swelling	0	0	1	0	0	0
Injection site urticaria	0	0	1	0	0	0
Localised oedema	0	1	0	0	0	0
Malaise	0	0	3	0	0	0
Multi-organ failure	1	0	0	0	0	0
Oedema peripheral	2	0	0	0	0	0
Peripheral swelling	1	0	0	0	0	0
Pyrexia	78	0	62	0	0	0
Sudden death	2	0	1	0	0	0
Sudden infant death syndrome	5	0	2	0	0	0
Systemic inflammatory response syndrome	1	0	0	0	0	0

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
SOC Sub Total	**125**	**1**	**87**	**0**	**0**	**0**
Investigations						
Acid base balance abnormal	1	0	0	0	0	0
Alanine aminotransferase increased	1	0	0	0	0	0
Aspartate aminotransferase increased	1	0	0	0	0	0
Aspiration bronchial	2	0	3	0	0	0
Biopsy liver	1	0	0	0	0	0
Blood alkaline phosphatase increased	1	0	0	0	0	0
Body temperature increased	2	0	0	0	0	0
Hepatic enzyme increased	1	0	0	0	0	0
Medical observation	1	0	0	0	0	0
Neurological examination	0	0	1	0	0	0
Oxygen saturation decreased	0	0	1	0	0	0
SOC Sub Total	**11**	**0**	**5**	**0**	**0**	**0**
Injury, poisoning and procedural complications						
Abdominal injury	1	0	1	0	0	0
Accident	1	0	0	0	0	0
Accidental exposure to product	49	0	6	0	0	0
Accidental exposure to product by child	0	1	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Accidental overdose	2	0	1	0	0	0
Accidental poisoning	4	0	3	0	0	0
Animal bite	10	0	3	0	0	0
Arthropod bite	2	0	1	0	0	0
Arthropod sting	8	0	5	0	0	0
Back injury	1	0	0	0	0	0
Brain contusion	5	0	7	0	0	0
Burns first degree	0	0	1	0	0	0
Burns second degree	12	0	10	0	0	0
Burns third degree	1	0	0	0	0	0
Carbon monoxide poisoning	2	0	1	0	0	0
Chemical injury	2	0	0	0	0	0
Chemical poisoning	24	0	21	0	0	0
Chest injury	1	0	1	0	0	0
Child maltreatment syndrome	0	0	2	0	0	0
Concussion	66	3	16	0	0	0
Contusion	36	0	10	0	0	0
Craniocerebral injury	42	0	38	0	0	0
Electric shock	5	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Electrical burn	1	0	1	0	0	0
Excoriation	1	0	0	0	0	0
Exposure to communicable disease	1	0	0	0	0	0
Exposure to toxic agent	4	0	5	0	0	0
Extradural haematoma	0	0	1	0	0	0
Eye burns	1	0	0	0	0	0
Eye injury	1	0	0	0	0	0
Eyelid injury	0	0	1	0	0	0
Face injury	0	0	2	0	0	0
Facial bones fracture	1	0	0	0	0	0
Fall	28	1	2	0	0	0
Femur fracture	8	0	8	0	0	0
Forearm fracture	0	0	1	0	0	0
Foreign body	25	0	16	0	0	0
Foreign body aspiration	2	0	1	0	0	0
Foreign body in eye	1	0	0	0	0	0
Fracture	4	0	3	0	0	0
Gingival injury	0	0	1	0	0	0
Greenstick fracture	0	0	1	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Hand fracture	2	0	3	0	0	0
Head injury	107	1	86	0	0	0
Heat stroke	1	0	0	0	0	0
Herbal toxicity	2	0	2	0	0	0
Humerus fracture	5	0	2	0	0	0
Incorrect route of drug administration	1	0	0	0	0	0
Injury	2	0	2	0	0	0
Joint dislocation	1	0	0	0	0	0
Kidney contusion	1	0	0	0	0	0
Laceration	7	0	0	0	0	0
Limb crushing injury	0	0	2	0	0	0
Limb injury	2	0	1	0	0	0
Limb traumatic amputation	2	0	1	0	0	0
Lip injury	1	0	0	0	0	0
Lower limb fracture	0	0	1	0	0	0
Mouth injury	2	0	3	0	0	0
Multiple injuries	26	0	33	0	0	0
Muscle rupture	1	0	0	0	0	0
Near drowning	8	0	3	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Open fracture	0	0	2	0	0	0
Overdose	2	0	0	0	0	0
Pharyngeal injury	1	0	0	0	0	0
Pneumonitis chemical	1	0	3	0	0	0
Poisoning	8	0	4	0	0	0
Postoperative fever	0	0	1	0	0	0
Procedural haemorrhage	0	0	1	0	0	0
Road traffic accident	4	0	3	0	0	0
Seroma	0	0	1	0	0	0
Shunt malfunction	0	0	1	0	0	0
Skull fracture	25	1	9	0	0	0
Skull fractured base	1	0	0	0	0	0
Spinal cord injury	0	0	1	0	0	0
Subcutaneous haematoma	1	0	0	0	0	0
Subdural haematoma	0	0	1	0	0	0
Tendon injury	0	0	1	0	0	0
Tendon rupture	1	0	0	0	0	0
Thermal burn	61	3	46	0	0	0
Tibia fracture	3	0	2	0	0	0

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Tongue injury	2	0	0	0	0	0
Tooth fracture	1	0	0	0	0	0
Toxicity to various agents	18	0	13	0	0	0
Traumatic haematoma	1	0	0	0	0	0
Upper limb fracture	3	0	4	0	0	0
Vaccination complication	1	0	0	0	0	0
Vulvovaginal injury	1	0	0	0	0	0
Wound	5	0	5	0	0	0
Wound dehiscence	1	0	0	0	0	0
SOC Sub Total	**664**	**10**	**409**	**0**	**0**	**0**
Surgical and medical procedures						
Finger amputation	1	0	0	0	0	0
Haemangioma removal	0	0	1	0	0	0
Hernia repair	1	0	0	0	0	0
Inguinal hernia repair	1	0	0	0	0	0
Therapeutic hypothermia	0	0	1	0	0	0
Toe amputation	0	0	1	0	0	0
SOC Sub Total	**3**	**0**	**3**	**0**	**0**	**0**
Social circumstances						

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Summary Tabulation of Serious Adverse Events

Preferred Term	DTPa-HBV-IPV+Hib	Blinded	Other IMPs	Non-IMPs	Placebo	No Therapy
Alcohol use	0	0	1	0	0	0
Child neglect	1	0	0	0	0	0
Physical abuse	1	0	2	0	0	0
SOC Sub Total	**2**	**0**	**3**	**0**	**0**	**0**
Grand Total	**8,587**	**79**	**5,765**	**10**	**0**	**1**

APPENDIX 2B : CUMULATIVE AND INTERVAL SUMMARY TABULATIONS FROM POST-MARKETING DATA SOURCES

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Infections and infestations	Abdominal abscess	0	0	0	1	1	0	0
	Abscess	8	18	5	33	51	0	0
	Abscess bacterial	1	1	1	3	4	0	0
	Abscess limb	9	17	1	3	20	0	0
	Abscess oral	1	1	0	0	1	0	0
	Abscess rupture	2	2	1	1	3	0	0
	Abscess soft tissue	0	0	1	2	2	0	0
	Acute hepatitis B	0	0	0	1	1	0	0
	Acute tonsillitis	0	1	1	4	5	0	0
	Adenovirus infection	1	1	0	1	2	0	0
	Alpha haemolytic streptococcal infection	1	1	0	0	1	0	0
	Appendicitis	1	1	0	0	1	0	0
	Application site abscess	2	2	0	0	2	0	0
	Atypical pneumonia	0	1	0	0	1	0	0
	Bacteraemia	2	6	0	0	6	0	0
	Bacterial infection	1	1	5	13	14	0	0
	Bacterial pyelonephritis	1	2	0	0	2	0	0
	Bacterial tracheitis	0	1	0	0	1	0	0
	Bone abscess	0	1	0	0	1	0	0
	Botulism	1	1	0	0	1	0	0
	Brain abscess	1	1	0	0	1	0	0
	Brain empyema	0	0	0	1	1	0	0
	Bronchiolitis	9	11	4	11	22	0	0
	Bronchitis	2	8	26	65	73	0	1
	Bronchitis bacterial	0	0	0	2	2	0	0
	Bronchitis viral	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Bronchopneumonia	6	14	0	0	14	0	0
	Candida infection	3	3	2	5	8	0	0
	Candida nappy rash	0	0	0	3	3	0	0
	Candiduria	1	1	0	0	1	0	0
	Cat scratch disease	0	0	1	1	1	0	0
	Cellulitis	9	36	0	0	36	0	0
	Clostridial infection	0	0	0	1	1	0	0
	Conjunctivitis	3	3	8	34	37	0	0
	Conjunctivitis bacterial	0	0	0	1	1	0	0
	Coxsackie viral infection	0	0	1	2	2	0	0
	Croup infectious	0	1	0	6	7	0	0
	Cystitis	0	0	1	1	1	0	0
	Cytomegalovirus colitis	1	1	0	0	1	0	0
	Cytomegalovirus infection	0	1	0	3	4	0	0
	Dermatitis infected	0	0	0	1	1	0	0
	Device related sepsis	0	1	0	0	1	0	0
	Ear infection	3	4	10	28	32	0	0
	Eczema herpeticum	0	1	0	0	1	0	0
	Eczema impetiginous	0	0	0	1	1	0	0
	Eczema infected	0	1	0	0	1	0	0
	Empyema	0	0	0	1	1	0	0
	Encephalitis	13	32	0	0	32	0	0
	Encephalitis brain stem	1	1	0	0	1	0	0
	Encephalitis viral	0	1	0	0	1	0	0
	Encephalomyelitis	0	1	0	0	1	0	0
	Enteritis infectious	1	4	0	1	5	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Enterovirus infection	1	2	0	0	2	0	0
	Epididymitis	1	1	0	0	1	0	0
	Epiglottitis	0	1	0	0	1	0	0
	Epstein-Barr virus infection	1	1	1	2	3	0	0
	Erysipelas	6	10	2	6	16	0	0
	Erysipeloid	0	0	0	1	1	0	0
	Erythema infectiosum	0	0	3	4	4	0	0
	Erythema migrans	0	1	1	1	2	0	0
	Escherichia infection	0	0	0	5	5	0	0
	Escherichia sepsis	1	1	0	0	1	0	0
	Escherichia urinary tract infection	1	1	0	3	4	0	0
	Exanthema subitum	0	2	4	11	13	0	0
	Febrile infection	1	3	1	19	22	0	0
	Fungal infection	0	0	4	7	7	0	0
	Fungal skin infection	0	0	3	4	4	0	0
	Furuncle	0	0	1	3	3	0	0
	Gastroenteritis	18	53	18	21	74	0	2
	Gastroenteritis Escherichia coli	1	2	0	0	2	0	0
	Gastroenteritis adenovirus	0	3	0	0	3	0	0
	Gastroenteritis astroviral	0	1	0	0	1	0	0
	Gastroenteritis bacterial	0	1	0	0	1	0	0
	Gastroenteritis norovirus	4	10	0	0	10	0	0
	Gastroenteritis rotavirus	7	27	0	0	27	0	1
	Gastroenteritis staphylococcal	0	1	0	0	1	0	0
	Gastroenteritis viral	1	4	5	5	9	0	0
	Gastrointestinal infection	1	1	6	10	11	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Genital candidiasis	0	0	0	3	3	0	0
	Gianotti-Crosti syndrome	0	4	4	13	17	0	0
	Groin abscess	0	2	0	0	2	0	0
	Group B streptococcus neonatal sepsis	1	1	0	0	1	0	0
	H1N1 influenza	1	1	1	2	3	0	0
	Haematoma infection	0	0	1	1	1	0	0
	Haemophilus infection	6	8	2	15	23	0	0
	Haemophilus sepsis	1	2	0	1	3	0	0
	Hand-foot-and-mouth disease	1	1	4	5	6	0	0
	Hepatitis A	0	0	1	1	1	0	0
	Hepatitis B	2	2	2	3	5	0	0
	Herpangina	0	0	0	1	1	0	0
	Herpes ophthalmic	0	0	0	1	1	0	0
	Herpes simplex	0	0	0	2	2	0	0
	Herpes simplex meningoencephalitis	0	2	0	0	2	0	0
	Herpes virus infection	0	0	1	3	3	0	0
	Herpes zoster	1	2	2	4	6	0	0
	Human herpesvirus 6 infection	0	1	1	2	3	0	0
	Impetigo	1	1	1	4	5	0	0
	Incision site abscess	0	0	0	8	8	0	0
	Infected fistula	0	0	1	1	1	0	0
	Infection	3	7	18	55	62	0	0
	Infection susceptibility increased	3	3	0	0	3	0	0
	Infectious mononucleosis	0	0	1	1	1	0	0
	Infective myositis	1	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Influenza	0	1	4	5	6	0	0
	Injection site abscess	67	103	17	81	184	1	1
	Injection site cellulitis	5	9	1	9	18	0	0
	Injection site infection	4	6	1	5	11	0	0
	Injection site pustule	1	1	2	4	5	0	0
	Labyrinthitis	0	0	0	1	1	0	0
	Laryngitis	0	1	5	10	11	0	0
	Localised infection	0	0	1	2	2	0	0
	Lower respiratory tract infection	1	1	0	0	1	0	0
	Lung infection	0	0	0	1	1	0	0
	Lymph node abscess	0	1	0	0	1	0	0
	Lymphangitis	2	2	0	1	3	0	0
	Mastoiditis	0	0	0	3	3	0	1
	Measles	0	0	0	1	1	0	0
	Measles post vaccine	0	0	0	1	1	0	0
	Meningitis	13	28	0	0	28	0	0
	Meningitis aseptic	1	3	0	0	3	0	0
	Meningitis bacterial	3	6	0	0	6	0	0
	Meningitis haemophilus	2	14	0	0	14	0	0
	Meningitis pneumococcal	2	8	0	0	8	0	0
	Meningitis viral	0	4	0	0	4	0	0
	Meningococcal bacteraemia	1	1	0	0	1	0	0
	Meningococcal sepsis	1	2	0	0	2	0	0
	Meningoencephalitis bacterial	1	2	0	0	2	0	0
	Meningoencephalitis viral	0	1	0	0	1	0	0
	Molluscum contagiosum	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Mycoplasma infection	0	0	2	3	3	0	0
	Myelitis	1	1	0	0	1	0	0
	Nasopharyngitis	1	7	39	77	84	0	0
	Necrotising fasciitis	0	1	0	0	1	0	0
	Necrotising ulcerative gingivostomatitis	0	1	0	0	1	0	0
	Neuroborreliosis	0	1	0	0	1	0	0
	Oral candidiasis	1	2	5	9	11	0	0
	Orchitis	0	1	0	0	1	0	0
	Osteomyelitis	1	4	0	0	4	0	0
	Osteomyelitis acute	1	1	0	0	1	0	0
	Otitis media	11	15	6	31	46	0	0
	Otitis media acute	2	2	0	3	5	0	1
	Otosalpingitis	0	0	0	1	1	0	0
	Parechovirus infection	1	1	0	0	1	0	0
	Parotitis	0	0	0	1	1	0	0
	Perichondritis	0	0	0	1	1	0	0
	Peritonitis	0	1	0	0	1	0	0
	Peritonsillar abscess	0	0	0	1	1	0	0
	Pertussis	152	165	45	191	356	10	10
	Pharyngitis	2	4	18	38	42	0	0
	Pharyngitis streptococcal	0	0	0	1	1	0	0
	Pharyngotonsillitis	0	0	0	2	2	0	0
	Pneumococcal infection	1	2	1	2	4	0	0
	Pneumococcal sepsis	0	0	0	2	2	0	0
	Pneumonia	24	51	0	3	54	0	0
	Pneumonia pneumococcal	0	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Pneumonia respiratory syncytial viral	1	2	0	0	2	0	0
	Pneumonia streptococcal	1	1	0	0	1	0	0
	Pneumonia viral	1	2	0	0	2	0	0
	Poliomyelitis post vaccine	2	2	0	0	2	0	0
	Proteus infection	0	1	0	0	1	0	0
	Pseudocroup	1	1	3	7	8	0	0
	Purulence	0	0	1	4	4	0	0
	Purulent discharge	0	0	5	9	9	0	0
	Pyelonephritis	7	13	0	0	13	0	0
	Pyelonephritis acute	3	4	0	0	4	0	0
	Pyuria	0	0	2	2	2	0	0
	Rash pustular	2	2	5	18	20	0	0
	Renal abscess	1	1	0	0	1	0	0
	Respiratory syncytial virus bronchiolitis	1	2	0	1	3	0	0
	Respiratory syncytial virus infection	3	6	4	9	15	0	0
	Respiratory tract infection	13	15	8	20	35	0	0
	Respiratory tract infection viral	1	2	1	1	3	0	0
	Rhinitis	0	1	56	123	124	0	0
	Rhinovirus infection	0	0	1	1	1	0	0
	Roseola	1	1	1	1	2	0	0
	Rotavirus infection	0	1	4	8	9	0	0
	Rubella	0	0	1	1	1	0	0
	Salmonella sepsis	0	1	0	0	1	0	0
	Salmonellosis	0	0	0	1	1	0	0
	Scarlet fever	0	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Sepsis	11	43	0	0	43	0	0
	Sepsis syndrome	0	0	0	2	2	0	0
	Septic shock	2	3	0	0	3	0	0
	Sinusitis	0	0	0	2	2	0	0
	Skin bacterial infection	0	0	1	1	1	0	0
	Skin infection	0	0	1	2	2	0	0
	Soft tissue infection	3	4	0	5	9	0	0
	Sphingomonas paucimobilis infection	1	1	0	0	1	0	0
	Sputum purulent	0	0	0	1	1	0	0
	Staphylococcal abscess	1	5	1	2	7	0	0
	Staphylococcal impetigo	1	1	0	0	1	0	0
	Staphylococcal infection	2	3	1	8	11	0	0
	Staphylococcal scalded skin syndrome	0	0	0	1	1	0	0
	Staphylococcal sepsis	0	2	0	0	2	0	0
	Staphylococcal skin infection	1	1	2	2	3	0	0
	Streptococcal abscess	0	0	0	3	3	0	0
	Streptococcal bacteraemia	0	0	1	1	1	0	0
	Streptococcal infection	0	1	0	0	1	0	0
	Subcutaneous abscess	0	0	0	1	1	0	0
	Superinfection	0	2	1	5	7	0	0
	Superinfection bacterial	0	0	0	1	1	0	0
	Superinfection fungal	1	1	0	0	1	0	0
	Suspected transmission of an infectious agent via product	1	2	0	0	2	0	0
	Systemic candida	1	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Tonsillitis	1	3	0	12	15	1	1
	Tracheitis	0	1	1	5	6	0	0
	Tuberculosis	1	1	1	1	2	0	0
	Upper respiratory tract infection	4	9	38	82	91	0	0
	Urinary tract infection	7	8	1	11	19	0	1
	Urinary tract infection enterococcal	1	1	0	0	1	0	0
	Urosepsis	1	1	0	0	1	0	0
	Vaccination site abscess	16	18	1	1	19	0	0
	Vaccination site cellulitis	2	2	0	0	2	0	0
	Vaccination site infection	0	0	0	1	1	0	0
	Vaccination site pustule	0	0	1	1	1	0	0
	Varicella	0	0	4	7	7	0	0
	Vertical infection transmission	0	0	3	3	3	0	0
	Vestibular neuronitis	0	0	0	1	1	0	0
	Viraemia	0	1	0	0	1	0	0
	Viral infection	4	11	22	47	58	0	0
	Viral pharyngitis	0	0	0	1	1	0	0
	Viral rash	0	1	5	11	12	0	0
	Viral upper respiratory tract infection	1	1	2	3	4	0	0
	Vulvitis	0	0	1	1	1	0	0
	Waterhouse-Friderichsen syndrome	1	3	0	0	3	0	0
	Wound infection	0	0	0	1	1	0	0
Subtotal		**553**	**993**	**486**	**1382**	**2375**	**12**	**19**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Acute lymphocytic leukaemia	1	1	0	0	1	0	1

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	B precursor type acute leukaemia	0	1	0	0	1	0	0
	Cerebral hygroma	0	0	0	2	2	0	0
	Ewing's sarcoma	0	1	0	0	1	0	0
	Fibroma	0	0	0	1	1	0	0
	Fibrous histiocytoma	0	0	1	1	1	0	0
	Haemangioma	0	0	3	6	6	0	0
	Haemangioma of skin	0	0	1	1	1	0	0
	Langerhans' cell histiocytosis	1	1	0	0	1	0	0
	Lipoma	0	0	2	2	2	0	0
	Lymphangioma	0	1	0	0	1	0	0
	Lymphoma	1	1	0	0	1	0	0
	Melanocytic naevus	0	0	1	1	1	0	0
	Myelodysplastic syndrome	0	1	0	0	1	0	0
	Neoplasm	1	1	1	1	2	0	0
	Neoplasm skin	0	1	0	0	1	0	0
	Neuroblastoma	0	2	0	0	2	0	0
	Optic glioma	0	1	0	0	1	0	0
	Pyogenic granuloma	0	0	1	1	1	0	0
	Rhabdomyoma	0	0	1	1	1	0	0
	Soft tissue neoplasm	0	2	0	0	2	0	0
Subtotal		**4**	**14**	**11**	**17**	**31**	**0**	**1**
Blood and lymphatic system disorders	Abdominal lymphadenopathy	0	0	0	1	1	0	0
	Agranulocytosis	0	3	0	0	3	0	0
	Anaemia	3	33	5	6	39	0	0
	Anaemia neonatal	1	1	0	0	1	0	0
	Anisocytosis	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Aplastic anaemia	0	1	0	0	1	0	0
	Autoimmune haemolytic anaemia	1	5	0	0	5	0	0
	Autoimmune neutropenia	2	3	0	0	3	0	0
	Bicytopenia	0	0	0	0	0	0	1
	Bone marrow failure	1	1	0	0	1	0	0
	Coagulopathy	0	3	1	1	4	0	0
	Coombs positive haemolytic anaemia	1	1	0	0	1	0	0
	Disseminated intravascular coagulation	1	6	0	0	6	0	0
	Eosinophilia	0	1	3	11	12	0	0
	Erythropenia	1	1	0	0	1	0	0
	Febrile neutropenia	1	2	0	0	2	0	0
	Granulocytopenia	1	6	0	0	6	0	0
	Haemolysis	0	5	0	0	5	0	0
	Haemolytic anaemia	4	7	0	0	7	0	0
	Haemolytic uraemic syndrome	0	1	0	0	1	0	0
	Haemorrhagic anaemia	2	5	0	0	5	0	0
	Haemorrhagic diathesis	1	6	0	0	6	0	0
	Histiocytosis haematophagic	1	2	0	0	2	0	0
	Hypergammaglobulinaemia	0	1	0	0	1	0	0
	Hypochromasia	0	1	0	0	1	0	0
	Hypochromic anaemia	1	5	2	2	7	0	0
	Immune thrombocytopenic purpura	16	47	0	0	47	0	0
	Increased tendency to bruise	0	0	1	1	1	0	0
	Iron deficiency anaemia	0	4	1	2	6	0	0
	Jaundice acholuric	0	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Leukocytosis	4	37	6	7	44	0	0
	Leukopenia	3	8	2	2	10	0	0
	Lymph node pain	1	1	3	7	8	0	0
	Lymphadenitis	1	2	10	15	17	0	0
	Lymphadenopathy	0	6	39	106	112	0	0
	Lymphatic disorder	0	1	0	0	1	0	0
	Lymphocytic infiltration	0	0	0	1	1	0	0
	Lymphocytosis	0	7	1	2	9	0	0
	Lymphopenia	0	2	0	0	2	0	0
	Microcytic anaemia	0	3	0	0	3	0	0
	Microcytosis	0	2	0	0	2	0	0
	Monocytosis	1	3	0	0	3	0	0
	Neutropenia	5	20	7	7	27	0	0
	Neutrophilia	0	1	0	0	1	0	0
	Normochromic normocytic anaemia	0	0	1	1	1	0	0
	Pancytopenia	2	5	0	0	5	0	0
	Protein deficiency anaemia	0	1	0	0	1	0	0
	Splenic infarction	1	1	0	0	1	0	0
	Splenitis	0	1	0	0	1	0	0
	Splenomegaly	0	6	0	0	6	0	0
	Thrombocytopenia	11	53	8	10	63	0	0
	Thrombocytopenic purpura	5	17	1	1	18	0	0
	Thrombocytosis	4	14	2	2	16	0	0
	Thymus enlargement	0	0	0	1	1	0	0
	Warm type haemolytic anaemia	0	1	0	0	1	0	0
	White blood cell disorder	0	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Subtotal		**76**	**345**	**94**	**187**	**532**	**0**	**1**
Immune system disorders	Allergy to metals	0	1	5	8	9	0	0
	Allergy to vaccine	0	1	2	4	5	0	0
	Anaphylactic reaction	9	24	0	0	24	0	0
	Anaphylactic shock	5	10	0	0	10	0	0
	Anaphylactoid reaction	3	6	0	0	6	0	0
	Anti-neutrophil cytoplasmic antibody positive vasculitis	1	1	0	0	1	0	0
	Atopy	0	0	0	1	1	0	0
	Decreased immune responsiveness	0	0	0	1	1	0	0
	Drug hypersensitivity	0	1	0	3	4	0	0
	Food allergy	1	1	2	5	6	0	0
	Hypersensitivity	15	33	61	119	152	0	0
	Hypogammaglobulinaemia	2	2	0	1	3	0	0
	Immune system disorder	1	1	0	3	4	0	0
	Immunisation reaction	1	2	0	1	3	0	0
	Immunodeficiency	3	3	1	2	5	0	0
	Milk allergy	0	0	7	8	8	0	0
	Multiple allergies	0	0	2	3	3	0	0
	Seasonal allergy	1	1	0	0	1	0	0
	Selective IgA immunodeficiency	0	0	0	1	1	0	0
	Serum sickness	0	1	1	1	2	0	0
	Type I hypersensitivity	0	0	0	1	1	0	0
	Type III immune complex mediated reaction	3	5	0	3	8	0	0
Subtotal		**45**	**93**	**81**	**165**	**258**	**0**	**0**

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
Endocrine disorders	Endocrine pancreatic disorder	0	0	0	1	1	0	0
	Hypothyroidism	0	5	1	1	6	0	0
	Inappropriate antidiuretic hormone secretion	1	1	0	0	1	0	0
Subtotal		**1**	**6**	**1**	**2**	**8**	**0**	**0**
Metabolism and nutrition disorders	Acidosis	2	4	1	5	9	0	0
	Alkalosis	0	0	0	1	1	0	0
	Appetite disorder	0	0	0	3	3	0	0
	Cow's milk intolerance	0	0	0	3	3	0	0
	Decreased appetite	3	12	238	489	501	0	0
	Dehydration	3	8	26	49	57	0	0
	Diabetic ketoacidosis	0	3	0	0	3	0	0
	Diet refusal	1	1	4	4	5	0	0
	Disaccharide metabolism disorder	0	0	0	1	1	0	0
	Electrolyte imbalance	0	0	0	1	1	0	0
	Enzyme abnormality	0	0	0	1	1	0	0
	Failure to thrive	1	3	2	2	5	0	0
	Feeding disorder	0	0	4	7	7	0	0
	Feeding disorder neonatal	3	4	8	13	17	0	0
	Feeding disorder of infancy or early childhood	1	1	2	12	13	0	0
	Fluid intake reduced	1	1	27	53	54	0	0
	Haemosiderosis	0	0	0	1	1	0	0
	Hyperammonaemia	0	0	1	3	3	0	0
	Hypercholesterolaemia	0	0	0	1	1	0	0
	Hyperglycaemia	0	0	1	5	5	0	0
	Hyperinsulinaemia	0	0	0	1	1	0	0

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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Hyperkalaemia	0	1	2	2	3	0	0
	Hyperlipidaemia	0	0	0	1	1	0	0
	Hypernatraemia	0	0	0	1	1	0	0
	Hypertriglyceridaemia	0	0	0	1	1	0	0
	Hyperuricaemia	0	0	0	1	1	0	0
	Hypoalbuminaemia	0	0	0	4	4	0	0
	Hypocalcaemia	0	0	1	1	1	0	0
	Hypochloraemia	0	0	1	1	1	0	0
	Hypoglycaemia	3	7	2	2	9	0	0
	Hypokalaemia	1	6	0	0	6	0	0
	Hypometabolism	0	0	1	1	1	0	0
	Hyponatraemia	0	0	4	10	10	0	0
	Hypophagia	2	2	28	44	46	0	0
	Hyposideraemia	0	0	1	1	1	0	0
	Hypovolaemia	0	0	0	1	1	0	0
	Increased appetite	0	0	2	4	4	0	0
	Iodine deficiency	0	0	0	1	1	0	0
	Iron deficiency	0	0	0	3	3	0	0
	Ketoacidosis	0	1	0	1	2	0	0
	Ketosis	0	0	1	2	2	0	0
	Lactic acidosis	3	5	0	0	5	0	0
	Lactose intolerance	0	0	5	6	6	0	0
	Malnutrition	0	1	1	3	4	0	0
	Metabolic acidosis	1	6	1	1	7	0	0
	Metabolic disorder	0	1	2	4	5	0	0
	Mitochondrial cytopathy	1	2	0	0	2	0	0

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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Oligodipsia	3	5	29	79	84	0	0
	Polydipsia	0	1	2	9	10	0	0
	Protein deficiency	0	0	0	1	1	0	0
	Tetany	0	2	0	0	2	0	0
	Type 1 diabetes mellitus	5	12	0	0	12	0	0
	Underweight	0	0	1	5	5	0	0
	Vitamin B12 deficiency	0	0	1	3	3	0	0
	Vitamin D deficiency	0	0	1	1	1	0	0
	Vitamin K deficiency	0	0	0	2	2	0	0
	Weight gain poor	1	2	13	16	18	0	0
Subtotal		**35**	**91**	**413**	**867**	**958**	**0**	**0**
Psychiatric disorders	Abnormal behaviour	0	1	27	62	63	0	0
	Affect lability	0	0	1	1	1	0	0
	Aggression	3	7	11	12	19	0	0
	Agitation	7	12	716	800	812	0	0
	Agitation neonatal	0	0	0	1	1	0	0
	Anger	0	0	7	8	8	0	0
	Antisocial behaviour	0	0	1	3	3	0	0
	Anxiety	2	4	33	59	63	0	0
	Anxiety disorder	0	0	1	1	1	0	0
	Anxiety disorder due to a general medical condition	0	0	0	1	1	0	0
	Apathy	8	17	80	186	203	0	0
	Attention deficit/hyperactivity disorder	3	3	0	1	4	0	0
	Autism spectrum disorder	1	2	0	0	2	0	0
	Automatism	0	0	1	1	1	0	0

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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Breath holding	1	3	15	28	31	0	0
	Bruxism	0	0	2	3	3	0	0
	Communication disorder	0	0	5	6	6	0	0
	Conduct disorder	1	1	0	0	1	0	0
	Confusional state	0	0	0	2	2	0	0
	Conversion disorder	0	0	4	4	4	0	0
	Daydreaming	0	0	2	6	6	0	0
	Decreased eye contact	0	0	11	16	16	0	0
	Decreased interest	0	0	5	8	8	0	0
	Delirium	1	2	0	0	2	0	0
	Delirium febrile	2	2	0	0	2	0	0
	Delusion	0	0	1	2	2	0	0
	Depressed mood	0	0	4	5	5	0	0
	Disorientation	0	0	3	10	10	0	0
	Dissociation	0	0	0	2	2	0	0
	Disturbance in social behaviour	0	0	0	1	1	0	0
	Dysphemia	0	1	0	0	1	0	0
	Dyssomnia	0	0	1	1	1	0	0
	Eating disorder	0	1	3	14	15	0	0
	Emotional disorder	1	1	2	2	3	0	0
	Emotional distress	0	0	12	28	28	0	0
	Euphoric mood	0	0	1	4	4	0	0
	Excessive masturbation	0	0	0	1	1	0	0
	Executive dysfunction	0	0	1	1	1	0	0
	Fear	0	0	6	11	11	0	0
	Food aversion	0	7	19	38	45	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Hallucination	0	0	1	1	1	0	0
	Head banging	0	0	0	1	1	0	0
	Hydrophobia	0	0	1	1	1	0	0
	Hypervigilance	0	0	0	1	1	0	0
	Illusion	0	1	2	3	4	0	0
	Impatience	0	0	1	2	2	0	0
	Inappropriate affect	0	1	0	2	3	0	0
	Indifference	0	0	0	3	3	0	0
	Initial insomnia	0	0	9	14	14	0	0
	Insomnia	2	5	59	141	146	0	0
	Intentional self-injury	1	2	0	0	2	0	0
	Irritability	5	13	663	988	1001	0	0
	Learning disorder	0	0	1	1	1	0	0
	Listless	1	1	44	71	72	0	0
	Mental disorder	0	0	0	1	1	0	0
	Mental disorder due to a general medical condition	0	0	1	1	1	0	0
	Merycism	0	0	0	1	1	0	0
	Middle insomnia	0	0	12	20	20	0	0
	Moaning	1	2	31	53	55	0	0
	Mood altered	0	0	9	15	15	0	0
	Mood swings	0	0	1	1	1	0	0
	Morose	0	0	0	2	2	0	0
	Mutism	0	0	1	2	2	0	0
	Negativism	0	0	3	4	4	0	0
	Nervousness	0	0	20	62	62	0	0
	Neurodevelopmental disorder	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Nightmare	0	0	0	1	1	0	0
	Panic attack	0	0	1	1	1	0	0
	Panic reaction	0	0	2	2	2	0	0
	Personality change	0	1	6	17	18	0	0
	Personality disorder	0	0	0	1	1	0	0
	Phobia	0	0	2	2	2	0	0
	Phonological disorder	0	1	0	0	1	0	0
	Psychomotor retardation	0	1	9	15	16	0	0
	Psychotic disorder	0	1	0	0	1	0	0
	Regressive behaviour	0	0	2	3	3	0	0
	Restlessness	0	11	343	706	717	0	0
	Screaming	0	12	130	210	222	0	0
	Self injurious behaviour	1	1	0	0	1	0	0
	Sleep disorder	2	4	66	148	152	0	0
	Sleep terror	0	0	2	2	2	0	0
	Social avoidant behaviour	0	0	7	15	15	0	0
	Sopor	0	0	3	6	6	0	0
	Staring	2	7	80	177	184	0	0
	Stereotypy	0	1	3	4	5	0	0
	Stress	0	0	2	2	2	0	0
	Tearfulness	1	1	7	17	18	0	0
	Tension	0	0	3	6	6	0	0
	Tic	0	0	0	1	1	0	0
	Trance	0	0	0	1	1	0	0
Subtotal		**46**	**130**	**2503**	**4058**	**4188**	**0**	**0**
Nervous system disorders	Acute disseminated encephalomyelitis	1	4	0	0	4	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Akathisia	0	0	3	5	5	0	0
	Akinesia	0	0	0	1	1	0	0
	Altered state of consciousness	11	26	0	1	27	0	0
	Aphasia	2	5	4	4	9	0	0
	Aphonia	0	0	4	4	4	0	0
	Apraxia	0	0	1	1	1	0	0
	Areflexia	0	1	1	9	10	0	0
	Ataxia	2	4	8	13	17	0	0
	Athetosis	0	0	0	1	1	0	0
	Atonic seizures	2	8	2	2	10	0	0
	Atypical benign partial epilepsy	0	0	1	1	1	0	0
	Aura	0	0	1	1	1	0	0
	Autism	16	21	0	0	21	0	0
	Autonomic nervous system imbalance	0	0	1	3	3	0	0
	Balance disorder	0	3	4	16	19	0	0
	Blood brain barrier defect	0	1	0	0	1	0	0
	Bradykinesia	0	0	0	1	1	0	0
	Brain hypoxia	0	3	0	0	3	0	0
	Brain injury	2	7	0	0	7	0	0
	Brain oedema	4	15	0	0	15	0	0
	Brain stem thrombosis	0	1	0	0	1	0	0
	Burning sensation	0	0	0	2	2	0	0
	Cataplexy	1	2	0	0	2	0	0
	Central nervous system haemorrhage	0	0	1	1	1	0	0
	Central nervous system	0	0	0	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	inflammation							
	Central nervous system necrosis	0	1	0	0	1	0	0
	Cerebellar ataxia	0	0	1	3	3	0	0
	Cerebellar syndrome	1	1	0	0	1	0	0
	Cerebral atrophy	5	10	0	1	11	0	0
	Cerebral cyst	1	1	0	0	1	0	0
	Cerebral disorder	0	1	1	7	8	0	0
	Cerebral haematoma	1	1	0	0	1	0	0
	Cerebral haemorrhage	3	8	0	0	8	0	0
	Cerebral infarction	1	2	0	0	2	0	0
	Cerebral ischaemia	2	2	0	0	2	0	0
	Cerebral ventricle dilatation	0	1	0	0	1	0	0
	Cerebrovascular accident	0	1	0	0	1	0	0
	Cerebrovascular disorder	0	1	1	1	2	0	0
	Cholinergic syndrome	0	0	0	2	2	0	0
	Choreoathetosis	0	0	0	2	2	0	0
	Circadian rhythm sleep disorder	0	0	3	7	7	0	0
	Clonic convulsion	4	13	0	0	13	0	0
	Clonus	3	4	13	36	40	0	0
	Cognitive disorder	2	2	3	5	7	0	0
	Coma	3	10	0	0	10	0	0
	Complex partial seizures	0	3	0	0	3	0	0
	Convulsion	175	521	0	2	523	4	4
	Convulsions local	3	4	0	0	4	0	0
	Coordination abnormal	1	3	4	12	15	0	0
	Decorticate posture	1	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Demyelinating polyneuropathy	0	1	0	0	1	0	0
	Demyelination	0	4	0	0	4	0	0
	Depressed level of consciousness	55	169	0	1	170	0	0
	Developmental coordination disorder	1	1	0	0	1	0	0
	Diplegia	2	2	0	0	2	0	0
	Disturbance in attention	0	0	5	12	12	0	0
	Dizziness	0	1	10	15	16	0	0
	Drooling	0	0	11	22	22	0	0
	Drop attacks	0	0	1	1	1	0	0
	Dysaesthesia	0	0	0	1	1	0	0
	Dysarthria	0	0	0	1	1	0	0
	Dyskinesia	2	8	53	105	113	0	0
	Dysstasia	0	0	4	11	11	0	0
	Dystonia	1	3	3	5	8	0	0
	Early infantile epileptic encephalopathy with burst-suppression	1	1	0	0	1	0	0
	Encephalitis haemorrhagic	0	1	0	0	1	0	0
	Encephalitis post immunisation	1	1	0	0	1	0	0
	Encephalopathy	26	40	0	0	40	0	0
	Epilepsy	37	103	0	0	103	1	1
	Extensor plantar response	0	0	1	1	1	0	0
	Extrapyramidal disorder	0	3	3	3	6	0	0
	Facial paresis	0	10	1	1	11	0	0
	Facial spasm	0	1	0	3	4	0	0
	Febrile convulsion	212	514	1	2	516	1	1

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Fontanelle bulging	6	10	20	29	39	0	0
	Fontanelle depressed	0	0	4	6	6	0	0
	Generalised tonic-clonic seizure	35	117	0	0	117	0	0
	Grimacing	0	0	4	6	6	0	0
	Gross motor delay	1	1	0	0	1	0	0
	Guillain-Barre syndrome	2	7	0	0	7	0	0
	Haemorrhage intracranial	3	3	0	0	3	0	0
	Hand-eye coordination impaired	0	0	2	2	2	0	0
	Head titubation	2	2	6	15	17	0	0
	Headache	0	0	24	32	32	0	0
	Hemiparesis	2	10	0	0	10	0	0
	Hemiplegia	2	6	0	0	6	0	0
	Hydrocephalus	1	6	0	0	6	0	0
	Hyperaesthesia	0	3	6	45	48	0	0
	Hyperkinesia	0	0	2	3	3	0	0
	Hyperreflexia	0	0	2	5	5	0	0
	Hypersomnia	0	4	35	56	60	0	0
	Hypertonia	0	9	55	124	133	0	0
	Hypoaesthesia	0	0	6	13	13	0	0
	Hypokinesia	2	6	16	51	57	0	0
	Hyporeflexia	1	2	4	8	10	0	0
	Hyporesponsive to stimuli	39	40	58	60	100	0	0
	Hypotonia	20	77	319	870	947	0	0
	Hypotonic-hyporesponsive episode	54	145	167	336	481	0	1
	Hypoxic-ischaemic encephalopathy	0	4	0	0	4	0	0
	IIIrd nerve disorder	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Inability to crawl	0	0	3	4	4	0	0
	Infantile spasms	33	56	0	40	96	0	0
	Intracranial pressure increased	3	7	0	0	7	0	0
	Juvenile myoclonic epilepsy	2	5	0	0	5	0	0
	Language disorder	0	0	1	1	1	0	0
	Lennox-Gastaut syndrome	2	2	0	0	2	0	0
	Lethargy	3	6	19	40	46	0	0
	Leukoencephalopathy	1	3	0	0	3	0	0
	Loss of consciousness	146	312	0	0	312	0	0
	Masked facies	0	0	0	2	2	0	0
	Memory impairment	0	0	1	2	2	0	0
	Meningeal disorder	0	0	1	1	1	0	0
	Meningism	2	4	5	9	13	0	0
	Mental impairment	9	9	0	8	17	0	0
	Mental retardation	4	4	3	9	13	0	0
	Monoparesis	0	5	0	0	5	0	0
	Monoplegia	0	5	0	0	5	0	0
	Motor developmental delay	1	2	5	10	12	0	0
	Motor dysfunction	1	2	9	26	28	0	0
	Movement disorder	0	1	10	35	36	0	0
	Multiple sclerosis	1	1	0	0	1	0	0
	Muscle contractions involuntary	1	2	2	8	10	0	0
	Muscle spasticity	0	0	2	5	5	0	0
	Muscle tone disorder	0	0	2	2	2	0	0
	Myelitis transverse	1	2	0	0	2	0	0
	Myoclonic epilepsy	3	7	0	0	7	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Myoclonus	3	9	45	84	93	0	0
	Nerve degeneration	0	0	0	1	1	0	0
	Nervous system disorder	1	4	8	19	23	0	0
	Neurodegenerative disorder	0	0	1	2	2	0	0
	Neurological decompensation	0	0	0	1	1	0	0
	Neurological symptom	1	2	3	4	6	0	0
	Neuromyopathy	1	1	0	1	2	0	0
	Neuropathy peripheral	0	0	0	2	2	0	0
	Neurotoxicity	0	1	0	0	1	0	0
	Nystagmus	2	5	13	28	33	0	0
	Opisthotonus	20	21	7	31	52	0	0
	Paraesthesia	0	0	2	2	2	0	0
	Paralysis	4	7	0	0	7	0	0
	Paralysis flaccid	3	5	0	0	5	0	0
	Paraparesis	1	1	0	0	1	0	0
	Paraplegia	0	1	0	0	1	0	0
	Paresis	0	4	2	2	6	0	0
	Paresis cranial nerve	0	1	0	0	1	0	0
	Partial seizures	12	38	0	1	39	0	0
	Partial seizures with secondary generalisation	3	3	0	0	3	0	0
	Periventricular leukomalacia	0	2	0	0	2	0	0
	Petit mal epilepsy	12	26	0	1	27	0	0
	Pleocytosis	0	0	1	2	2	0	0
	Polyneuropathy	2	2	0	0	2	0	0
	Poor quality sleep	0	0	20	30	30	0	0
	Poor sucking reflex	0	0	0	3	3	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Post-traumatic epilepsy	0	1	0	0	1	0	0
	Postictal paralysis	0	1	0	0	1	0	0
	Postictal state	0	0	7	8	8	0	0
	Presyncope	9	32	23	28	60	0	0
	Profound mental retardation	1	1	0	0	1	0	0
	Psychomotor hyperactivity	0	0	9	22	22	0	0
	Psychomotor skills impaired	4	5	10	21	26	0	0
	Quadriparesis	3	7	0	0	7	0	0
	Quadriplegia	1	1	0	0	1	0	0
	Radiculitis	0	0	0	1	1	0	0
	Radiculitis brachial	0	0	0	2	2	0	0
	Reflexes abnormal	0	0	0	1	1	0	0
	Sedation	0	0	2	2	2	0	0
	Seizure anoxic	0	1	0	0	1	0	0
	Seizure like phenomena	3	6	0	0	6	0	0
	Sensorimotor disorder	0	0	0	1	1	0	0
	Sensory disturbance	0	0	2	2	2	0	0
	Sensory loss	0	0	0	1	1	0	0
	Severe mental retardation	1	1	0	0	1	0	0
	Simple partial seizures	2	2	0	0	2	0	0
	Sleep phase rhythm disturbance	0	0	3	4	4	0	0
	Slow response to stimuli	15	127	103	107	234	0	0
	Somnolence	8	21	640	924	945	0	0
	Somnolence neonatal	0	0	2	2	2	0	0
	Spastic diplegia	1	1	0	0	1	0	0
	Speech disorder	1	1	13	18	19	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Speech disorder developmental	1	2	9	13	15	0	0
	Spinal cord compression	0	0	0	1	1	0	0
	Status epilepticus	10	24	0	0	24	0	0
	Stupor	1	3	3	14	17	0	0
	Subarachnoid haemorrhage	0	3	0	0	3	0	0
	Subdural effusion	0	0	0	3	3	0	0
	Subdural hygroma	0	1	2	4	5	0	0
	Syncope	18	59	29	29	88	0	0
	Tardive dyskinesia	0	0	1	2	2	0	0
	Tethered cord syndrome	0	1	0	0	1	0	0
	Thalamus haemorrhage	0	1	0	0	1	0	0
	Tongue paralysis	1	2	0	0	2	0	0
	Tonic clonic movements	7	8	3	9	17	0	0
	Tonic convulsion	9	21	0	0	21	1	1
	Toxic encephalopathy	1	1	0	0	1	0	0
	Tremor	6	16	66	148	164	0	0
	Unresponsive to stimuli	66	104	0	13	117	0	0
	VIIth nerve paralysis	5	8	0	0	8	0	0
	VIth nerve paralysis	1	5	0	0	5	0	0
	Vasculitis cerebral	0	1	0	0	1	0	0
	Visual field defect	0	0	0	1	1	0	0
	White matter lesion	0	1	0	0	1	0	0
Subtotal		**1208**	**3044**	**1973**	**3788**	**6832**	**7**	**8**
Eye disorders	Anisometropia	0	0	0	1	1	0	0
	Asthenopia	0	0	0	1	1	0	0
	Astigmatism	0	0	3	4	4	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Binocular eye movement disorder	0	0	0	2	2	0	0
	Blepharospasm	0	0	2	6	6	0	0
	Blindness cortical	2	2	0	0	2	0	0
	Cataract	0	0	1	1	1	0	0
	Conjunctival haemorrhage	2	2	0	4	6	0	0
	Conjunctival hyperaemia	0	0	3	9	9	0	0
	Conjunctival irritation	0	0	1	1	1	0	0
	Conjunctival oedema	0	0	1	1	1	0	0
	Conjunctival vascular disorder	0	1	0	0	1	0	0
	Corneal bleeding	0	1	0	0	1	0	0
	Corneal leukoma	1	1	0	0	1	0	0
	Dark circles under eyes	0	0	2	2	2	0	0
	Diplopia	0	0	0	1	1	0	0
	Erythema of eyelid	0	0	5	11	11	0	0
	Excessive eye blinking	0	0	2	3	3	0	0
	Exophthalmos	1	1	0	0	1	0	0
	Eye discharge	0	0	2	5	5	0	0
	Eye disorder	1	2	14	40	42	0	0
	Eye haemorrhage	1	1	0	0	1	0	0
	Eye inflammation	0	0	0	1	1	0	0
	Eye irritation	0	0	1	1	1	0	0
	Eye movement disorder	2	11	62	156	167	0	0
	Eye oedema	0	0	0	3	3	0	0
	Eye pain	0	0	0	1	1	0	0
	Eye pruritus	1	1	0	4	5	0	0
	Eye swelling	0	0	12	19	19	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Eyelid disorder	0	0	5	12	12	0	0
	Eyelid function disorder	0	0	1	2	2	0	0
	Eyelid oedema	5	9	21	49	58	0	0
	Eyelid ptosis	0	0	7	12	12	0	0
	Eyelids pruritus	0	0	1	1	1	0	0
	Gaze palsy	73	141	0	0	141	0	0
	Heterophoria	0	0	1	1	1	0	0
	Hypermetropia	0	0	1	3	3	0	0
	Lacrimation decreased	0	0	1	1	1	0	0
	Lacrimation increased	0	0	6	15	15	0	0
	Lagophthalmos	0	0	1	1	1	0	0
	Lid sulcus deepened	0	0	1	1	1	0	0
	Miosis	0	0	2	2	2	0	0
	Mydriasis	1	1	5	7	8	0	0
	Noninfective conjunctivitis	0	0	1	1	1	0	0
	Ocular discomfort	0	0	0	1	1	0	0
	Ocular hyperaemia	0	0	10	15	15	0	0
	Ocular icterus	0	0	1	1	1	0	0
	Oculogyric crisis	3	6	0	0	6	0	0
	Ophthalmoplegia	0	3	0	0	3	0	0
	Opsoclonus myoclonus	0	0	0	2	2	0	0
	Optic nerve sheath haemorrhage	1	1	0	0	1	0	0
	Orbital oedema	0	0	0	1	1	0	0
	Parinaud syndrome	2	2	0	0	2	0	0
	Periorbital oedema	0	0	1	7	7	0	0
	Photophobia	0	0	3	7	7	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Pupil fixed	0	0	1	2	2	0	0
	Pupillary reflex impaired	0	0	2	3	3	0	0
	Pupils unequal	1	1	2	5	6	0	0
	Retinal haemorrhage	4	8	0	0	8	0	0
	Saccadic eye movement	0	0	0	1	1	0	0
	Scleral disorder	0	0	2	2	2	0	0
	Strabismus	1	3	17	45	48	0	0
	Uveitis	1	1	0	0	1	0	0
	Vision blurred	0	0	0	2	2	0	0
	Visual acuity reduced	1	1	0	1	2	0	0
	Visual impairment	0	1	4	8	9	0	0
Subtotal		**104**	**201**	**208**	**488**	**689**	**0**	**0**
Ear and labyrinth disorders	Auricular swelling	0	0	1	2	2	0	0
	Cerumen impaction	0	0	0	1	1	0	0
	Deafness	3	5	0	0	5	0	0
	Deafness neurosensory	0	1	0	0	1	0	0
	Deafness transitory	1	1	0	0	1	0	0
	Ear disorder	0	0	2	2	2	0	0
	Ear pain	1	2	2	5	7	0	0
	Ear swelling	0	1	2	8	9	0	0
	Hearing impaired	0	0	2	2	2	0	0
	Hyperacusis	0	0	2	3	3	0	0
	Neurosensory hypoacusis	0	0	1	1	1	0	0
	Otorrhoea	0	0	1	3	3	0	0
	Tympanic membrane disorder	0	0	1	3	3	0	0
	Tympanic membrane hyperaemia	1	2	4	11	13	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Tympanic membrane perforation	0	0	0	2	2	0	0
	Vertigo	0	1	2	2	3	0	0
Subtotal		**6**	**13**	**20**	**45**	**58**	**0**	**0**
Cardiac disorders	Aortic valve incompetence	0	1	0	0	1	0	0
	Arrhythmia	1	2	2	6	8	0	0
	Arteritis coronary	0	2	0	0	2	0	0
	Atrial septal defect acquired	0	0	0	1	1	0	0
	Atrial tachycardia	1	2	0	0	2	0	0
	Atrioventricular block	0	1	0	0	1	0	0
	Bradycardia	9	12	16	58	70	0	0
	Bradycardia neonatal	2	2	0	0	2	0	0
	Bundle branch block right	1	1	0	0	1	0	0
	Cardiac aneurysm	1	1	0	0	1	0	0
	Cardiac arrest	11	23	0	0	23	0	0
	Cardiac failure	7	13	0	0	13	0	0
	Cardiac failure acute	0	1	0	0	1	0	0
	Cardio-respiratory arrest	3	8	0	0	8	0	0
	Cardiogenic shock	1	2	0	0	2	0	0
	Cardiomegaly	0	0	4	6	6	0	0
	Cardiomyopathy	0	1	0	0	1	0	0
	Cardiopulmonary failure	3	7	0	0	7	0	0
	Cardiovascular disorder	1	4	3	15	19	0	0
	Cardiovascular insufficiency	2	4	0	0	4	0	0
	Carditis	1	1	0	0	1	0	0
	Congestive cardiomyopathy	5	8	0	0	8	0	0
	Coronary artery aneurysm	2	3	0	0	3	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Coronary artery dilatation	0	0	0	2	2	0	0
	Coronary artery disease	0	0	0	1	1	0	0
	Cyanosis	69	304	99	160	464	0	1
	Dilatation ventricular	0	0	1	1	1	0	0
	Endocardial fibrosis	1	1	0	1	2	0	0
	Extrasystoles	0	1	0	0	1	0	0
	Left ventricular dysfunction	0	0	1	1	1	0	0
	Left ventricular failure	2	2	0	0	2	0	0
	Left ventricular hypertrophy	0	0	1	1	1	0	0
	Mitral valve disease	0	0	0	2	2	0	0
	Mitral valve incompetence	0	1	0	0	1	0	0
	Myocardial infarction	1	2	0	0	2	0	0
	Myocardial ischaemia	1	1	0	0	1	0	0
	Myocardial necrosis	0	2	0	0	2	0	0
	Myocarditis	2	5	0	0	5	0	0
	Pericardial effusion	1	6	0	0	6	0	0
	Pericarditis	0	1	0	0	1	0	0
	Pulmonary valve stenosis	0	1	0	0	1	0	0
	Right ventricular failure	1	1	0	0	1	0	0
	Right ventricular hypertrophy	0	0	1	1	1	0	0
	Sinus arrhythmia	0	0	0	1	1	0	0
	Sinus bradycardia	0	1	0	0	1	0	0
	Sinus tachycardia	0	0	2	3	3	0	0
	Supravalvular aortic stenosis	0	0	0	1	1	0	0
	Supraventricular tachycardia	1	2	0	0	2	0	0
	Systolic dysfunction	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Tachyarrhythmia	1	1	0	0	1	0	0
	Tachycardia	5	9	24	61	70	0	0
	Tachycardia paroxysmal	0	0	1	1	1	0	0
	Ventricular asystole	0	1	0	0	1	0	0
	Ventricular dysfunction	0	0	1	1	1	0	0
	Ventricular flutter	0	1	0	0	1	0	0
	Ventricular hypertrophy	0	0	1	1	1	0	0
	Ventricular tachycardia	0	1	0	0	1	0	0
	Wolff-Parkinson-White syndrome	0	2	0	0	2	0	0
Subtotal		**136**	**445**	**158**	**326**	**771**	**0**	**1**
Vascular disorders	Aneurysm	1	2	0	0	2	0	0
	Angiopathy	0	1	2	2	3	0	0
	Bloody discharge	0	0	1	1	1	0	0
	Capillary disorder	0	0	0	1	1	0	0
	Circulatory collapse	19	56	0	0	56	0	0
	Embolism	0	1	0	0	1	0	0
	Extravasation blood	0	0	0	1	1	0	0
	Flushing	0	3	15	34	37	0	0
	Haematoma	1	7	16	57	64	0	0
	Haemorrhage	1	8	0	0	8	0	0
	Haemorrhagic vasculitis	1	1	0	0	1	0	0
	Hot flush	0	0	0	1	1	0	0
	Hyperaemia	2	5	26	75	80	0	0
	Hypertension	0	0	2	9	9	0	0
	Hypertensive crisis	1	1	0	0	1	0	0
	Hypotension	1	3	12	25	28	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Hypovolaemic shock	1	2	0	0	2	0	0
	Intermittent claudication	0	0	1	1	1	0	0
	Ischaemia	0	1	0	0	1	0	0
	Jugular vein thrombosis	0	1	0	0	1	0	0
	Kawasaki's disease	16	25	3	15	40	1	1
	Lymphoedema	0	1	3	6	7	0	0
	Pallor	13	37	335	857	894	0	0
	Peripheral circulatory failure	0	1	0	0	1	0	0
	Peripheral coldness	0	0	14	35	35	0	0
	Peripheral vascular disorder	1	1	2	3	4	0	0
	Phlebitis	0	0	1	1	1	0	0
	Poor peripheral circulation	1	2	1	1	3	0	0
	Shock	10	21	0	0	21	0	0
	Thrombosis	0	2	0	0	2	0	0
	Vasculitis	9	32	1	1	33	0	0
	Vasodilatation	0	0	0	7	7	0	0
	Vasospasm	0	0	0	2	2	0	0
Subtotal		**78**	**214**	**435**	**1135**	**1349**	**1**	**1**
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	0	1	0	0	1	0	0
	Acute respiratory failure	2	4	0	0	4	0	0
	Adenoidal hypertrophy	0	0	1	1	1	0	0
	Allergic bronchitis	0	0	0	1	1	0	0
	Anoxia	1	1	0	0	1	0	0
	Apnoea	83	214	0	1	215	0	1
	Apnoea neonatal	6	7	0	0	7	0	0
	Apnoeic attack	15	20	5	14	34	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Apparent life threatening event	22	54	0	1	55	0	1
	Asphyxia	6	11	0	2	13	0	0
	Aspiration	6	9	1	10	19	0	0
	Asthma	4	11	8	11	22	0	0
	Atelectasis	1	3	0	1	4	0	0
	Bradypnoea	0	0	1	3	3	0	0
	Bronchial hyperreactivity	0	0	1	2	2	0	1
	Bronchial obstruction	0	0	0	1	1	0	0
	Bronchitis chronic	0	0	0	4	4	0	0
	Bronchospasm	0	4	6	18	22	0	0
	Catarrh	0	0	2	4	4	0	0
	Choking	9	16	0	0	16	0	0
	Choking sensation	1	1	0	3	4	0	0
	Cough	4	10	193	344	354	0	1
	Cyanosis central	1	1	0	2	3	0	0
	Dry throat	0	0	0	1	1	0	0
	Dysphonia	0	0	7	19	19	0	0
	Dyspnoea	10	18	82	161	179	0	0
	Emphysema	0	0	0	3	3	0	0
	Epistaxis	0	0	5	11	11	0	0
	Grunting	0	0	8	9	9	0	0
	Haemoptysis	0	0	1	1	1	0	0
	Haemothorax	0	0	0	1	1	0	0
	Hiccups	0	1	0	1	2	0	0
	Hyperventilation	0	1	1	1	2	0	0
	Hypopnoea	0	0	3	8	8	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Hypoventilation	0	3	0	1	4	0	0
	Hypoxia	4	8	0	0	8	0	0
	Increased bronchial secretion	0	0	0	1	1	0	0
	Increased upper airway secretion	0	0	0	2	2	0	0
	Increased viscosity of bronchial secretion	0	0	1	1	1	0	0
	Interstitial lung disease	0	3	0	0	3	0	0
	Kussmaul respiration	0	1	0	0	1	0	0
	Laryngeal oedema	1	2	0	0	2	0	0
	Laryngospasm	0	1	3	7	8	0	0
	Lower respiratory tract inflammation	0	0	1	1	1	0	0
	Lung disorder	0	0	0	1	1	0	0
	Lung infiltration	0	0	0	1	1	0	0
	Nasal congestion	0	0	7	11	11	0	0
	Nasal obstruction	0	0	1	3	3	0	0
	Obstructive airways disorder	2	4	3	5	9	0	0
	Oropharyngeal pain	0	0	3	8	8	0	0
	Painful respiration	0	0	1	1	1	0	0
	Pharyngeal disorder	0	0	0	3	3	0	0
	Pharyngeal erythema	0	2	18	56	58	0	0
	Pharyngeal exudate	0	0	1	1	1	0	0
	Pharyngeal inflammation	0	0	0	1	1	0	0
	Pharyngeal oedema	0	0	0	1	1	0	0
	Pleural effusion	0	2	0	0	2	0	0
	Pneumonia aspiration	0	7	0	0	7	0	0
	Pneumonitis	0	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Pneumothorax	1	1	0	0	1	0	0
	Productive cough	0	1	13	23	24	0	0
	Prolonged expiration	0	0	1	1	1	0	0
	Pulmonary embolism	0	1	0	0	1	0	0
	Pulmonary haemorrhage	1	1	0	0	1	0	0
	Pulmonary hypertension	0	1	0	0	1	0	0
	Pulmonary oedema	1	5	0	0	5	0	1
	Rales	0	2	6	7	9	0	0
	Reflux laryngitis	0	0	1	1	1	0	0
	Respiration abnormal	2	4	15	49	53	0	0
	Respiratory acidosis	0	0	1	2	2	0	0
	Respiratory alkalosis	0	0	0	1	1	0	0
	Respiratory arrest	32	68	0	0	68	0	0
	Respiratory depression	1	2	0	0	2	0	0
	Respiratory disorder	2	4	13	41	45	0	0
	Respiratory distress	9	13	0	0	13	0	0
	Respiratory failure	5	13	0	0	13	0	0
	Respiratory tract congestion	0	0	1	2	2	0	0
	Respiratory tract inflammation	0	2	2	5	7	0	0
	Rhinitis allergic	0	1	0	1	2	0	0
	Rhinorrhoea	0	1	13	26	27	0	0
	Rhonchi	0	0	3	3	3	0	0
	Sleep apnoea syndrome	0	1	5	7	8	0	0
	Sneezing	0	0	0	2	2	0	0
	Snoring	0	0	1	3	3	0	0
	Sputum increased	0	0	0	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Stridor	4	12	4	4	16	0	0
	Suffocation feeling	0	1	0	1	2	0	0
	Tachypnoea	0	4	16	32	36	0	0
	Throat irritation	1	1	0	0	1	0	0
	Tonsillar disorder	0	0	1	2	2	0	0
	Tonsillar hypertrophy	0	0	3	6	6	0	0
	Tonsillar ulcer	0	0	1	1	1	0	0
	Upper respiratory tract congestion	0	0	0	1	1	0	0
	Upper respiratory tract inflammation	0	1	3	5	6	0	0
	Use of accessory respiratory muscles	0	0	0	2	2	0	0
	Wheezing	1	1	10	16	17	0	0
	Yawning	0	0	0	1	1	0	0
Subtotal		**238**	**562**	**477**	**990**	**1552**	**0**	**5**
Gastrointestinal disorders	Abdominal discomfort	0	0	4	7	7	0	0
	Abdominal distension	0	2	21	36	38	0	0
	Abdominal mass	0	0	1	1	1	0	0
	Abdominal pain	4	5	102	132	137	0	0
	Abdominal pain upper	0	0	6	7	7	0	0
	Abdominal rigidity	2	2	0	1	3	0	0
	Abnormal faeces	0	0	12	32	32	0	0
	Acetonaemic vomiting	0	0	0	1	1	0	0
	Acute abdomen	0	1	0	0	1	0	0
	Anal fistula	0	0	0	1	1	0	0
	Anal sphincter atony	0	0	1	1	1	0	0
	Aphagia	1	1	0	1	2	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Aphthous stomatitis	1	3	1	6	9	0	0
	Ascites	1	6	0	0	6	0	0
	Change of bowel habit	0	0	2	2	2	0	0
	Chapped lips	0	0	1	5	5	0	0
	Cheilitis	0	0	4	11	11	0	0
	Coeliac disease	1	1	3	3	4	0	0
	Colitis	0	4	1	1	5	0	0
	Constipation	0	2	44	53	55	0	0
	Crohn's disease	1	1	0	0	1	0	0
	Diarrhoea	12	21	327	558	579	1	3
	Diarrhoea haemorrhagic	9	21	0	1	22	0	0
	Duodenitis	0	0	0	2	2	0	0
	Dysbacteriosis	0	0	0	1	1	0	0
	Dyskinesia oesophageal	0	0	0	1	1	0	0
	Dyspepsia	0	0	3	6	6	0	0
	Dysphagia	2	3	11	20	23	0	0
	Enteritis	2	11	7	9	20	0	0
	Enterocolitis	1	2	0	0	2	0	0
	Enterocolitis haemorrhagic	1	1	0	0	1	0	0
	Eosinophilic colitis	0	1	0	0	1	0	0
	Eructation	0	0	2	2	2	0	0
	Faecal incontinence	0	1	1	2	3	0	0
	Faeces discoloured	2	4	22	38	42	0	0
	Faeces hard	0	0	1	1	1	0	0
	Faeces pale	0	0	1	2	2	0	0
	Faeces soft	0	0	3	9	9	0	0

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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Flatulence	1	1	18	28	29	0	0
	Frequent bowel movements	0	0	7	10	10	0	0
	Gastric dilatation	0	0	2	2	2	0	0
	Gastric haemorrhage	1	1	0	0	1	0	0
	Gastritis	1	1	0	2	3	0	0
	Gastroenteritis eosinophilic	0	2	0	0	2	0	0
	Gastrointestinal disorder	2	2	11	16	18	0	0
	Gastrointestinal haemorrhage	0	1	0	0	1	0	0
	Gastrointestinal hypermotility	0	0	1	2	2	0	0
	Gastrointestinal hypomotility	0	0	0	1	1	0	0
	Gastrointestinal inflammation	0	0	0	2	2	0	0
	Gastrointestinal motility disorder	0	1	5	5	6	0	0
	Gastrointestinal pain	0	0	6	10	10	0	0
	Gastrointestinal sounds abnormal	0	0	2	3	3	0	0
	Gastrointestinal tract irritation	0	0	0	2	2	0	0
	Gastrooesophageal reflux disease	0	2	13	28	30	0	1
	Gingival bleeding	0	0	0	2	2	0	0
	Glossodynia	0	0	0	1	1	0	0
	Glossoptosis	0	0	1	1	1	0	0
	Haematemesis	6	6	0	0	6	0	0
	Haematochezia	38	46	0	17	63	0	0
	Hyperchlorhydria	0	0	0	1	1	0	0
	Hypertrophy of tongue papillae	0	0	0	1	1	0	0
	Ileus	1	1	0	0	1	0	0
	Ileus paralytic	0	3	0	0	3	0	0
	Infantile colic	0	0	1	1	1	0	0

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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Infantile spitting up	0	0	5	6	6	0	0
	Infrequent bowel movements	0	0	3	4	4	0	0
	Inguinal hernia	0	0	0	2	2	0	0
	Intestinal dilatation	0	0	0	2	2	0	0
	Intestinal haemorrhage	0	1	0	0	1	0	0
	Intestinal mucosal hypertrophy	0	0	1	2	2	0	0
	Intestinal obstruction	2	3	0	0	3	0	0
	Intussusception	18	26	0	0	26	0	0
	Lip discolouration	0	0	3	3	3	0	0
	Lip disorder	0	0	0	2	2	0	0
	Lip dry	0	0	2	3	3	0	0
	Lip haematoma	0	0	0	1	1	0	0
	Lip oedema	0	1	3	8	9	0	0
	Lip swelling	1	1	4	10	11	0	0
	Malabsorption	0	0	1	2	2	0	0
	Melaena	2	4	0	0	4	0	0
	Mouth haemorrhage	0	2	2	7	9	0	0
	Mucous stools	0	0	15	23	23	0	0
	Nausea	0	0	19	33	33	0	0
	Necrotising enterocolitis neonatal	1	1	0	0	1	0	0
	Oesophagitis	0	0	2	4	4	0	0
	Oral discharge	0	0	0	1	1	0	0
	Oral disorder	0	0	1	1	1	0	0
	Oral mucosal blistering	0	0	2	3	3	0	0
	Oral mucosal discolouration	0	0	1	1	1	0	0
	Oral mucosal eruption	0	0	0	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Oral mucosal erythema	0	1	0	0	1	0	0
	Parotid gland enlargement	0	0	1	3	3	0	0
	Peritoneal disorder	0	0	0	1	1	0	0
	Post-tussive vomiting	0	0	2	3	3	0	0
	Proctitis	0	0	1	1	1	0	0
	Protrusion tongue	0	0	6	8	8	0	0
	Rectal discharge	0	0	2	2	2	0	0
	Rectal haemorrhage	1	5	0	0	5	0	0
	Regurgitation	0	0	12	17	17	0	0
	Retching	0	0	5	13	13	0	0
	Saliva altered	0	0	1	1	1	0	0
	Salivary hypersecretion	0	0	26	65	65	0	0
	Sandifer's syndrome	0	0	2	2	2	0	0
	Steatorrhoea	0	0	0	1	1	0	0
	Stomatitis	0	1	2	4	5	0	0
	Stomatitis haemorrhagic	0	1	0	0	1	0	0
	Strawberry tongue	0	0	1	1	1	0	0
	Subileus	0	1	0	0	1	0	0
	Swollen tongue	1	1	4	7	8	0	0
	Teething	0	0	1	1	1	0	0
	Tongue discolouration	0	0	2	3	3	0	0
	Tongue movement disturbance	1	2	0	0	2	0	0
	Tongue oedema	0	0	2	3	3	0	0
	Toothache	0	0	1	1	1	0	0
	Umbilical hernia	0	0	1	2	2	0	0
	Vomiting	11	35	434	860	895	0	1

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Vomiting projectile	0	0	6	12	12	0	0
Subtotal		**128**	**246**	**1224**	**2218**	**2464**	**1**	**5**
Hepatobiliary disorders	Acute hepatic failure	1	2	0	0	2	0	0
	Cholecystitis	0	1	0	0	1	0	0
	Cholelithiasis	0	0	0	1	1	0	0
	Cholestasis	1	2	0	0	2	0	0
	Gallbladder disorder	0	0	0	1	1	0	0
	Hepatic failure	0	2	0	0	2	0	0
	Hepatic function abnormal	0	1	1	3	4	0	0
	Hepatic pain	0	0	1	1	1	0	0
	Hepatic steatosis	0	1	0	0	1	0	0
	Hepatitis	1	1	0	0	1	0	1
	Hepatitis acute	0	1	0	0	1	0	0
	Hepatitis neonatal	0	1	0	0	1	0	0
	Hepatocellular injury	2	2	0	0	2	0	0
	Hepatomegaly	1	1	3	6	7	0	0
	Hepatosplenomegaly	0	0	1	5	5	0	0
	Hepatotoxicity	1	1	0	0	1	0	0
	Hyperbilirubinaemia	1	1	0	0	1	0	0
	Hypertransaminasaemia	0	1	1	1	2	0	0
	Jaundice	1	9	3	3	12	0	0
	Jaundice cholestatic	1	1	0	0	1	0	0
	Liver disorder	0	0	4	8	8	0	0
Subtotal		**10**	**28**	**14**	**29**	**57**	**0**	**1**
Skin and subcutaneous tissue disorders	Acne	0	0	3	6	6	0	0
	Acne infantile	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Acute haemorrhagic oedema of infancy	2	3	1	1	4	0	0
	Alopecia	0	0	2	3	3	0	0
	Angioedema	19	52	0	2	54	0	0
	Blister	1	3	23	54	57	0	0
	Butterfly rash	1	1	0	0	1	0	0
	Chronic pigmented purpura	0	0	0	1	1	0	0
	Circumoral oedema	0	0	0	2	2	0	0
	Cold sweat	1	1	17	27	28	0	0
	Cold urticaria	1	1	1	1	2	0	0
	Cutaneous vasculitis	2	3	1	1	4	0	0
	Decubitus ulcer	0	0	0	1	1	0	0
	Dermal cyst	0	0	0	2	2	0	0
	Dermatitis	1	4	15	46	50	0	0
	Dermatitis acneiform	0	0	1	1	1	0	0
	Dermatitis allergic	2	8	7	31	39	0	0
	Dermatitis atopic	3	7	26	49	56	0	0
	Dermatitis bullous	6	12	0	1	13	0	0
	Dermatitis contact	0	1	0	1	2	0	0
	Dermatitis diaper	0	0	2	11	11	0	0
	Dermatitis exfoliative	0	0	2	4	4	0	0
	Dermatosis	0	0	0	2	2	0	0
	Diffuse cutaneous mastocytosis	0	0	1	1	1	0	0
	Drug eruption	0	2	3	5	7	0	0
	Dry skin	0	0	10	21	21	0	0
	Ecchymosis	0	3	8	24	27	0	0
	Eczema	2	3	56	113	116	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Eczema asteatotic	0	0	0	1	1	0	0
	Eczema nummular	0	0	2	2	2	0	0
	Eczema vesicular	0	0	0	1	1	0	0
	Eczema weeping	0	0	0	1	1	0	0
	Erythema	5	22	315	836	858	0	0
	Erythema annulare	0	0	1	2	2	0	0
	Erythema marginatum	0	0	0	1	1	0	0
	Erythema multiforme	11	26	0	0	26	0	0
	Erythema nodosum	1	2	0	2	4	0	0
	Erythrosis	0	0	0	1	1	0	0
	Exfoliative rash	0	0	1	3	3	0	0
	Generalised erythema	0	1	17	33	34	0	0
	Granuloma skin	0	0	0	2	2	0	0
	Haemorrhage subcutaneous	0	0	0	2	2	0	0
	Hair growth abnormal	0	0	2	3	3	0	0
	Henoch-Schonlein purpura	2	9	0	0	9	0	0
	Hirsutism	0	0	0	1	1	0	0
	Hyperhidrosis	0	4	26	85	89	0	0
	Hyperkeratosis	0	1	0	2	3	0	0
	Hypersensitivity vasculitis	3	5	0	0	5	0	0
	Hypertrichosis	0	0	5	7	7	0	0
	Hypohidrosis	0	0	0	1	1	0	0
	Intertrigo	0	0	0	1	1	0	0
	Keloid scar	0	0	2	3	3	0	0
	Lichen striatus	0	0	0	1	1	0	0
	Lichenification	0	0	0	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Lipoatrophy	1	1	0	0	1	0	0
	Lipodystrophy acquired	0	0	0	1	1	0	0
	Livedo reticularis	4	6	9	17	23	0	0
	Lividity	0	2	9	30	32	0	0
	Lymphomatoid papulosis	0	0	1	1	1	0	0
	Macule	0	0	4	10	10	0	0
	Madarosis	0	0	2	2	2	0	0
	Mechanical urticaria	0	0	0	1	1	0	0
	Melanoderma	0	0	0	1	1	0	0
	Miliaria	0	0	4	5	5	0	0
	Neurodermatitis	5	12	8	49	61	0	0
	Night sweats	0	0	1	1	1	0	0
	Pain of skin	0	0	1	1	1	0	0
	Palmar erythema	0	0	0	4	4	0	0
	Palmar-plantar erythrodysaesthesia syndrome	0	0	1	2	2	0	0
	Panniculitis	1	1	0	0	1	0	0
	Papule	0	1	11	31	32	0	0
	Peau d'orange	0	0	0	1	1	0	0
	Pemphigoid	5	7	0	0	7	0	0
	Petechiae	19	36	104	249	285	0	0
	Photosensitivity reaction	0	0	0	2	2	0	0
	Pigmentation disorder	0	0	1	3	3	0	0
	Piloerection	0	0	1	1	1	0	0
	Pityriasis rosea	0	0	1	3	3	0	0
	Plantar erythema	0	0	0	1	1	0	0
	Post inflammatory pigmentation	0	0	0	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	change							
	Prurigo	0	0	0	8	8	0	0
	Pruritus	3	5	43	121	126	0	0
	Pruritus generalised	0	0	1	2	2	0	0
	Purpura	3	11	15	38	49	0	0
	Purpura fulminans	1	1	0	0	1	0	0
	Rash	11	33	263	698	731	0	0
	Rash erythematous	2	3	27	76	79	0	0
	Rash generalised	3	12	86	124	136	0	0
	Rash macular	4	7	73	151	158	0	0
	Rash maculo-papular	3	11	58	128	139	0	0
	Rash morbilliform	1	3	20	39	42	0	0
	Rash papular	1	3	27	57	60	0	0
	Rash pruritic	1	2	21	39	41	0	0
	Rash rubelliform	0	0	4	6	6	0	0
	Rash scarlatiniform	0	0	1	2	2	0	0
	Rash vesicular	1	2	7	17	19	0	0
	Scab	0	1	2	7	8	0	0
	Seborrhoea	0	0	0	1	1	0	0
	Seborrhoeic dermatitis	0	0	1	6	6	0	0
	Skin depigmentation	0	0	1	7	7	0	0
	Skin discolouration	4	8	115	186	194	0	0
	Skin discomfort	0	0	0	1	1	0	0
	Skin disorder	0	0	4	13	13	0	0
	Skin erosion	0	0	0	1	1	0	0
	Skin exfoliation	0	0	8	22	22	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Skin fissures	0	0	0	1	1	0	0
	Skin haemorrhage	0	1	4	6	7	0	0
	Skin hyperpigmentation	0	0	0	3	3	0	0
	Skin hypertrophy	0	0	2	4	4	0	0
	Skin induration	0	0	1	6	6	0	0
	Skin irritation	0	0	3	5	5	0	0
	Skin lesion	0	1	7	13	14	0	0
	Skin mass	0	0	9	21	21	0	0
	Skin necrosis	1	3	0	0	3	0	0
	Skin odour abnormal	0	0	0	1	1	0	0
	Skin oedema	0	0	1	2	2	0	0
	Skin plaque	1	1	6	9	10	0	0
	Skin reaction	1	1	10	16	17	0	0
	Skin striae	0	0	1	3	3	0	0
	Skin swelling	0	0	6	6	6	0	0
	Skin tightness	0	0	0	1	1	0	0
	Skin ulcer	0	0	1	4	4	0	0
	Skin warm	0	3	24	64	67	0	0
	Skin wrinkling	0	0	1	1	1	0	0
	Spider naevus	0	0	0	1	1	0	0
	Stevens-Johnson syndrome	0	1	0	0	1	1	1
	Swelling face	0	0	22	32	32	0	0
	Systemic lupus erythematosus rash	1	1	2	2	3	0	0
	Toxic skin eruption	0	0	0	2	2	0	0
	Urticaria	25	57	246	682	739	0	0
	Urticaria chronic	1	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Urticaria papular	0	0	2	9	9	0	0
	Urticaria pressure	0	0	0	2	2	0	0
	Vasculitic rash	1	2	1	2	4	0	0
	Vitiligo	0	0	2	2	2	0	0
	Xeroderma	0	0	0	1	1	0	0
	Yellow skin	2	7	1	1	8	0	0
Subtotal		**169**	**421**	**1838**	**4473**	**4894**	**1**	**1**
Musculoskeletal and connective tissue disorders	Arthralgia	1	2	11	21	23	0	0
	Arthritis	2	5	2	9	14	0	0
	Arthropathy	0	0	1	3	3	0	0
	Bone disorder	0	0	0	1	1	0	0
	Bone pain	0	0	0	1	1	0	0
	Delayed fontanelle closure	0	0	1	2	2	0	0
	Diastasis recti abdominis	0	0	1	1	1	0	0
	Facial asymmetry	0	0	0	1	1	0	0
	Fasciitis	0	0	1	1	1	0	0
	Fistula	0	0	2	2	2	0	0
	Floppy infant	0	0	0	1	1	0	0
	Foot deformity	0	0	0	1	1	0	0
	Groin pain	0	0	0	1	1	0	0
	Growth retardation	4	4	2	4	8	0	0
	Haemarthrosis	0	0	0	1	1	0	0
	Head deformity	0	0	1	1	1	0	0
	Hip deformity	0	0	0	1	1	0	0
	Hypermobility syndrome	0	0	1	1	1	0	0
	Hypotonia neonatal	0	2	0	4	6	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Joint contracture	0	1	0	1	2	0	0
	Joint hyperextension	0	1	4	10	11	0	0
	Joint range of motion decreased	0	0	2	4	4	0	0
	Joint stiffness	0	0	1	2	2	0	0
	Joint swelling	2	5	6	16	21	0	0
	Juvenile idiopathic arthritis	1	2	1	1	3	0	0
	Limb asymmetry	0	0	0	1	1	0	0
	Limb deformity	0	1	0	0	1	0	0
	Limb discomfort	0	0	0	4	4	0	0
	Lordosis	0	0	1	2	2	0	0
	Mastication disorder	0	0	2	4	4	0	0
	Mobility decreased	0	1	18	46	47	0	0
	Muscle contracture	0	1	1	6	7	0	0
	Muscle disorder	0	1	2	6	7	0	0
	Muscle haemorrhage	1	1	0	0	1	0	0
	Muscle hypertrophy	0	0	0	2	2	0	0
	Muscle rigidity	0	1	19	32	33	0	0
	Muscle spasms	5	11	38	90	101	0	0
	Muscle swelling	0	0	1	4	4	0	0
	Muscle tightness	1	1	5	6	7	0	0
	Muscle twitching	0	3	26	66	69	0	0
	Muscular weakness	0	0	12	35	35	0	0
	Musculoskeletal discomfort	0	0	2	2	2	0	0
	Musculoskeletal disorder	0	0	1	2	2	0	0
	Musculoskeletal pain	0	0	1	2	2	0	0
	Musculoskeletal stiffness	1	2	49	97	99	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Myalgia	0	1	10	16	17	0	0
	Myofascitis	0	2	1	1	3	0	0
	Myopathy	0	0	0	1	1	0	0
	Myosclerosis	0	1	0	2	3	0	0
	Myositis	1	4	1	4	8	0	0
	Neck pain	0	0	1	1	1	0	0
	Nuchal rigidity	0	0	1	5	5	0	0
	Osteitis	0	1	0	0	1	0	0
	Osteopenia	0	0	1	1	1	0	0
	Osteoporosis	1	1	0	0	1	0	0
	Pain in extremity	0	5	101	211	216	0	0
	Pathological fracture	1	1	0	0	1	0	0
	Polyarthritis	0	1	0	0	1	0	0
	Posture abnormal	0	2	7	19	21	0	0
	Rhabdomyolysis	1	2	0	0	2	0	0
	Rickets	1	1	0	0	1	0	0
	Scoliosis	0	1	0	0	1	0	0
	Soft tissue disorder	0	3	0	0	3	0	0
	Soft tissue haemorrhage	0	1	0	0	1	0	0
	Soft tissue necrosis	0	2	0	0	2	0	0
	Spinal disorder	0	0	2	2	2	0	0
	Spinal pain	0	0	1	1	1	0	0
	Synovial cyst	0	0	0	1	1	0	0
	Synovitis	0	0	2	2	2	0	0
	Toe walking	0	0	2	2	2	0	0
	Torticollis	0	0	1	6	6	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Trismus	0	0	15	18	18	0	0
	Weight bearing difficulty	0	0	1	1	1	0	0
Subtotal		**23**	**74**	**362**	**792**	**866**	**0**	**0**
Renal and urinary disorders	Anuria	2	4	1	1	5	0	0
	Azotaemia	0	0	1	1	1	0	0
	Bladder disorder	0	0	1	1	1	0	0
	Bladder fibrosis	1	1	0	0	1	0	0
	Chromaturia	0	0	1	2	2	0	0
	Dysuria	0	0	1	2	2	0	0
	Enuresis	0	0	3	6	6	0	0
	Glomerulonephritis	1	1	0	0	1	0	0
	Glycosuria	0	0	1	1	1	0	0
	Haematuria	0	0	3	7	7	0	0
	Hydronephrosis	1	1	0	1	2	0	0
	Hypocitraturia	0	0	1	1	1	0	0
	Incontinence	0	1	1	1	2	0	0
	Kidney enlargement	0	0	1	1	1	0	0
	Leukocyturia	0	0	0	1	1	0	0
	Micturition disorder	0	0	2	2	2	0	0
	Nephritic syndrome	0	1	0	0	1	0	0
	Nephritis	1	1	0	0	1	0	0
	Nephrotic syndrome	1	3	0	1	4	0	0
	Oliguria	0	0	3	8	8	0	0
	Polyuria	0	0	2	5	5	0	0
	Proteinuria	0	0	1	2	2	0	0
	Pyelocaliectasis	0	0	0	2	2	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Renal disorder	0	0	1	1	1	0	0
	Renal failure	4	6	0	1	7	0	0
	Renal failure acute	0	3	0	0	3	0	0
	Renal hypertension	0	0	0	1	1	0	0
	Renal impairment	0	1	1	1	2	0	0
	Tubulointerstitial nephritis	2	2	0	0	2	0	0
	Ureteric stenosis	0	0	0	1	1	0	0
	Urinary incontinence	0	0	0	1	1	0	0
	Urinary tract disorder	0	0	0	1	1	0	0
	Urine odour abnormal	0	0	1	1	1	0	0
	Vesicoureteric reflux	0	0	1	1	1	0	0
Subtotal		**13**	**25**	**27**	**55**	**80**	**0**	**0**
Pregnancy, puerperium and perinatal conditions	Live birth	0	0	0	1	1	0	0
	Neonatal disorder	0	0	1	1	1	0	0
	Poor weight gain neonatal	0	0	1	2	2	0	0
Subtotal		**0**	**0**	**2**	**4**	**4**	**0**	**0**
Reproductive system and breast disorders	Acquired phimosis	0	1	0	0	1	0	0
	Balanoposthitis	0	0	0	1	1	0	0
	Genital labial adhesions	0	0	1	1	1	0	0
	Genital rash	0	0	2	2	2	0	0
	Lactation disorder	0	0	0	1	1	0	0
	Oedema genital	0	0	0	3	3	0	0
	Ovarian cyst	0	0	1	1	1	0	0
	Pelvic pain	0	0	0	1	1	0	0
	Perineal erythema	0	0	0	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Scrotal erythema	0	0	0	1	1	0	0
	Scrotal pain	0	0	0	1	1	0	0
	Scrotal swelling	0	0	0	1	1	0	0
	Testicular retraction	0	0	0	1	1	0	0
Subtotal		**0**	**1**	**4**	**15**	**16**	**0**	**0**
Congenital, familial and genetic disorders	Aicardi's syndrome	0	1	0	0	1	0	0
	Alpers' disease	1	1	0	0	1	0	0
	Atrial septal defect	1	6	0	0	6	0	0
	Benign familial neonatal convulsions	0	1	0	0	1	0	0
	Cerebral palsy	4	8	0	0	8	0	0
	Congenital generalised lipodystrophy	1	1	0	0	1	0	0
	Congenital neuropathy	0	1	0	0	1	0	0
	Cytogenetic abnormality	0	1	0	0	1	0	0
	Dysmorphism	0	1	0	0	1	0	0
	Epidermal naevus	0	1	0	0	1	0	0
	Familial mediterranean fever	0	1	0	0	1	0	0
	Glycogen storage disorder	0	1	0	0	1	0	0
	Haemophilia	1	2	0	0	2	0	0
	Heart disease congenital	1	1	0	0	1	0	0
	Hydrocele	0	2	0	2	4	0	0
	Hypertrophic cardiomyopathy	1	2	0	0	2	0	0
	Infantile genetic agranulocytosis	0	2	0	0	2	0	0
	Intestinal malrotation	1	1	0	0	1	0	0
	Krabbe's disease	1	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Leukodystrophy	1	3	0	0	3	0	0
	Lissencephaly	0	1	0	0	1	0	0
	Macrocephaly	1	1	1	1	2	0	0
	Methylmalonic aciduria	1	2	0	0	2	0	0
	Microcephaly	6	9	0	0	9	0	0
	Microencephaly	0	1	0	0	1	0	0
	Mitochondrial encephalomyopathy	0	1	0	0	1	0	0
	Muscular dystrophy	1	1	0	0	1	0	0
	Naevus flammeus	0	0	1	1	1	0	0
	Neuronal ceroid lipofuscinosis	1	1	0	0	1	0	0
	Pachygyria	1	1	0	0	1	0	0
	Phimosis	1	2	0	0	2	0	0
	Plagiocephaly	0	2	4	4	6	0	0
	Polymicrogyria	2	2	1	1	3	0	0
	Pyloric stenosis	0	0	0	1	1	0	0
	Renal hypoplasia	0	1	0	0	1	0	0
	Rett's disorder	0	1	0	0	1	0	0
	Skull malformation	0	0	0	1	1	0	0
	Talipes	0	1	0	0	1	0	0
	Thymus hypoplasia	0	1	0	0	1	0	0
	Tuberous sclerosis	1	3	0	0	3	0	0
	Williams syndrome	1	1	0	0	1	0	0
Subtotal		**29**	**70**	**7**	**11**	**81**	**0**	**0**
General disorders and administration site conditions	Abasia	1	1	4	16	17	0	0
	Abscess sterile	5	27	2	4	31	0	0
	Adverse drug reaction	0	1	0	0	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Adverse event	0	0	12	25	25	0	0
	Adverse reaction	0	0	3	5	5	0	0
	Application site discolouration	0	1	0	0	1	0	0
	Application site erythema	0	0	3	3	3	0	0
	Application site exfoliation	0	0	2	2	2	0	0
	Application site haematoma	1	1	0	0	1	0	0
	Application site induration	0	0	2	2	2	0	0
	Application site oedema	0	0	2	2	2	0	0
	Application site pain	0	0	2	2	2	0	0
	Application site pallor	0	0	0	1	1	0	0
	Application site papules	0	0	1	1	1	0	0
	Application site rash	0	0	0	1	1	0	0
	Application site scar	0	0	1	1	1	0	0
	Asthenia	3	8	53	133	141	0	0
	Atrophy	0	1	1	1	2	0	0
	Axillary pain	0	0	1	1	1	0	0
	Brain death	0	2	0	0	2	0	0
	Chest discomfort	0	0	1	2	2	0	0
	Chest pain	0	0	0	1	1	0	0
	Chills	0	0	29	63	63	0	0
	Condition aggravated	2	5	10	16	21	0	0
	Crepitations	0	0	1	1	1	0	0
	Crying	45	99	1353	2579	2678	0	1
	Cyst	0	1	0	4	5	0	0
	Death	10	29	0	0	29	1	1
	Decreased activity	0	2	15	25	27	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Developmental delay	3	8	34	74	82	0	0
	Device dislocation	0	0	0	2	2	0	0
	Discomfort	0	2	7	17	19	0	0
	Disease recurrence	0	0	0	1	1	0	0
	Drug ineffective	0	0	0	56	56	0	0
	Dysplasia	0	0	1	3	3	0	0
	Effusion	0	0	0	1	1	0	0
	Embolia cutis medicamentosa	1	4	0	0	4	0	0
	Enanthema	0	0	0	2	2	0	0
	Encapsulation reaction	0	0	0	1	1	0	0
	Energy increased	0	0	3	3	3	0	0
	Exercise tolerance decreased	0	0	1	1	1	0	0
	Extensive swelling of vaccinated limb	42	48	476	531	579	0	0
	Extravasation	0	0	1	1	1	0	0
	Face oedema	2	3	12	25	28	0	0
	Facial pain	0	0	1	1	1	0	0
	Fatigue	3	5	88	201	206	0	0
	Feeling abnormal	0	1	6	12	13	0	0
	Feeling cold	0	0	8	14	14	0	0
	Feeling hot	2	3	32	71	74	0	0
	Feeling jittery	0	0	1	1	1	0	0
	Feeling of body temperature change	0	0	1	2	2	0	0
	Feeling of relaxation	0	1	4	8	9	0	0
	Fibrosis	0	0	0	8	8	0	0
	Foaming at mouth	0	0	7	25	25	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Foreign body reaction	0	0	1	6	6	0	0
	Gait deviation	0	0	0	1	1	0	0
	Gait disturbance	0	3	46	115	118	0	0
	General physical health deterioration	0	4	24	85	89	0	0
	General symptom	0	0	0	2	2	0	0
	Generalised oedema	0	0	2	3	3	0	0
	Granuloma	0	0	8	32	32	0	0
	Hunger	0	0	1	1	1	0	0
	Hyperplasia	0	0	0	3	3	0	0
	Hyperpyrexia	209	221	39	167	388	0	0
	Hyperthermia	2	7	15	44	51	0	0
	Hypertrophy	0	0	0	1	1	0	0
	Hypothermia	9	9	1	18	27	0	0
	Ill-defined disorder	1	9	90	205	214	0	0
	Immediate post-injection reaction	0	0	1	1	1	0	0
	Induration	0	3	26	83	86	0	0
	Inflammation	0	2	19	104	106	0	0
	Influenza like illness	1	1	9	10	11	0	0
	Infusion site haemorrhage	0	0	1	1	1	0	0
	Injected limb mobility decreased	2	2	24	53	55	0	0
	Injection site abscess sterile	3	9	9	22	31	0	0
	Injection site atrophy	0	1	0	0	1	0	0
	Injection site bruising	0	0	18	28	28	0	0
	Injection site coldness	0	0	1	1	1	0	0
	Injection site cyst	0	1	7	12	13	0	0
	Injection site dermatitis	0	0	4	5	5	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Injection site discharge	0	0	5	5	5	0	0
	Injection site discolouration	1	1	43	102	103	1	1
	Injection site discomfort	0	0	4	6	6	0	0
	Injection site dryness	0	0	5	5	5	0	0
	Injection site eczema	1	1	10	16	17	0	0
	Injection site erosion	0	0	1	1	1	0	0
	Injection site erythema	21	46	1066	2166	2212	0	0
	Injection site exfoliation	0	0	0	1	1	0	0
	Injection site extravasation	5	9	49	99	108	0	0
	Injection site fibrosis	0	0	2	3	3	0	0
	Injection site granuloma	4	9	41	121	130	0	0
	Injection site haematoma	4	6	30	64	70	0	0
	Injection site haemorrhage	1	4	11	21	25	0	0
	Injection site hypersensitivity	0	1	5	7	8	0	0
	Injection site hypoaesthesia	0	0	0	1	1	0	0
	Injection site induration	7	25	270	725	750	0	0
	Injection site inflammation	13	17	289	401	418	0	0
	Injection site injury	0	0	2	2	2	0	0
	Injection site irritation	0	0	1	11	11	0	0
	Injection site joint movement impairment	0	0	1	1	1	0	0
	Injection site lymphadenopathy	0	0	1	2	2	0	0
	Injection site macule	0	0	0	3	3	0	0
	Injection site mass	3	4	25	90	94	0	0
	Injection site movement impairment	0	0	2	3	3	0	0
	Injection site necrosis	2	8	0	2	10	0	0
	Injection site nodule	6	10	102	179	189	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Injection site oedema	4	14	227	454	468	0	0
	Injection site pain	5	11	662	1012	1023	0	0
	Injection site pallor	0	0	0	5	5	0	0
	Injection site papule	0	0	10	21	21	0	0
	Injection site pruritus	1	1	47	106	107	0	0
	Injection site rash	1	1	54	71	72	0	0
	Injection site reaction	18	50	152	563	613	0	0
	Injection site recall reaction	0	0	2	2	2	0	0
	Injection site scab	0	0	2	4	4	0	0
	Injection site scar	0	0	8	11	11	0	0
	Injection site swelling	2	30	686	1553	1583	0	0
	Injection site urticaria	3	3	17	45	48	0	0
	Injection site vasculitis	2	2	0	0	2	0	0
	Injection site vesicles	2	3	11	33	36	0	0
	Injection site warmth	1	8	176	392	400	0	0
	Injury associated with device	0	0	1	1	1	0	0
	Irritability postvaccinal	1	1	38	39	40	0	0
	Local reaction	1	5	11	92	97	0	0
	Local swelling	0	0	6	32	32	0	0
	Localised oedema	0	0	1	14	14	0	0
	Malaise	8	12	155	244	256	0	0
	Mass	0	0	1	2	2	0	0
	Mucosal discolouration	0	0	1	3	3	0	0
	Mucosal dryness	0	0	0	1	1	0	0
	Mucosal haemorrhage	0	1	0	1	2	0	0
	Mucosal inflammation	0	0	1	2	2	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Mucous membrane disorder	0	0	1	2	2	0	0
	Multi-organ failure	3	10	0	0	10	0	0
	Necrosis	3	6	0	0	6	0	0
	Needle issue	0	0	0	1	1	0	0
	No adverse event	0	1	0	64	65	0	0
	No therapeutic response	0	0	16	37	37	0	0
	Nodule	0	0	4	19	19	0	0
	Nonspecific reaction	0	0	3	8	8	0	0
	Obstruction	0	0	1	1	1	0	0
	Oedema	0	1	15	59	60	0	0
	Oedema peripheral	3	14	55	163	177	0	0
	Pain	1	3	99	263	266	0	0
	Peripheral swelling	4	17	116	322	339	0	0
	Pneumatosis	0	0	0	1	1	0	0
	Product commingling	0	0	1	1	1	0	0
	Product packaging issue	0	0	2	2	2	0	0
	Product quality issue	0	0	52	193	193	0	0
	Product reconstitution issue	0	0	1	1	1	0	0
	Puncture site induration	0	0	1	1	1	0	0
	Puncture site pain	0	0	1	1	1	0	0
	Pyrexia	150	286	4243	8289	8575	1	3
	Sense of oppression	0	0	0	1	1	0	0
	Sluggishness	0	0	1	4	4	0	0
	Soft tissue inflammation	0	0	1	1	1	0	0
	Sudden cardiac death	0	1	0	0	1	0	0
	Sudden death	3	12	0	0	12	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Sudden infant death syndrome	17	86	0	0	86	13	15
	Swelling	1	7	49	151	158	0	0
	Syringe issue	0	0	0	1	1	0	0
	Systemic inflammatory response syndrome	2	4	0	0	4	0	0
	Tenderness	0	1	1	7	8	0	0
	Terminal state	1	1	0	0	1	0	0
	Therapeutic reaction time decreased	0	0	0	1	1	0	0
	Therapeutic response decreased	0	0	11	19	19	0	0
	Thirst	0	0	1	2	2	0	0
	Thirst decreased	0	0	1	3	3	0	0
	Ulcer	0	0	0	1	1	0	0
	Vaccination site abscess sterile	21	22	0	0	22	0	0
	Vaccination site discolouration	0	0	2	2	2	0	0
	Vaccination site discomfort	0	0	1	1	1	0	0
	Vaccination site erythema	2	2	25	28	30	0	0
	Vaccination site eschar	1	1	0	0	1	0	0
	Vaccination site granuloma	0	0	7	12	12	0	0
	Vaccination site haematoma	0	0	2	2	2	0	0
	Vaccination site induration	0	0	26	32	32	0	0
	Vaccination site inflammation	1	1	9	9	10	0	0
	Vaccination site necrosis	1	1	0	0	1	0	0
	Vaccination site nodule	1	1	7	7	8	0	0
	Vaccination site oedema	1	1	4	7	8	0	0
	Vaccination site pain	0	0	22	23	23	0	0
	Vaccination site papule	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Vaccination site pruritus	0	0	4	4	4	0	0
	Vaccination site reaction	3	3	6	7	10	0	0
	Vaccination site swelling	0	0	28	32	32	0	0
	Vaccination site vesicles	0	0	1	1	1	0	0
	Vaccination site warmth	0	0	11	11	11	0	0
Subtotal		**683**	**1290**	**11593**	**23493**	**24783**	**16**	**21**
Investigations	Activated partial thromboplastin time prolonged	0	0	0	1	1	0	0
	Adenovirus test positive	0	0	0	1	1	0	0
	Alanine aminotransferase increased	2	12	0	1	13	0	0
	Allergy test positive	0	0	0	1	1	0	0
	Ammonia increased	0	0	0	2	2	0	0
	Antibody test negative	0	0	1	2	2	0	0
	Anticonvulsant drug level above therapeutic	0	0	0	1	1	0	0
	Aspartate aminotransferase increased	3	12	0	1	13	0	0
	Aspiration tracheal	1	1	0	0	1	0	0
	Autoantibody positive	0	0	0	1	1	0	0
	Bacterial test positive	0	0	0	1	1	0	0
	Bleeding time prolonged	0	1	1	1	2	0	0
	Blood alkaline phosphatase increased	0	0	1	2	2	0	0
	Blood bilirubin increased	1	2	0	0	2	0	0
	Blood creatine phosphokinase increased	0	0	1	2	2	0	0
	Blood elastase increased	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Blood glucose increased	0	0	3	4	4	0	0
	Blood immunoglobulin A decreased	0	0	1	1	1	0	0
	Blood immunoglobulin A increased	0	1	0	0	1	0	0
	Blood immunoglobulin E increased	0	0	0	1	1	0	0
	Blood immunoglobulin M decreased	0	0	1	2	2	0	0
	Blood immunoglobulin M increased	0	1	0	1	2	0	0
	Blood iron decreased	0	0	0	1	1	0	0
	Blood ketone body decreased	0	0	1	1	1	0	0
	Blood lactate dehydrogenase increased	0	0	0	3	3	0	0
	Blood lactic acid increased	0	0	0	2	2	0	0
	Blood osmolarity increased	0	0	0	1	1	0	0
	Blood pH decreased	0	0	0	1	1	0	0
	Blood pressure decreased	0	0	0	2	2	0	0
	Blood pressure immeasurable	0	1	0	0	1	0	0
	Blood prolactin increased	0	0	1	1	1	0	0
	Blood sodium decreased	0	0	1	2	2	0	0
	Blood thromboplastin decreased	0	0	0	1	1	0	0
	Body height below normal	0	0	1	3	3	0	0
	Body mass index decreased	0	0	0	1	1	0	0
	Body temperature	0	0	4	6	6	0	0
	Body temperature decreased	0	0	11	16	16	0	0
	Body temperature fluctuation	0	0	0	1	1	0	0
	Body temperature increased	10	14	131	251	265	0	0
	Bordetella test	0	0	0	1	1	0	0
	Bordetella test negative	0	2	1	5	7	0	0

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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Bordetella test positive	0	0	4	7	7	0	0
	Brain scan abnormal	0	0	1	1	1	0	0
	Brain stem auditory evoked response abnormal	0	0	1	1	1	0	0
	Breath sounds abnormal	0	0	4	7	7	0	0
	C-reactive protein increased	1	6	12	46	52	0	0
	CSF culture positive	1	1	0	0	1	0	0
	Cardiac murmur	0	0	1	10	10	0	0
	Carnitine decreased	0	0	0	1	1	0	0
	Clostridium test	0	0	0	1	1	0	0
	Clostridium test negative	0	0	8	13	13	0	0
	Coma scale	0	0	1	1	1	0	0
	Coombs test positive	0	0	0	1	1	0	0
	Corynebacterium test negative	0	0	3	7	7	0	0
	Cytomegalovirus test positive	0	0	0	1	1	0	0
	Electrocardiogram ST segment elevation	1	1	0	0	1	0	0
	Electroencephalogram abnormal	0	0	1	9	9	0	0
	Electromyogram abnormal	0	0	0	1	1	0	0
	Escherichia test positive	0	0	1	1	1	0	0
	Faecal elastase concentration abnormal	0	0	1	1	1	0	0
	Gamma-glutamyltransferase increased	0	0	1	1	1	0	0
	Gastric emptying study	0	0	0	1	1	0	0
	General physical condition abnormal	0	0	1	1	1	0	0

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		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Glucose urine present	0	0	0	1	1	0	0
	Granulocyte count decreased	0	0	1	1	1	0	0
	Grip strength	0	0	1	1	1	0	0
	Haematocrit decreased	0	1	0	0	1	0	0
	Haemoglobin decreased	0	1	0	4	5	0	0
	Head circumference abnormal	0	0	0	1	1	0	0
	Heart rate decreased	0	1	2	4	5	0	0
	Heart rate increased	0	1	3	13	14	0	0
	Heart sounds abnormal	0	0	1	2	2	0	0
	Hepatic enzyme increased	0	7	1	1	8	0	0
	Hepatitis B antibody abnormal	0	0	1	2	2	0	0
	Hepatitis B antibody negative	0	0	6	14	14	0	0
	Hepatitis B antibody positive	0	0	0	1	1	0	0
	Hepatitis B antigen positive	0	0	0	2	2	0	0
	Hepatitis B surface antibody negative	0	0	22	24	24	0	0
	Hepatitis B surface antigen positive	0	0	0	1	1	0	0
	Immunoglobulins decreased	0	1	1	1	2	0	0
	Immunology test abnormal	0	0	0	1	1	0	0
	Inflammatory marker increased	0	0	0	2	2	0	0
	Influenza virus test negative	0	0	1	1	1	0	0
	Laboratory test abnormal	0	0	0	1	1	0	0
	Liver function test abnormal	0	1	1	1	2	0	0
	Liver palpable subcostal	0	1	0	0	1	0	0
	Lymph node palpable	0	0	0	2	2	0	0
	Lymphocyte count increased	0	0	2	3	3	0	0
	Mycoplasma test positive	0	0	1	2	2	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	N-terminal prohormone brain natriuretic peptide increased	0	0	1	1	1	0	0
	Neurological examination abnormal	0	0	0	1	1	0	0
	Neutrophil count decreased	0	0	0	1	1	0	0
	Neutrophil count increased	0	0	0	1	1	0	0
	Neutrophil toxic granulation present	0	0	0	1	1	0	0
	Otoacoustic emissions test abnormal	0	0	0	1	1	0	0
	Oxygen saturation	0	0	1	1	1	0	0
	Oxygen saturation decreased	2	4	20	57	61	0	0
	Peripheral pulse decreased	0	0	0	1	1	0	0
	Physical examination abnormal	0	0	0	1	1	0	0
	Platelet count abnormal	0	1	0	1	2	0	0
	Platelet count decreased	0	1	2	7	8	0	0
	Platelet count increased	0	0	1	4	4	0	0
	Polymerase chain reaction	0	0	1	1	1	0	0
	Protein total increased	0	0	0	1	1	0	0
	Prothrombin time prolonged	0	0	0	1	1	0	0
	Pulse abnormal	0	0	1	2	2	0	0
	Pulse absent	0	1	0	1	2	0	0
	Pulse pressure increased	0	0	0	1	1	0	0
	Red blood cell burr cells present	0	0	1	1	1	0	0
	Red blood cell count increased	0	0	0	1	1	0	0
	Red blood cell sedimentation rate increased	0	0	0	3	3	0	0
	Reflex test normal	0	0	0	1	1	0	0
	Respiratory rate decreased	0	0	1	4	4	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Respiratory rate increased	0	0	5	9	9	0	0
	Rotavirus test positive	0	0	2	5	5	0	0
	Serum ferritin increased	0	0	0	1	1	0	0
	Shift to the left	0	0	0	1	1	0	0
	Skin test positive	0	0	0	1	1	0	0
	Skin turgor decreased	0	0	2	3	3	0	0
	Sputum abnormal	0	0	1	1	1	0	0
	Staphylococcus test positive	0	0	2	3	3	0	0
	Stool analysis abnormal	0	0	0	1	1	0	0
	Transaminases increased	0	18	6	7	25	0	0
	Urine analysis abnormal	0	0	1	1	1	0	0
	Urine output decreased	0	0	3	5	5	0	0
	Urine output increased	0	0	1	1	1	0	0
	Viral test positive	0	0	2	7	7	0	0
	Weight decreased	2	3	12	28	31	0	1
	White blood cell count decreased	0	0	1	3	3	0	0
	White blood cell count increased	0	2	1	10	12	0	0
	White blood cells urine positive	0	0	0	1	1	0	0
Subtotal		**24**	**99**	**313**	**707**	**806**	**0**	**1**
Injury, poisoning and procedural complications	Accidental exposure to product	0	0	9	20	20	0	0
	Accidental overdose	0	0	27	54	54	0	0
	Adverse event following immunisation	0	0	2	2	2	0	0
	Arthropod bite	0	0	0	2	2	0	0
	Brain herniation	1	1	0	0	1	0	0
	Carbon monoxide poisoning	0	0	0	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Child maltreatment syndrome	2	2	1	3	5	0	0
	Circumstance or information capable of leading to medication error	0	0	1	1	1	0	0
	Concussion	0	1	1	1	2	0	0
	Contusion	1	2	3	17	19	0	0
	Craniocerebral injury	0	1	0	0	1	0	0
	Drug administered at inappropriate site	0	0	0	3	3	0	0
	Drug administered to patient of inappropriate age	0	0	440	612	612	0	0
	Drug administration error	0	0	0	30	30	0	0
	Drug dispensing error	0	0	10	13	13	0	0
	Drug prescribing error	0	0	8	9	9	0	0
	Eschar	0	0	0	1	1	0	0
	Excoriation	0	0	0	1	1	0	0
	Expired product administered	0	1	70	118	119	0	0
	Exposure during pregnancy	0	0	0	2	2	0	0
	Exposure to communicable disease	0	0	0	3	3	0	0
	Extra dose administered	1	1	44	145	146	0	0
	Fall	0	1	13	27	28	0	0
	Forearm fracture	0	1	0	0	1	0	0
	Foreign body	0	0	1	1	1	0	0
	Foreign body in eye	0	0	0	1	1	0	0
	Fracture	0	0	1	1	1	0	0
	Head injury	0	0	2	3	3	0	0
	Inappropriate schedule of drug	0	0	583	893	893	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	administration							
	Incomplete course of vaccination	0	0	19	19	19	0	0
	Incorrect dosage administered	0	0	0	5	5	0	0
	Incorrect dose administered	0	0	1	11	11	0	0
	Incorrect product formulation administered	0	0	1	13	13	0	0
	Incorrect product storage	0	0	141	324	324	0	0
	Incorrect route of drug administration	0	0	68	135	135	0	0
	Injury	1	1	0	1	2	0	0
	Intentional overdose	0	0	1	1	1	0	0
	Intercepted drug dispensing error	0	0	1	1	1	0	0
	Joint dislocation	0	2	0	0	2	0	0
	Labelled drug-disease interaction medication error	0	0	1	1	1	0	0
	Laceration	0	0	0	1	1	0	0
	Limb injury	0	0	1	2	2	0	0
	Medication error	0	1	5	17	18	0	0
	Muscle strain	0	0	5	5	5	0	0
	Overdose	0	1	40	106	107	0	0
	Poisoning	0	1	0	0	1	0	0
	Poor quality drug administered	0	0	1	2	2	0	0
	Post procedural oedema	0	0	1	1	1	0	0
	Post vaccination syndrome	1	1	3	3	4	0	0
	Prescribed overdose	0	0	2	9	9	0	0
	Rib fracture	1	1	0	0	1	0	0
	Scar	0	0	6	21	21	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Scratch	0	0	4	9	9	0	0
	Seroma	0	0	0	1	1	0	0
	Skull fracture	0	1	0	0	1	0	0
	Soft tissue injury	0	0	1	2	2	0	0
	Subdural haematoma	5	7	0	0	7	0	0
	Subdural haemorrhage	1	1	0	0	1	0	0
	Thermal burn	0	0	1	1	1	0	0
	Tongue injury	0	0	1	1	1	0	0
	Toxicity to various agents	0	0	0	1	1	0	0
	Underdose	0	0	33	90	90	0	0
	Vaccination complication	5	16	23	95	111	0	0
	Vaccination error	0	0	0	12	12	0	0
	Vaccination failure	183	290	0	1	291	2	2
	Vascular injury	1	1	0	0	1	0	0
	Wound	0	0	0	2	2	0	0
	Wound secretion	0	0	1	1	1	0	0
	Wrong drug administered	0	0	158	386	386	0	0
	Wrong patient received medication	0	0	1	1	1	0	0
	Wrong technique in drug usage process	1	3	290	593	596	0	0
Subtotal		**204**	**338**	**2026**	**3838**	**4176**	**2**	**2**
Surgical and medical procedures	Abscess drainage	0	0	1	4	4	0	0
	Arm amputation	0	0	0	1	1	0	0
	Colectomy	0	0	0	1	1	0	0
	Debridement	0	0	0	1	1	0	0
	Emergency care	0	0	0	1	1	0	0
	Endotracheal intubation	2	2	0	1	3	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Enteral nutrition	0	0	0	1	1	0	0
	Haemostasis	0	0	0	4	4	0	0
	Hyperthermia therapy	0	0	0	1	1	0	0
	Ileostomy	0	0	0	1	1	0	0
	Injection	0	0	0	2	2	0	0
	Interchange of vaccine products	0	0	2	2	2	0	0
	Light anaesthesia	0	0	0	1	1	0	0
	Limb immobilisation	1	1	1	2	3	0	0
	Macrophage activation	0	0	0	1	1	0	0
	Mechanical ventilation	1	1	0	3	4	0	0
	Neurosurgery	0	0	0	1	1	0	0
	Off label use	0	0	60	90	90	0	0
	Orchidectomy	0	1	0	0	1	0	0
	Oxygen supplementation	1	1	0	2	3	0	0
	Resuscitation	1	1	2	13	14	0	0
	Skin lesion excision	0	0	0	1	1	0	0
	Small intestinal resection	0	0	0	1	1	0	0
	Surgery	0	0	0	3	3	0	0
	Tenotomy	0	0	1	1	1	0	0
Subtotal		**6**	**7**	**67**	**139**	**146**	**0**	**0**
Social circumstances	Bottle feeding	0	0	1	1	1	0	0
	Disability	2	3	0	2	5	0	0
	Immobile	5	5	0	4	9	0	0
	Mentally late developer	0	0	0	1	1	0	0
	Partner stress	0	0	2	2	2	0	0
	Treatment noncompliance	0	0	1	1	1	0	0

Numbers of Adverse Drug Reactions by Term from Post-marketing Sources								
System Organ Class	Preferred Term	Spontaneous Including competent authorities (worldwide) and literature				Total Spontaneous	Non-Interventional Postmarketing Study and reports from other solicited sources	
		Serious		Non-Serious			Serious	
		Interval	Cumulative	Interval	Cumulative	Cumulative all	Interval	Cumulative
	Walking disability	0	0	1	3	3	0	0
Subtotal		**7**	**8**	**5**	**14**	**22**	**0**	**0**
		0	0	0	0	0	0	0
Subtotal		**0**	**0**	**0**	**0**	**0**	**0**	**0**
Grand Total		**3826**	**8758**	**24342**	**49238**	**57996**	**40**	**67**

APPENDIX 3 : TABULAR SUMMARY OF SAFETY SIGNALS

Table 5 Safety Signals, Ongoing or Closed During the Reporting Interval

Infanrix hexa:

Reporting interval: 23 October 2011 to 22 October 2014

Signal Term	Date Detected (Month and Year)	Status (Ongoing or Closed) *	Date Closed (for closed signals)	Source or Trigger for Signal	Reason for Evaluation and Summary of Key Data and Conclusion	Method of Signal Evaluation	Action(s) Taken or Planned
Waning of acellular pertussis vaccine-induced immunity	August 2012	Closed	April 2013	Literature review	US CDC California effectiveness data for DTaP suggests that the immune response to pertussis boosting at pre-school age wanes, and may not be sufficient to maintain adequate protection until the next pertussis booster dose in adolescence. However, the company considered it more appropriate to categorize this signal as important identified risk. Indeed the data that triggered this signal increased the risk's importance, while waning of acellular pertussis vaccine-immunity as such was already an identified risk for acellular pertussis vaccines. See Appendix 7B.1.	NA	Signal added among important identified risks

Signal Term	Date Detected (Month and Year)	Status (Ongoing or Closed) *	Date Closed (for closed signals)	Source or Trigger for Signal	Reason for Evaluation and Summary of Key Data and Conclusion	Method of Signal Evaluation	Action(s) Taken or Planned
Increased risk of HHE and convulsions with or without fever following co-administration of *Infanrix hexa* with Prevenar13™	January 2014	Closed	February 2014	PRAC recommendation	On 21 January 2014 GSK was informed by the European's Medicines Agency (EMA) about the fact that, on 19 September 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted Opinion on the periodic safety update report (PSUR) of Prevenar 13 (pneumococcal polysaccharide conjugate vaccine, 13-valent, adsorbed). This Opinion was based on a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) and recommended that the Product Information (PI) for Prevenar 13 be updated with a warning on the observed increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) following concomitant administration of Prevenar 13 and Infanrix hexa. The PRAC was of the opinion that the identified safety information and corresponding PI changes are also relevant for Infanrix hexa. Therefore, as Marketing Authorization Holder (MAH) of Infanrix hexa, GSK was requested to assess the need to update the PI of Infanrix hexa. Post-marketing data evaluated during this period supported this PRAC recommendation: a potential increased risk of HHE and convulsions with and without fever following coadministration of Infanrix hexa with Prevenar™ 13 (PCV13) was observed when compared to Infanrix hexa administered alone. Frequency categories of these events following Infanrix hexa-PCV co-administration are expected to remain unchanged compared to Infanrix hexa single administration. A Type II variation regarding this topic was submitted to EMA and accepted. Convulsions with or without fever remain listed with a frequency 'very rare'. As a result of this evaluation the company acknowledges that following the introduction of pneumococcal vaccines into infant vaccination schedules, there is an observed increase in febrile reactions and fever-associated adverse events. The RSI of Infanrix hexa has been updated with the following	Quantitative evaluation of spontaneous reports	RSI updated

Signal Term	Date Detected (Month and Year)	Status (Ongoing or Closed) *	Date Closed (for closed signals)	Source or Trigger for Signal	Reason for Evaluation and Summary of Key Data and Conclusion	Method of Signal Evaluation	Action(s) Taken or Planned
					information: *'Analysis of postmarketing reporting rates suggests a potential increased risk of convulsions (with or without fever) and HHE when comparing groups which reported use of Infanrix hexa with Prevenar 13 to those which reported use of Infanrix hexa alone.'* This signal was categorized as new information regarding important identified risks (HHE and Convulsions). See Appendix 7B.2		

Signal Term	Date Detected (Month and Year)	Status (Ongoing or Closed) *	Date Closed (for closed signals)	Source or Trigger for Signal	Reason for Evaluation and Summary of Key Data and Conclusion	Method of Signal Evaluation	Action(s) Taken or Planned
Guillain-Barré Syndrome	November 2013	Closed	May 2014	Spontaneous case reports	Review of a case of Guillain-Barré Syndrome (GBS) following vaccination with Infanrix-IPV-Hib reported spontaneously to GSK in November 2013 triggered an evaluation of GBS following DTPa-containing vaccines. Review of recent literature found case reports or case series describing at least a temporal association between GBS and immunization for various vaccines, however large epidemiological studies have not been able to conclusively prove a causal link. Review of GBS cases after vaccination with the *Infanrix* family of vaccines within GSK's database found generally poor documentation of diagnosis or reasonable alternative causes for most cases, however some cases with reasonable documentation do not have an alternative explanation. One case would appear to show a positive rechallenge to *Infanrix* antigens. An internal observed to expected ratio analysis found no overall excess of cases, but an excess of cases within a certain age group, but many fewer cases than expected in the age group most represented. The majority of cases used for this analysis had incomplete assessments of GBS. In addition, the observed to expected analysis was undertaken without a precise incidence rate for the largest group vaccinated. It is GSK's position that there is currently insufficient evidence of a causal link between the *Infanrix* family of vaccines and Guillain-Barré Syndrome. GSK will continue to monitor all cases of GBS through routine pharmacovigilance. A complete evaluation of GBS among all DTaP vaccines is in Appendix 7B.3.	Literature review, individual case review, observed-to-expected evaluation	None

Signal Term	Date Detected (Month and Year)	Status (Ongoing or Closed) *	Date Closed (for closed signals)	Source or Trigger for Signal	Reason for Evaluation and Summary of Key Data and Conclusion	Method of Signal Evaluation	Action(s) Taken or Planned
Extensive swelling of vaccinated limb	May 2014	Closed	November 2014	Spontaneous case reports	In 2013 and 2014, increased ELS spontaneous reporting frequencies were observed for Infanrix, Infanrix-IPV, Infanrix-IPV/Hib, Infanrix hexa and Boostrix. Thirteen different countries were involved: Poland, Czech Republic, Sweden, the Netherlands, Belgium, Ireland, Italy, Slovakia, Slovenia, Poland, France, Germany and China. The following were the most likely root causes for increased ELS reporting rates observed in the above countries: • Increased attention, specifically to ELS, by Polish authorities, also possibly triggered by pertussis outbreaks, and regardless of (increasing or decreasing) sales • Increased vaccine use due to introduction of GSK vaccines in local national immunization programmes leading to an overall increase in local spontaneous reporting including, but not limited to, ELS • National/regulatory initiatives to increase local spontaneous reporting, specifically of ELS or not • Pre-school boosting following switch from DTPw priming to DTPa priming • Pertussis vaccination catch-up programmes • Local studies and communications related to ELS GSK considers that the identified ELS signal did not indicate a safety concern and closed this signal. A complete evaluation of ELS among all DTaP vaccines is in Appendix 7B.4.	Quantitative evaluation of spontaneous reports	None

APPENDIX 4A : LISTING OF ALL MAH SPONSORED INTERVENTIONAL TRIALS WITH THE PRIMARY AIM OF IDENTIFYING, CHARACTERISING, OR QUANTIFYING A SAFETY HAZARD OR CONFIRMING THE SAFETY PROFILE OF THE MEDICINAL PRODUCT. No data during the reporting period.

APPENDIX 4B : LISTING OF ALL MAH SPONSORED NON-INTERVENTIONAL STUDIES CONDUCTED WITH THE PRIMARY AIM OF IDENTIFYING, CHARACTERISING, OR QUANTIFYING A SAFETY HAZARD OR CONFIRMING THE SAFETY PROFILE OF THE MEDICINAL PRODUCT, OR OF MEASURING THE EFFECTIVENESS OF RISK MANAGEMENT MEASURES. No data during the reporting period.

APPENDIX 5 : LIST OF THE SOURCES OF INFORMATION USED TO PREPARE THE PBRER (IF APPLICABLE). Not applicable.

APPENDIX 6 : EU REGIONAL APPENDIX/APPENDICES

Appendix 6.1 Proposed Product Information

This information is supplied in Module 1.3.1 of the PBRER submission if changes are proposed to the product information.

Appendix 6.2 Ongoing & Planned Regulatory Procedures

This information is supplied in Module 5.3.6 of the PBRER submission.

Appendix 6.3 Proposed additional pharmacovigilance and risk minimisation activities

No data during the reporting period.

Appendix 6.4 Summary of ongoing safety concerns

Important identified risks	- Hypersensitivity to any component of the vaccine - Syncope - Temperature of ≥ 40.0 C within 48 hours, not due to another identifiable cause - Hypotonic-hyporesponsive episode (HHE) - Apnoea in infants born prematurely - Convulsions with or without fever, occurring within 3 days - Waning of acellular pertussis induced-immunity
Important potential risks	- Encephalopathy of unknown aetiology, occurring within 7 days following previous vaccination with pertussis containing vaccine
Missing information	None

Appendix 6.5 Reporting of results from post-authorisation safety studies

No data during the reporting period.

Appendix 6.6 Effectiveness of risk minimisation

Currently no additional risk minimisation activities other than routine risk minimisation activities are implemented for *Infanrix hexa.*

APPENDIX 7A : GVP VACCINES SPECIFIC REQUIREMENTS

- Potential impact on safety of changes in the manufacturing process (Appendix 7A.1).
- Batch related issues (Appendix 7A.2).
    - Batch A21CB094A (2 fatal cases)
    - Batch A21CC054A (1 fatal case, temporary suspended in Czech Republic)
    - Batch A21CC196A (shorter needles in Australia)
    - Batch A21CB581A (4 cases of (macular) rash in Australia)
    - Potential microbiological contamination (*Bacillus cereus*)
- Age-related adverse reactions (Appendix 7A.3).
- Vaccination errors (Appendix 7A.4).
- Vaccination failure (Appendix 7A.5).
- Vaccination anxiety-related reactions such as syncope (Appendix 7A.6).

APPENDIX 7A.1 : Potential impact on safety of changes in the manufacturing process

No manufacturing or microbiological changes were made for *Infanrix hexa* during this reporting period relating to safety.

APPENDIX 7A.2 : Batch related issues

Following receipt of two fatal cases [redacted] and [redacted]) for batch **A21CB094A**, the MAH was requested by EMA to provide further follow-up on the cases linked to this batch.

Autopsy results were received for cases [redacted] and [redacted] which were both initially reported in PSUR 16. Note that most of the autopsy results of case [redacted] were already described in Section 8.2 Late breaking information of PSUR 16. Follow-up data newly received compared to PSUR 16 is highlighted below in ***bold italic***.

[redacted] ([redacted]): **Death, *Pyrexia, Restlessness***

This case was reported by a [redacted] regulatory authority ([redacted]) and described the occurrence of unexplained death in a 9-week-old male subject who was vaccinated with *Infanrix hexa*. Co-suspect vaccinations included Prevenar 13. Pregnancy and birth had been normal. The subject's medical history included neonatal jaundice. The subject was developing normal. Family history included no allergies. Concurrent medical conditions included suspicion of congenital hip dysplasia. Hip ultrasonography, performed on [redacted], showed type IIa left and type I right. Follow-up hip ultrasonography, performed on [redacted] showed type I both sides. At the time of vaccination, on [redacted], the subject was well. The subject showed small white plaques in oral mucus (oropharyngeal plaques) left but most likely no oral candidiasis. Previous vaccination with Rotavirus vaccine (non-GSK) (RotaTeq; Sanofi Pasteur MSD), given orally at 2 ml on [redacted], was well tolerated. Concurrent medications included colecalciferol + sodium fluoride (D-Fluoretten) and paracetamol (Ben-u-ron). On [redacted] the subject received the first dose of *Infanrix hexa* and the first dose of Prevenar 13. Approximately two days post vaccination, on [redacted], the subject died. The cause of death was unknown (death unexplained). The event had also been reported as life threatening. An autopsy was performed on [redacted] at an institute for forensic pathology. ~~At the time of reporting, on [redacted] examinations had not been finished and no autopsy results have been reported.~~ Quality test result was received on [redacted]. A complete review of the batch records has been performed by Quality Assurance and Production. No deviation that could impact the quality of the product has been highlighted during the GlaxoSmithKline Biologicals investigation. ***The autopsy report mentioned that the subject's mother was known to be a consumer of narcotic drugs. From [redacted] to [redacted] the subject was in foster care. On [redacted] in the evening, the subject developed fever which was treated with paracetamol (Ben-u-ron). On [redacted] the subject returned to the mother who had moved to a mother subject home for the time being. In the evening, the subject was fed with formula milk on [redacted] at 20:15. After drinking the formula milk the subject was restless and had fever (38 degC). Subsequently, the subject administered a suppository (Ben-u-ron). On [redacted] at 20:30 a youth care worker entered the mother's room and saw that the subject was sleeping. On [redacted] at 23:30 the subject was bottle-fed again, burped and fell asleep afterwards. On [redacted] at 03:00 in the morning the mother fed the subject for a last time with formula milk. On [redacted] at 08:05 a youth care worker found the subject lifeless lying in his bed in supine position. The subject's mother was drowsy. An emergency physician was called. The subject showed no vital signs. The emergency physician performed cardiopulmonary resuscitation for about 30 minutes which has been unsuccessful. A police investigation was launched. The autopsy was performed on [redacted]. Significant findings included: The causes of death***

remained unclear. The subject has been in good general and nutritional condition. The subject showed neither external nor internal malformations. The subject showed no evidence for external forceful impact. Post-mortem lividity was found both in the front (face, inner sides of both thighs) and on the back. This finding was not in line with the depicted facts and circumstances. Post-mortem lividity was more pronounced on the back with empty areas due to supine position when found. Some findings including still liquid blood in the heart and petechial hemorrhage in the parietal pleura pointed towards death from suffocation. For further assessments to determine the causes of death chemical, toxicological and histological investigations were indicated. Upon inquiry the public prosecutor reported that additional chemical, toxicological and histological examinations have been ordered. The results of these examinations were outstanding. The public prosecutor informed that the proceedings will be closed and that the ordered toxicological and histological examinations will not be performed. No further information will be available.

Company comment: This case described a SUDI in a 9 week-old male subject two days after combined vaccination with Infanrix hexa and Prevenar. ***According to the autopsy report the subject possibly died from suffocation. The mother was a known user of narcotic drugs.***

[redacted] ([redacted]): ***Respiratory failure,*** **Shock,** ***Cardiovascular insufficiency, Screaming,*** **Pallor,** ***Restlessness, Renal failure, Hyperkalaemia, Pneumonia viral, Rash macular, Sinus tachycardia, Anuria, Vomiting, Hypotonia, Irritability, Faeces discoloured, Lactic acidosis,*** ~~**Circulatory collapse, Sepsis, Crying**~~

This case was reported by a [redacted] regulatory authority and described the occurrence of respiratory failure in a 5-month-old male subject who was vaccinated with *Infanrix hexa*. Co-suspect vaccination included Prevenar 13. First vaccination with both vaccines on 23 August 2011 was well tolerated. Information on medical history and concomitant medication was not provided. On [redacted] the subject received second doses of *Infanrix hexa* and Prevenar. On [redacted] 1 day after vaccination, the subject experienced circulatory depression, differential diagnosis was symptoms of acute sepsis. The subject died from circulatory depression or possible sepsis. An autopsy was performed. Different lot numbers were reported on follow-up. Approximately 20 hours after vaccination with *Infanrix hexa* and Prevenar 13, the subject experienced shock with circulatory failure. An emergency physician was called and the subject was hospitalized on emergency to an intensive care unit. Approximately 10 hours after onset of symptoms the subject died despite intensive care. The lot number A21CB094A was documented in vaccination certificate, while there was no documentation for the mentioned lot numbers A21CB105A and A21CB115A. Quality test result was received on [redacted]. A complete review of the batch records has been performed by Quality Assurance and Production. No deviation that could impact the quality of the product has been highlighted during the GlaxoSmithKline Biologicals investigation. A duplicate case was reported by a physician, via a sales representative and stated the following: On [redacted] in the evening, less than one day after vaccination with *Infanrix hexa* and Prevenar, the subject had been crying and turned grey while lying in bed. The vaccinating physician was consulted and admitted the infant to hospital, where the subject died on [redacted] Information about anamnesis was provided by a hospital report from intensive care treatment after birth. The mother had been pregnant for the first time. The mother had former surgery because of false lung vein opening and received permanent treatment with bisoprolol. The subject was delivered prematurely in

31+4 weeks of gestation, by section from breech presentation after pathologic CTG. There was no premature rupture of the amnion and amniotic fluid was clear. The subject had an APGAR of 6/10/10, a weight of 1490 g, length of 39 cm, head circumference of 32.6 cm, navel artery pH was 7.16. After birth the subject had neonatal respiratory distress syndrome grade I with continuous positive airway pressure for 24 hours. The subject developed possible meconium ileus due to microcolon, transient intestinal transportation disorder, cholestatic hepatosis after parenteral nutrition, with increased transaminases (alanine aminotransferase 131 U/l, aspartate aminotransferase 100 U/l, creatine kinase 342 U/l, total bilirubin 3 mg/dl, direct bilirubin 2.75 mg/dl). Additional diagnoses after birth included neonatal anemia and iron deficiency, asymmetry from lying, small hemangioma right gluteal and dystrophic growth and weight increase. On the sixth day of life, the subject's condition worsened and he was transferred to an intensive care unit for neonates. Intravenous antibiotics were given for seven days. The subject had abdominal distension since birth and not yet passed meconium. Acute abdomen was suspected on the seventh day of life. The subject was transferred to a pediatric chirurgic unit for further intervention, but after conservative treatment the symptoms resolved. Test results were normal for ions, blood gases, immune reactive trypsin (tested on [redacted] and [redacted]), sonogram of head, abdomen and hip (Graf classification Ib) and hearing screening. Cytomegalovirus (CMV) and toxoplasmosis IgM and IgG antibodies were negative. Initially increased Thyroid stimulating hormone normalised on control. Bile acid was increased (74.6 mcmol/l), pancreatic kinase was decreased (68 mcg/g). Eye examination showed vascularisation limit zone III at both sides. The subject was discharged after 39 days in good condition and received rachitis prophylaxis and iron substitution. No further details about the reported event were provided. An autopsy report was received via the [redacted] regulatory authority [redacted] on [redacted] Autopsy was performed on [redacted]. According to the report, events after vaccination also included nocturnal restlessness, increasing pallor, renal failure and hyperkaliemia. Pre-existing underlying medical condition included subacute florid lymphocytic interstitial pneumonia, probably of viral origin, significant activation of the bronchio-alveolar lymphatic system, accumulation of alveolar macrophages, focal beginning alveolar reaction, capillary ectasia and occlusion of the big bronchia by mucus. The cause of death was identified as respiratory failure with protracted shock due to interstitial pneumonia, probably of viral origin. Pathogenic microorganisms were not detected. Evidences of shock included Paltauf dots at the pleura visceralis, fresh necrosis of the kidneys, disseminated hemorrhage of the small intestine, hemorrhage of the mucous membrane of the stomach, multiple stasis hemorrhage of the spleen. Additional findings showed macular exanthema situated at the right lower leg and cervical and para-oesophageal soft tissue hemorrhage. There was no reaction at the injection site. Hemorrhages were also considered to be caused by intensive care measures. Follow-up received on [redacted] included a complete hospital report. The subject was hospitalized on [redacted] at 09:30. In hospital the subject was diagnosed with death after ventricular tachycardia with hyperkaliemia and acute circulatory shock of unclear genesis with anuria and hyperkaliemia. According to the hospital report, the subject had developed normally within the last months. Childhood examination U4 (performed in 3rd to 4th month of life) showed anemia (hemoglobin 8.5 g/dl). The subject's mother had arterial hypertension and received bisoprolol. She formerly underwent surgery because of wrong lung vein ostium. After the subject had received the vaccinations, there was nothing abnormal during the day. In the night, around 01:00 o'clock the subject had been drinking about 200 ml. At 03:00 the subject started crying, which increased despite treatment with simethicone (Sab). He was

vomiting twice. There was a transient improvement after receiving caraway suppository at 05:00. In the morning the subject became pale with strange breathing. When hospitalized, the subject was in bad condition, with circulatory depression, tachycardia with heart rate over 210 per min, pallor, muscle hypotonia, high irritability, moaning breathing. Green stool was excreted once. Supraventricular tachycardia could be excluded by electrocardiogram (ECG), which showed sinus tachycardia. Blood gas analysis showed acidosis with increased lactate and potassium. The subject received volume bolus via infusion on the head. After sudden worsening of condition with fall in oxygen saturation the subject received ketamine and diazepam. There was a short phase of bradycardia with the need for cardiac massage. The subject received further volume via intra-osseous access, as well as dobutamine, adrenaline (Adrenalin), claforan for suspected sepsis and hydrocortisone for circulatory support. Echocardiogram excluded dilated cardiomyopathy, but showed reduced pump function of heart. Sonogram of head excluded acute bleeding. Abdominal sonogram was normal. The subject's body temperature had decreased to 33.1 degC rectal and exogenous warmth treatment was started. Blood test results challenged the diagnosis of sepsis, without fever and with no relevant inflammatory signs. Ammonia was increased, which was considered a possible sign for metabolic disorder. The subject received central vein catheter in V. jugularis interna and arterial catheter in V. femoralis at the right, but no stabilization could be achieved. Katecholamines were increased. The subject still had no diuresis and was treated with frusemide (Lasix). In further course the subject developed increasing potassium values, T-wave elevation, ventricular tachycardia, anuria and no improvement of the situation. Further treatment was without success. At 16:20 further cardiac problems developed, but because of the bad situation no defibrillation was started. The subject died at 16:21 in the parent's presence. The hospital physician stated that after exclusion of cardiac, cerebral and abdominal causes, the event was most likely an atypical sepsis without fever and inflammatory signs. However, postmortal cultures of blood and cerebrospinal fluid also showed no germs. Despite of the autopsy results, the cause of death still kept unclear for the hospital physician. He stated that there were no radiologic signs for pneumonia and artificial respiration had been successful, with normalization of blood gas values. A metabolic disorder was considered possible, but it was more likely that lactic acidosis and hyperammonia were a secondary effect of shock. ***Brain examinations, including macroscopic, histologic and immunhistologic examinations, were without pathologic findings.***

Company comment: Death was identified in the autopsy as respiratory failure with protracted shock due to interstitial pneumonia, probably of viral origin. The cause of death in the autopsy and the hospital report were not congruent. Cumulatively, 19 cases linked to batch A21CB094A were reported to GSK. Sixteen were serious reports and two had a fatal outcome [redacted] *and* [redacted]*, see Section 6.7). No fatal case related to this batch was received during the period of the present PSUR. A complete review of the batch records was performed by Quality Assurance and Production. No deviation that could impact the quality of the product was highlighted by the GlaxoSmithKline Biologicals investigation.*

Until the data lock point of the present PBRER (22-OCT-2014), 24 cases linked to batch A21CB094A were received. No further fatal case was reported compared to the previous period. These cases are described in Table 1.

The information received with these cases did not provide evidence of a specific pattern nor safety signal for batch A21CB094A. Considering that the manufacturing investigation did not highlight any deviation that could have impacted product quality, the MAH closes monitoring of this batch.

Table 1 Line listing of cases linked to batch A21CB094A (DLP 22-OCT-2014)

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Female	8 Sep 11	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	1		Hypersensitivity, Swollen tongue, Eyelid oedema		Yes Resolved
[redacted] .17 Male	[redacted]	Regulatory Authority	Historical Condition:Jaundice neonatal;Current Condition:Developmental hip dysplasia, Oropharyngeal plaque, Foster care;Parent Med History:Drug abuse	[Infanrix hexa], [Prevenar 13]	1	[RotaTeq], [D-fluoretten], [Ben-u-ron]	Death, Pyrexia, Restlessness	2 Days	Yes Fatal
[redacted] .42 Male	[redacted]	Regulatory Authority, Other Health Professional, Physician, Consumer	Historical Condition:Premature baby, Neonatal respiratory distress syndrome, Continuous positive airway pressure, Meconium ileus, Gastrointestinal disorder, Liver disorder, Anaemia neonatal, Iron deficiency, Haemangioma, Ill-defined disorder, Acute abdomen;Current Condition:Interstitial lung disease, Pneumonia viral, Respiratory tract congestion, Anaemia	[Infanrix hexa], [Prevenar 13]	2		Respiratory failure, Shock, Cardiovascular insufficiency, Screaming, Pallor, Restlessness, Renal failure, Hyperkalaemia, Pneumonia viral, Rash macular, Sinus tachycardia, Anuria, Vomiting, Hypotonia, Irritability, Faeces discoloured, Lactic acidosis	1 Days	Yes Fatal

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Male	29 Sep 11	Regulatory Authority		[Infanrix hexa], [Synflorix]			Shock, Pallor, Vomiting, Hypophagia		Yes Improved
[redacted] 1.25 Male	4 Oct 11	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	3		Febrile convulsion, Epilepsy, Rash, Pyrexia, Dyskinesia, Salivary hypersecretion, Eye movement disorder, Somnolence, Pallor, Tachycardia, Injection site erythema, Injection site swelling	355 Days	Yes Unknown
[redacted] .17 Male	5 Oct 11	Physician		[Infanrix hexa], [Prevenar]	1		Peripheral swelling, Erythema		No Resolved
[redacted] .25 Male	20 Oct 11	Regulatory Authority, Physician	Current Condition:Frequent bowel movements, Flatulence	[Rotarix], [Infanrix hexa], [Prevenar 13]	1		Haematochezia, Gastrointestinal pain, Pyrexia, Hypersomnia, Gastroenteritis, Rash maculo-papular	1 Days	Yes Resolved
[redacted] .42 Male	2 Nov 11	Regulatory Authority, Physician	Current Condition:Posture abnormal, Agitation, Familial risk factor, Osteopathic treatment, Physiotherapy, Nervousness;Historical Condition:Bronchitis	[Infanrix hexa], [Prevenar 13]	3	[Infanrix hexa], [Prevenar 13]	Convulsion, Gaze palsy, Juvenile myoclonic epilepsy, Myoclonic epilepsy, Opisthotonus, Dyskinesia, Muscle tightness, Head titubation, Tension, Tremor		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Male [redacted]	18 Nov 11	Regulatory Authority	Historical Condition:Premature baby	[Infanrix hexa], [Prevenar 13], [RotaTeq]	1		Convulsion, Generalised tonic-clonic seizure, Pyrexia, Musculoskeletal stiffness, Respiratory arrest, Sputum abnormal, Somnolence, Erythropenia, Thrombocytosis, Nasal congestion, Abdominal distension	1 Days	Yes Resolved
[redacted] .42 Female [redacted]	13 Dec 11	Regulatory Authority, Physician	Historical Condition:Cyanosis, Apnoea, Stridor	[Infanrix hexa], [Rotarix], [Prevenar 13]	2		Febrile convulsion, Epilepsy, Strabismus, Staring, Muscle twitching, Hypotonia, Eye movement disorder, Pyrexia	1 Days	Yes Resolved
[redacted] .33 Female [redacted]	19 Dec 11	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Prevenar 13]	2		Febrile convulsion, Pyrexia		Yes Resolved
[redacted] .58 Male [redacted]	20 Dec 11	Regulatory Authority		[Infanrix hexa], [Prevenar 13], [RotaTeq]	2	[Infanrix hexa], [Prevenar 13], [RotaTeq]	Febrile convulsion		Yes Resolved
[redacted] 1.33 Male [redacted]	19 Dec 11	Physician, Consumer, Regulatory Authority		[Infanrix hexa]	4		Rash papular, Pruritus	1 Days	No Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .75 Male	18 Jan 12	Physician, Consumer		[Infanrix hexa]	2		Vaccination site abscess		Yes Resolved with Sequelae
[redacted] 1.17 Female [redacted]	8 Feb 12	Regulatory Authority, Physician		[Infanrix hexa]	3		Abscess sterile, Vaccination site granuloma, Injection site erythema, Injection site swelling, Injection site induration, Injection site cyst, Injection site inflammation, Injection site haematoma, Injection site abscess	1 Weeks	Yes Unresolved
[redacted] .25 Female [redacted]	13 Feb 12	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	1		Hypotonic-hyporesponsive episode		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Female [redacted]	12 Mar 12	Regulatory Authority		[Infanrix hexa], [Rotarix], [Prevenar 13], [Topiramate]	2	[D-fluoretten]	Epilepsy, Partial seizures, Eye movement disorder, Depressed level of consciousness, Retching, Oral disorder, Psychomotor skills impaired, Metabolic acidosis, Hypocitraturia, Gaze palsy, Tardive dyskinesia, Hypotonia, Joint hyperextension, Hypertonia, Visual acuity reduced, Polymicrogyria, Apathy, General physical health deterioration, Oligodipsia, Choking, Nystagmus, Pyrexia, Rash, Blindness cortical	15 Days	Yes Unknown
[redacted] .15 Female [redacted]	11 Jul 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	1		Rash macular, Body temperature increased, Injection site extravasation, Injection site erythema	32 Days	No Resolved
[redacted] .12 Female [redacted]	30 Jul 12	Regulatory Authority		[Infanrix hexa], [RotaTeq]			Developmental delay, Infantile spasms, Visual impairment, Akathisia, Encephalopathy, Crying, Gastrooesophageal reflux disease, Nervousness, Abdominal pain, Eye movement disorder		Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 1.42 Female [redacted]	21 Dec 12	Regulatory Authority, Other Health Professional		[Infanrix hexa]	4		Pertussis, Vaccination failure	107 Days	Yes Unknown
[redacted] .83 Male [redacted]	6 Mar 13	Regulatory Authority, Physician	Current Condition:Infection	[Infanrix hexa]	2		Injection site abscess, Injection site swelling, Injection site erythema, Injection site pain, Injection site induration, Injection site discolouration, Injection site warmth	1 Days	Yes Unknown
[redacted] .15 Female [redacted]	28 Aug 13	Regulatory Authority, Other Health Professional	Current Condition:Cough, Sleep disorder, Constipation	[Infanrix hexa], [Prevenar 13]	1		Pneumonia, Dyspnoea, Pyrexia, Poor quality sleep, Middle insomnia, Sleep disorder	1 Days	Yes Unresolved
[redacted] 3 Male [redacted]	8 Nov 13	Physician		[Infanrix hexa]	4		Pertussis, Vaccination failure, No therapeutic response, Inappropriate schedule of drug administration	2 Years	Yes Unresolved
[redacted] 4 Female [redacted]	21 Nov 14	Other Health Professional		[Infanrix hexa]	4		Pertussis, Vaccination failure, Cough, Retching		Yes Unknown

The following issues related to batch (es) of *Infanrix hexa* during the reporting period were found:

- Batch **A21CC054A** was temporary suspended in Czech Republic until the investigation was completed of a fatal case reported with this batch. This preventative suspension of distribution, dispensing and medicinal usage was issued on 23 September 2014. The batch was released for distribution, dispensing and medicinal usage on the 27 November 2014. The review of the case with the available data concluded that except from a temporal relationship to *Infanrix hexa* administration there is no other scientific or medical evidence of the causal role of the vaccination in the subject's death. The physician who did report this case stated that the child died of a probable sudden death, and that there was a possibility of aspiration as well. The results of the autopsy were requested to the Regulatory Authority.

  The batch documentation review has been performed by GSK Vaccines Quality Assurance (QA) and Quality Control (QC) and according to GSK procedures: No deviation that could impact the quality of the product has been highlighted. GSK has reviewed the manufacturing investigation results and concluded that there was no deviation or manufacturing incident that could have an impact on the safety of the subjects vaccinated with batch **A21CC054A**. A Dear Health Care Professional Letter was submitted with this information.

- GSK Austria received a request / complaint from a customer regarding *Infanrix hexa* batch **A21CC196A** which contains shorter needles than the ones currently used for this market: 25G 5/8" (= diameter 0.5mm / length 16mm) instead of 25 G1" (= diameter 0.5mm / length 25mm). Both needle sizes are registered for *Infanrix hexa* vaccination via centralized procedure. Both needle sizes lead to a comparable immunogenicity although the use of a shorter needle for vaccination may lead to a higher risk of local reactions. Therefore decisions on needle size remain under the health care professional responsibility for each person depending on the subject morphology and the vaccination technique. Even with a shorter needle (16 mm) the benefit of the vaccination with *Infanrix hexa* remains favourable over the risk of experiencing injection site adverse events. The next batch will be shipped again with needle size 25G1 from the manufacturing site. A Dear Health Care Professional Letter was submitted with this information.

- Request from Australian authorities for safety information about the receipt of a cluster of 4 cases of hypersensitivity reactions (e.g. rash and macular rash) after vaccination with Infanrix hexa involving batch **A21CB581A** only distributed in Australia. The adverse reactions reported with this batch are considered as listed events in the current reference safety information of Infanrix hexa. In addition the review of the available safety data for all batches coming from the same hierarchical family as batch A21CB581A does not show a trend in events of rash, rash macular and urticaria. The cumulative data received does not provide evidence of a specific safety concern. Considering that the manufacturing investigation did not highlight any deviation that could have impacted product quality and that the data quality control at release of the concerned batch was within the specifications, none of the reported events could be related to a manufacturing issue.

- GSK Biologicals initiated a voluntary recall on 05 October 2012 for specific batches of Infanrix hexa in different countries due to a potential microbiological contamination (*Bacillus cereus*). The safety data reviewed did not show any clinical evidence of the

potential presence of a contamination of the vaccine. See Section 3 of the present PBRER.

No significant safety concerns related to batch (es) were detected for Infanrix hexa during this reporting period.

APPENDIX 7A.3 : Age related adverse reactions

Use in Children

Since *Infanrix hexa* is indicated for active immunisation in infants from the age of six weeks against disease caused by diphtheria, tetanus, polio, pertussis, hepatitis B and disease caused by *Haemophilus influenza* type b the vaccination of this subject group means they are not considered a particular at-risk sub-population.

APPENDIX 7A.4 : Vaccination errors

The GSK worldwide safety database was searched on 6 December 2014 using the following criteria:

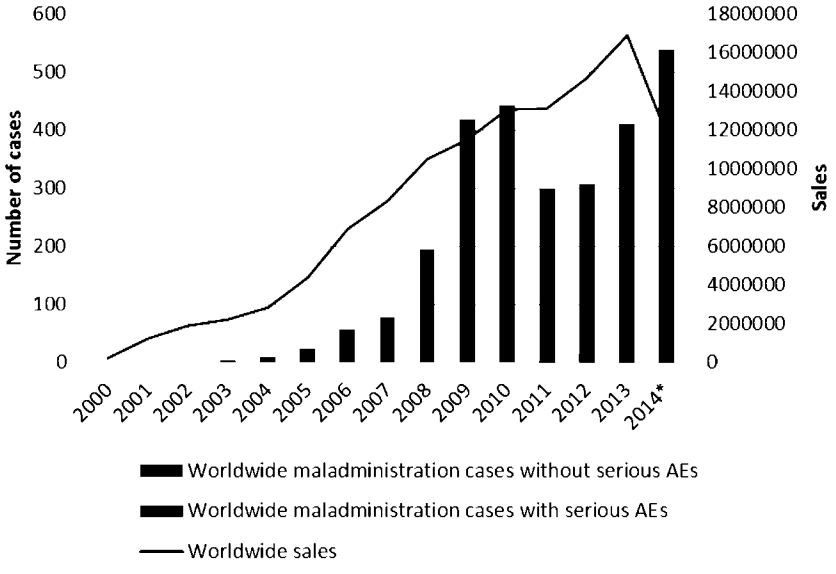
- **Data lock point**: all cases with an initial GSK receipt date on or before 22 October 2014
- **Report types**: All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred terms**: Subpopulation 'Overdose'. This subpopulation retrieves all cases including at least one PT part of the GSK MedDRA Query (MQ) 'Overdose' (see PT list in Table 1)

In order to fulfill the requirements for the 1-year international PBRER and the 3-year EU PBRER, period-specific data in the present evaluation is provided for 2 different periods: from 23 October 2013 to 22 October 2014 (1 year period), and from 23 October 2011 to 22 October 2014 (3 year period).

MALADMINISTRATION

Six hundred and thirty four (634) cases of potential maladministration have been received in the period between 23 October 2013 and 22 October 2014, and 1312 in the period between 23 October 2011 and 22 October 2014. In 2013 and 2014 the number of reported maladministration cases increased by more than 100 cases compared to the previous calendar year, while Infanrix hexa sales increased in 2013 but not in 2014 (Figure 1).

Figure 1 Number of maladministration cases received and Infanrix hexa sales by calendar year



*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

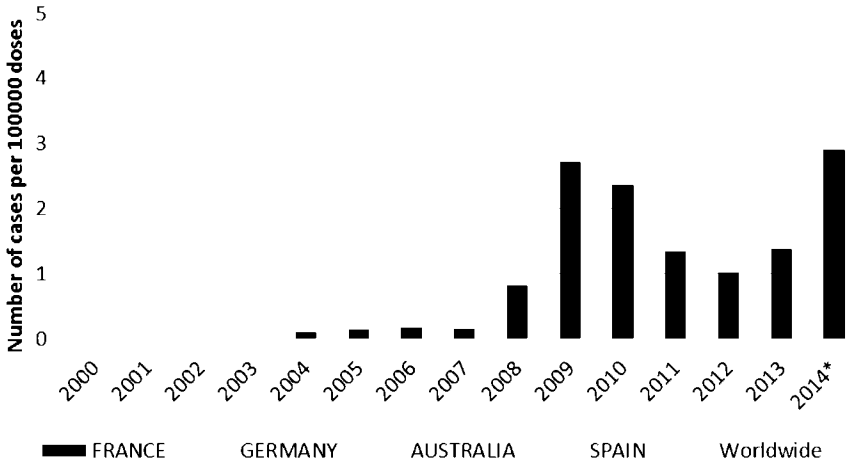
Table 1 PTs included in the GSKMQ 'Overdose' (MedDRA version 17.0*)

Accidental exposure to product	Intentional overdose
Accidental exposure to product by child	Intentional underdose
Accidental overdose	Intercepted drug administration error
Accidental poisoning	Intercepted drug dispensing error
Accidental use of placebo	Intercepted drug prescribing error
Booster dose missed	Intercepted medication error
Cinchonism	Intercepted wrong patient selected
Circumstance or information capable of leading to medication error	Labelled drug-disease interaction medication error
Citrate toxicity	Labelled drug-drug interaction medication error
Completed suicide	Labelled drug-food interaction medication error
Counterfeit drug administered	Lack of injection site rotation
Documented hypersensitivity to administered drug	Medication error
Drug administered at inappropriate site	Medication monitoring error
Drug administered in wrong device	Multiple use of single-use product
Drug administered to patient of inappropriate age	Off label use
Drug administration error	Overdose
Drug administration monitoring procedure incorrectly performed	Poisoning
Drug administration monitoring procedure not performed	Poisoning deliberate
Drug dispensed to wrong patient	Poor quality drug administered
Drug dispensing error	Prescribed overdose
Drug dose omission	Prescribed underdose
Drug prescribing error	Prescription form tampering
Drug titration error	Product label confusion
Ergot poisoning	Product label on wrong product
Expired drug administered	Product name confusion
Exposure to toxic agent	Product packaging confusion
Extra dose administered	Radiation overdose
Herbal toxicity	Radiation underdose
Hypervitaminosis	Suicide attempt
Inappropriate schedule of drug administration	Therapeutic drug monitoring analysis incorrectly performed
Incomplete course of vaccination	Therapeutic drug monitoring analysis not performed
Incorrect dosage administered	Tobacco poisoning
Incorrect dose administered	Toxicity to various agents
Incorrect dose administered by device	Treatment noncompliance
Incorrect drug administration duration	Underdose
Incorrect drug administration rate	Vaccination error
Incorrect drug dosage form administered	Wrong drug administered
Incorrect product storage	Wrong patient received medication
Incorrect route of drug administration	Wrong technique in drug usage process
Intentional drug misuse	

Note that the GSKMQ 'Overdose' used for the present query was related to MedDRA version 17.1. However, the PTs in this table are related to MedDRA version 17.0 because the actual list of PTs in the current GSKMQ 'Overdose' (MedDRA version 17.1) was not available at the time the present evaluation was written. Thus this PT list is only intended to give an overall idea of the content of the GSKMQ 'Overdose'. The PT list in the actual GSKMQ presents (minor) differences compared to the above list.

These cases represent a reporting frequency of 3.9 and 2.8 cases per 100000 doses distributed, respectively for the two periods considered. In 2014, the reporting frequency increased from 2.4 to 4.6 cases per 100000 doses distributed (Figure 2). This increase was driven by maladministration cases reported from France. None of the other countries from which most maladministration cases were reported led to a change in the worldwide maladministration reporting frequency (Figure 2).

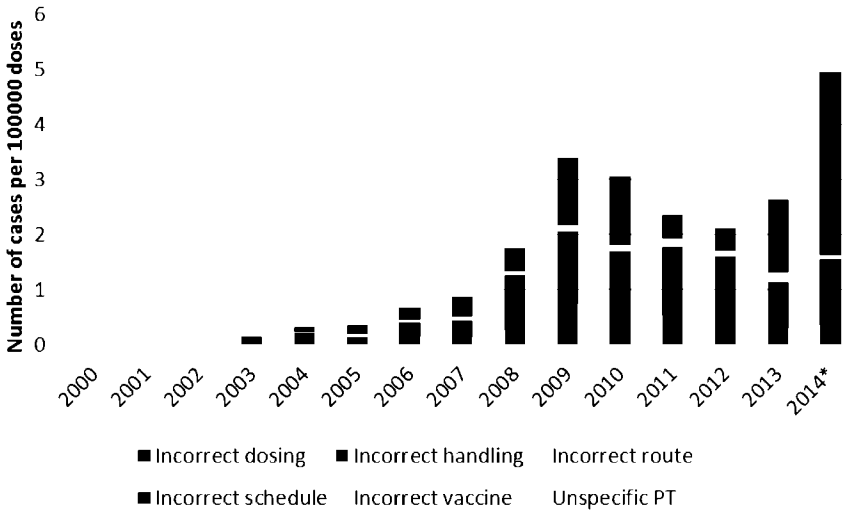
Figure 2 **Reporting frequency of maladministration cases per 100000 doses distributed by calendar year and respective contributions of the four countries from which most maladministration cases were reported**



*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

The evolution over time of the nature of the five maladministration categories (incorrect vaccine, incorrect route of administration, incorrect dosing, incorrect vaccination schedule, and incorrect handling of the vaccine) is displayed in Figure 3. This data shows that the reporting frequency of maladministration categories remained stable over time, except for the 'Incorrect schedule' category which increased up to 3.3 cases per 100000 doses distributed in 2014.

Figure 3 **Reporting frequency of maladministration cases per 100000 doses distributed by calendar year and respective contributions of the five maladministration categories**



*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

During the one year period between 23 October 2013 and 22 October 2014, and the three year period between 23 October 2011 and 22 October 2014, 20% and 46% of worldwide Infanrix hexa cases (regardless of event) were received, respectively (see Section 16.3). Details on reported preferred terms (PTs), including proportions, are provided in Table.The proportion of most maladministration events reported during both periods was similar or lower than 20% and 46% (i.e. the overall Infanrix hexa proportions regardless of events).

Exceptions were rarely reported events: 'Intentional overdose', 'Drug dispensing error', 'Incomplete course of vaccination', 'Treatment noncompliance', 'Drug prescribing error', 'Labelled drug-disease interaction medication error', 'Wrong patient received medication', 'Circumstance or information capable of leading to medication error', 'Medication error', 'Vaccination error'. The higher reporting proportions computed for these events resulted from their rarity and were thus not considered maladministration concerns.

'Drug administered to patient of inappropriate age' and 'Inappropriate schedule of drug administration' were the two PTs involved in the variations over time of the worldwide

maladministration reporting frequency; both were mainly reported in France and most were reported without a root cause. This increase was mainly triggered by the implementation of new coding rules in GSK for maladministrations as of April 2013. The new coding rules consisted in extending the range of incorrect schedules to be encoded:

- shortened *and* delayed schedules are now entered in the safety database while before April 2013 only shortened schedules were entered
- doses not administered which should have been administered are now entered while these were not entered prior to April 2013

Additionally in April 2013, the French pertussis vaccination recommendations were amended. Initially, the French childhood acellular pertussis vaccine schedule recommended a primary course at 2, 3 and 4 months and two boosters at 16-18 months and 11-13 years old [Bonmarin, 2007]. In April 2013, the 3+1 schedule was turned into a 2+1 schedule in France (at 2, 4 and 11 months), the booster at 11-13 years was maintained and a booster at 6 years of age was added [INVS, 2013]. Few cases actually reported that the maladministration was due to health care providers not following the new French pertussis vaccination recommendations, but this is likely to have been the root cause of many of these French maladministration reports.

Taken together, the simultaneous amendments to the GSK coding rules and the French pertussis vaccination recommendations are believed to have caused the observed increase of incorrect schedules in France. These cases do not represent a maladministration or safety concern since Infanrix hexa is indicated for multiple schedules. GSK will continue monitoring all reports of maladministration.

Cumulatively, 16% of maladministration cases included at least one adverse event (AE) and 5% included at least one serious AE (SAE). During the 1 and 3 year periods, 17.4% and 17.8% of maladministration cases included AEs, while 8.7% and 7.5% included SAEs, respectively. Figure shows that maladministration cases including SAEs started to be reported as of 2011 and that their yearly reported number increased since then together with the overall number of maladministration cases. The most frequently reported events (AEs and SAEs as serious cases might also include non-serious events) in these serious maladministration cases were pyrexia and other events reflecting reactogenicity (which are listed), as well as events expected in a pediatric population. Other events were only reported sporadically. No particular increased reporting tendency was observed in any of the 2 periods and the safety profile of serious maladministration cases did not tend to be different from the overall Infanrix hexa safety profile (Table). The data provided for cases including unlisted events did not indicate a causal relation to Infanrix hexa maladministration. Thus this increase in serious maladministration cases did not indicate a safety concern.

No new significant safety information was received with maladministration cases. The Infanrix hexa indication is appropriately described in the Product Information (PI); therefore the Company does not consider updating the PI in view of the above maladministration reports.

Table 2 Number of maladministration cases[a] reported during the period and their proportion among the cumulative number of maladministration events since launch

Maladministration PT	23-OCT-2013 22-OCT-2014		23-OCT-2011 22-OCT-2014		Cumulative until 22 October 2014
Incorrect dosing	**54**	**(13.0%)**	**143**	**(34.5%)**	**415**
Accidental overdose	7	(13.0%)	27	(50.0%)	54
Extra dose administered	18	(12.8%)	43	(30.5%)	141
Incorrect dosage administered	0	(0.0%)	0	(0.0%)	5
Incorrect dose administered	1	(9.1%)	1	(9.1%)	11
Intentional overdose	0	(0.0%)	1	(100%)	1
Overdose	15	1(4.3%)	39	(37.1%)	105
Poisoning	0	(0.0%)	0	(0.0%)	1
Prescribed overdose	0	(0.0%)	2	(22.2%)	9
Toxicity to various agents	0	(0.0%)	0	(0.0%)	1
Underdose	13	(14.9%)	30	(34.5%)	87
Incorrect handling	**161**	**(14.6%)**	**507**	**(46.0%)**	**1101**
Accidental exposure to product	1	(6.3%)	7	(43.8%)	16
Drug administration error	0	(0.0%)	0	(0.0%)	30
Drug dispensing error	5	(38.5%)	10	(76.9%)	13
Expired product administered	17	(14.3%)	70	(58.8%)	119
Incorrect product formulation administered	0	(0.0%)	1	(7.7%)	13
Incorrect product storage	41	(12.7%)	140	(43.3%)	323
Poor quality drug administered	0	(0.0%)	1	(50.0%)	2
Wrong technique in drug usage process	97	(16.6%)	278	(47.5%)	585
Incorrect route of administration	**17**	**(12.6%)**	**66**	**(48.9%)**	**135**
Drug administered at inappropriate site	0	(0.0%)	0	(0.0%)	3
Incorrect route of drug administration	17	(12.9%)	66	(50.0%)	132
Incorrect vaccination schedule	**599**	**(44.7%)**	**874**	**(65.3%)**	**1339**
Drug administered to patient of inappropriate age	270	(47.3%)	404	(70.8%)	571
Inappropriate schedule of drug administration	313	(41.7%)	452	(60.3%)	750
Incomplete course of vaccination	16	(94.1%)	17	(100%)	17
Treatment noncompliance	0	(0.0%)	1	(100%)	1
Incorrect vaccine	**89**	**(22.6%)**	**165**	**(41.9%)**	**394**
Drug prescribing error	8	(88.9%)	8	(88.9%)	9
Intercepted drug dispensing error	0	(0.0%)	1	(100%)	1
Labelled drug-disease interaction medication error	1	(100%)	1	(100%)	1
Wrong drug administered	79	(20.7%)	154	(40.3%)	382
Wrong patient received medication	1	(100%)	1	(100%)	1
Unspecific PTs	**1**	**(3.2%)**	**6**	**(19.4%)**	**31**
Circumstance or information capable of leading to medication error	0	(0.0%)	1	(100%)	1
Medication error	1	(5.6%)	5	(27.8%)	18
Vaccination error	0	(0.0%)	0	(0.0%)	12

[a] In view of the varying ways in which reports of overdose and medication errors are described and coded, there is often much overlap between these concepts. It should be noted that more than one event can be reported per case, thus the same case can be counted in multiple categories and for multiple events. This explains why the total number of maladministration cases computed in the above table is greater than the total number of cases actually reported.

Table 3 Most frequently reported events in serious maladministration cases for the 2 considered periods and cumulatively

Event PT	23 October 2013 - 22 October 2014
Pyrexia	11
Pertussis	11
Injection site erythema	8
Cough	8
Injection site induration	5
Vaccination site inflammation	5
Loss of consciousness	5
Extensive swelling of vaccinated limb	4
Vomiting	3
Injection site granuloma	3

Event PT	23 October 2011 - 22 October 2014
Pyrexia	24
Pertussis	17
Injection site erythema	13
Cough	12
Injection site induration	9
Malaise	8
Extensive swelling of vaccinated limb	7
Pallor	7
Vomiting	6
Hypotonia	6

Event PT	Cumulative until 22 October 2014
Pyrexia	156
Injection site erythema	71
Crying	40
Injection site swelling	36
Injection site induration	28
Extensive swelling of vaccinated limb	24
Vomiting	24
Pertussis	23
Irritability	21
Injection site pain	21

OFF LABEL USE

The European Medicine Agency defines off-label use as "Situations where a medicinal product is *intentionally* used for a medical purpose not in accordance with the authorized product information".

The cumulative reporting frequency of potential off-label use cases was 0.073 cases per 100000 doses distributed. Seventeen (17) potential off-label use cases have been received in the period between 23 October 2013 and 22 October 2014 (representing a reporting frequency of 0.106 cases per 100000 doses distributed), and 58 in the period between 23 October 2011 and 22 October 2014 (representing a reporting frequency of 0.124 cases per 100000 doses distributed). The increase of the maladministration reporting frequency was

caused by cases from France, which represented 82%, 90% and 70% during the 1-year period, the 3-year period and cumulatively since launch, respectively.

In most cases received during the 1-year period (58.8%) and 3-year period (86%) the off-label use consisted in Infanrix hexa administration to subjects older than 36 months (between 3 and 17 years of age during the 1 year period, and between 3 and 64 years of age during the 3 year period). Whether the off-label use was intentional or not was rarely reported. Other off-label use scenarios were intentional mixing of Infanrix hexa with Prevenar before injection (1 case), administration to a subject allergic to lactose (1 case), and non-compliance with the recommended interval between doses (2 cases plus several cases also reporting administration to subjects older than 36 months). In 3 cases the off label use was not related to Infanrix hexa, but to another vaccine.

During the 1-year and 3-year periods, 16 (94%) and 30 (52%) potential off-label use cases also included maladministration PTs, respectively; these were included in the above maladministration evaluation.

During the 1-year and 3-year periods, 1 (6%) and 3 (5%) potential off-label use cases also included SAEs, respectively (Table). The events in cases [redacted] and [redacted] are listed, while those in case [redacted] occurred in a subject suffering leukemia, and were therefore not considered related to Infanrix hexa.

Table 4 Serious potential off-label use cases

Argus Case ID	Initial Central Receipt Date	Country of Occurrence	List of events PT	Age at vaccination
[redacted]	7 May 13	[redacted]	Extensive swelling of vaccinated limb, Inflammation, Pyrexia, Off label use	3 years
[redacted]	5 Jun 14		Injection site erythema, Drug administered to patient of inappropriate age, Off label use	5 years
[redacted]	21 Oct 13		Thrombocytopenia, Epistaxis, Off label use	5 years

CONCLUSION

No new important safety information regarding maladministration and off-label use has been identified during the reporting periods.

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Institut de Veille Sanitaire (INVS). Bulletin Epidemiologique Hebdomadaire. Le Calendrier des vaccinations et les recommandations vaccinales 2013 selon l'avis du Haut Conseil de la santé publique (16 avril 2013). Accessed 18 November 2014: invs.sante.fr/content/download/62968/248437/version/6/file/BEH_14_15_2013.pdf.

APPENDIX 7A.5 : Vaccination failure

According to the Guideline on Good Pharmacovigilance Practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases (effective 13 December 2013), additional information on vaccine failure, lack of efficacy / effectiveness should be summarized and analyzed in the PBRER.

DATABASE SEARCH STRATEGY

The GSK worldwide safety database was queried using the following criteria:

- **Data lock point**: Since launch until 15 of September 2014.
- **Report types**: All spontaneous cases.
- **Suspect vaccine**: *Infanrix hexa.*
- **MedDRA preferred terms**: GSK MedDRA query (MQ) for *Infanrix hexa* Lack of efficacy.

DEFINITION OF LACK OF EFFICACY

Confirmed Vaccination Failure

The occurrence of specific vaccine-preventable disease in a person who is appropriately and fully vaccinated taking into account the incubation period and the normal delay for the protection to be acquired as a result of immunization. This definition requires clinical and laboratory confirmation that the actual disease is vaccine preventable, i.e. that the pathogen and clinical manifestations are specifically targeted by the vaccine.

Infanrix hexa vaccine-preventable diseases: diphtheria, tetanus, pertussis, hepatitis B, polio, and *Haemophilus influenzae* type b infection (meningitis, pneumonia, epiglottitis).

Appropriately and fully vaccinated children are the ones who completed primary vaccination schedule (two or three doses in the first year of life) and a booster dose in the second year of life.

Normal delay for protection: minimum thirty days after full schedule.

Suspected Vaccination Failure

Suspected vaccination failure is defined as the occurrence of disease in an appropriately and fully vaccinated person, but the disease is not confirmed to be the specific vaccine preventable disease.

EVALUATION OF VACCINATION FAILURE

Since launch until 12 September 2012 an evaluation of vaccination failure was done, with the search criteria *Infanrix hexa* LOE GSK MQ obtaining 261 cases, where 56 cases were confirmed vaccination failure, 13 suspected cases, 16 with unknown vaccination status, and 176 cases non vaccination failure cases. Among the suspected cases the median time to onset was 1.1 years and for confirmed cases was 2.3 years.

Following the inclusion of pertussis waning immunity as an identified risk in GSK Periodic Safety Reports, another evaluation of lack of efficacy cases was performed since 12 September 2012 until 15 Sep 2014, where 232 cases with *Infanrix hexa* LOE GSK MQ were retrieved. Confirmed cases of vaccination failure were 98 cases, and suspected cases were 39. The rest of the cases were vaccination failure reported with 'unknown' primary vaccination status, or other diseases such as 'drug not responded without pertussis disease', or another

disease. The age of the majority of cases was among 3 to 4 years of age and the country with the majority of cases was Germany. The time to onset was in most of the cases between 2-3 years of age and in 1-2 years of age. The proportion rates were up to 0.04 vaccination failure cases reported over all adverse events reported. Two peaks were observed in the year 2004-2005 and 2012-2013.

In total since launch until 15 September 2014 there were 493 cases of lack of efficacy with *Infanrix hexa* reported in our safety database. Upon analysis confirmed cases in total are 154 cases and 52 suspected cases. The rest of the cases are other diseases, or cases where a laboratory test was done and found no induced pertussis immunity after vaccination but there was no pertussis disease. The mean time to onset of lack of efficacy cases was 2 years. Refer to Figure for the distribution of lack of efficacy cases among time and their proportion rates (LOE cases among all adverse events reported with *Infanrix hexa*).

Figure 1 **Distribution of Lack of efficacy Proportion Rates (LOE cases vs. All events) among time**

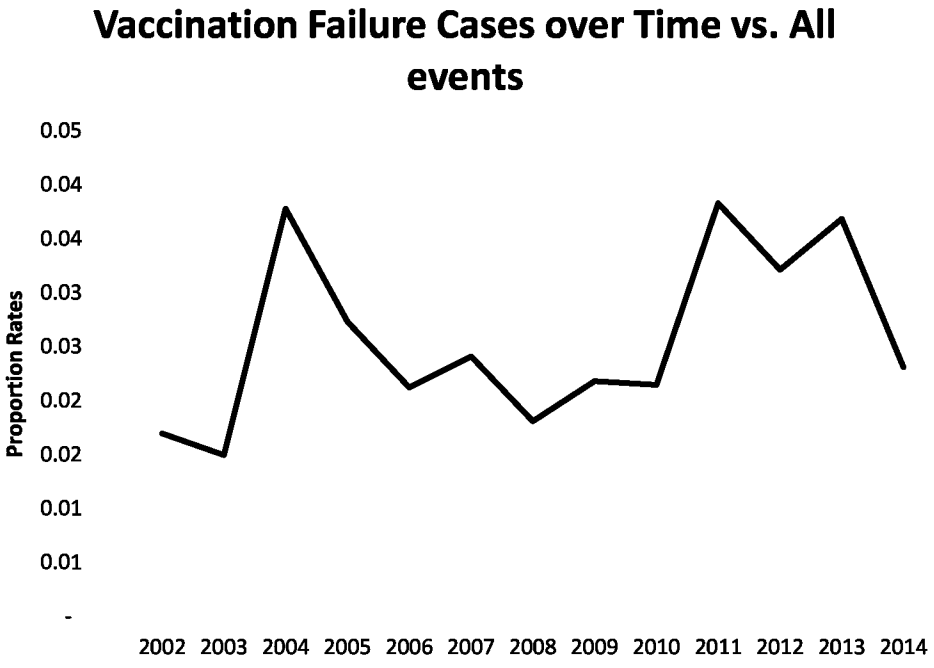


Figure 2 **Distribution of time to onset of Vaccination Failure cases with *Infanrix hexa***

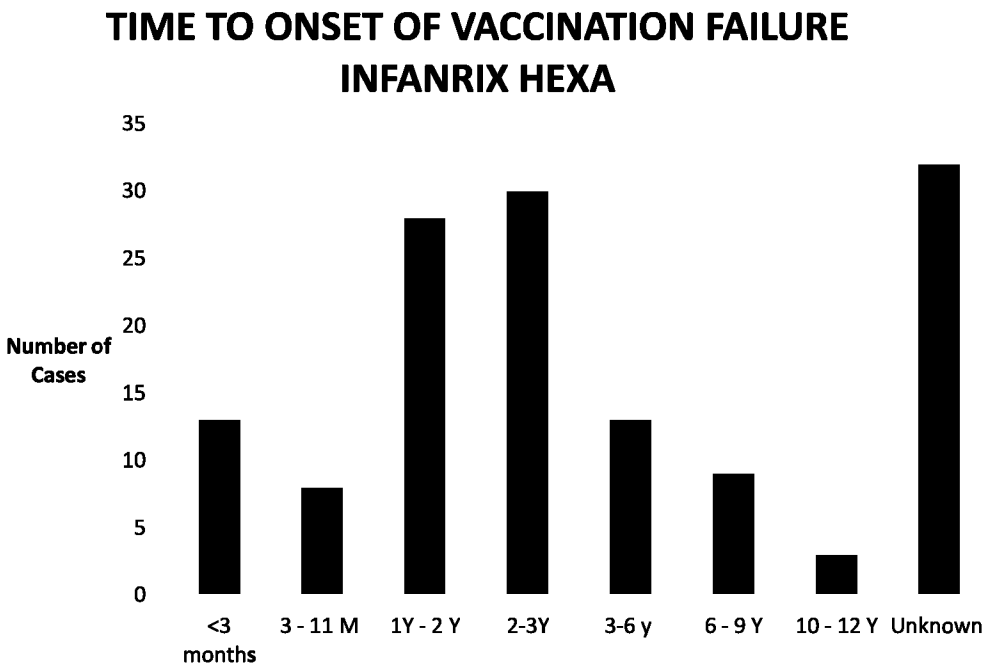
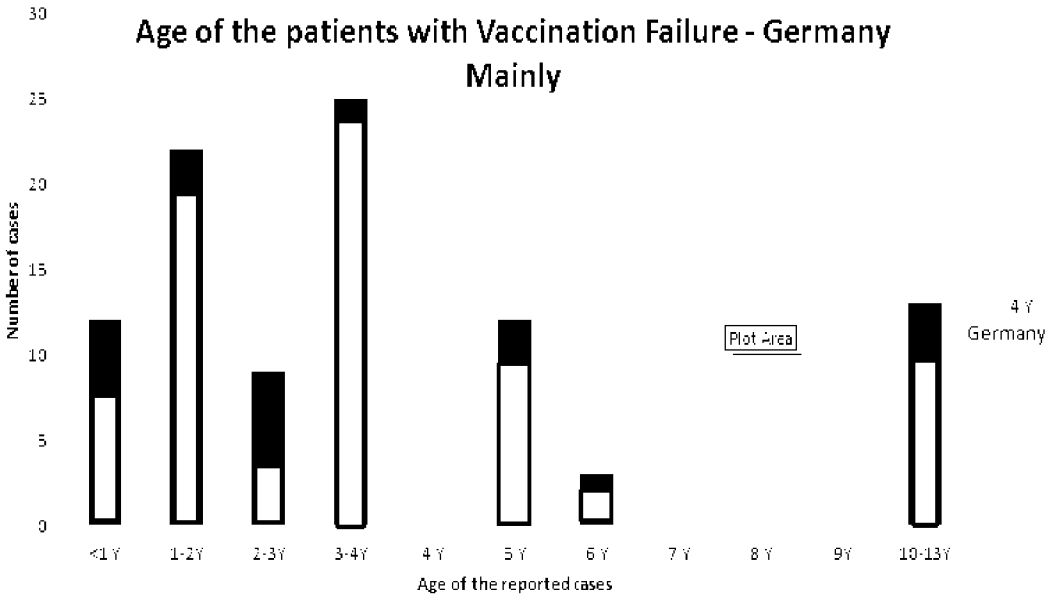


Figure 3 **Distribution of the age of the patients reported with vaccination failure with Infanrix hexa (Germany reported cases in orange color)**



CONCLUSION

In this analysis it is important to mention that cases consider as vaccination failure for *Infanrix hexa*, may be also reported for another vaccine of the DTP line (i.e. Infanrix™, Boostrix™, Infanrix™ IPV, Infanrix™ IPV/Hib) , in case the patient did receive a mixed schedule.

Spontaneous data have different confounding factors, such as reporting bias, underreporting bias, incomplete reporting, unknown full vaccination status, mixed schedules and vaccines from different manufacturers, increase in disease awareness in recent years (leading to increase in reporting in recent years), the variety of vaccines used for primary vaccination (whole cell versus acellular pertussis containing vaccines), changes in surveillance methods globally, in diagnostic methods, in vaccine coverage and vaccine schedule. Other confounding variables could include genetic changes in *Bordetella pertussis* and the general variation of specificity in PCR laboratory tests. For time since vaccination, the assessment of the risk of vaccination failure based on spontaneous reports is confounded by the reporting bias: reporting levels decrease according to time since vaccination whereas the risk of breakthrough disease increases with time since vaccination.

Upon review of Lack of efficacy cases of *Infanrix hexa* the company concludes there is no new safety concern. GSK will continue to monitor vaccination failure as part of the routine pharmacovigilance activities.

REFERENCES

CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Vaccination failure. Position Paper. Endorsed: April 29, 2008.

APPENDIX 7A.6 : Vaccination anxiety-related reactions such as syncope

The GSK worldwide safety database was searched on 26 of November using the following criteria:

- **Data lock point**: since launch until 22 October 2014.
- **Report types**: All spontaneous cases
- **Suspect vaccine**: *Infanrix hexa*
- **MedDRA preferred terms**: Syncope and Presyncope.

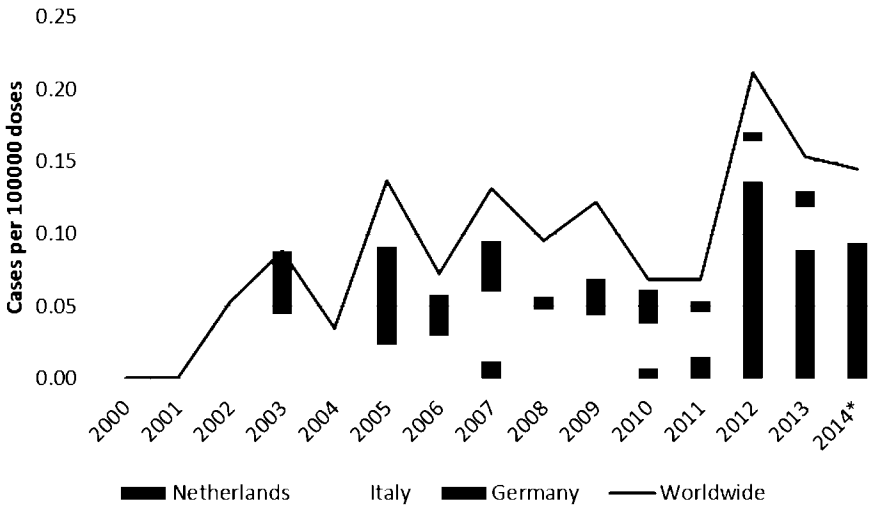
A total of 142 reports (cases) were retrieved from the GSK worldwide safety database since launch in 2000, of which 74 were reported during the period between 23 October 2011 and 22 October 2014.

Figure 4 shows that, since launch, the worldwide reporting frequency of cases including the PTs Syncope or Presyncope was stable and varied between 0.04 and 0.14 cases per 100000 doses sold, and increased as of 2012 up to 0.21.

The analysis of respective contributions of the three countries from which most syncope cases were reported shows that the increase in 2012 was exclusively triggered by cases reported from the Netherlands.

The increase in the Netherlands in 2012 was not specific to syncope as all events reported from the Netherlands increased in 2012. This was due to the extension of the Dutch target population for Infanrix hexa vaccination from only children at risk for hepatitis B infection in 2006, to children with Down syndrome as of 2008 and finally to all new-borns as of 2011. Also, overall reporting in the Netherlands decreased again after 2013, which was expected in view of decreasing sales as of 2014 (data not shown). No new information was received with these cases.

Figure 4 **Yearly reporting frequency for cases including the PTs Syncope or Presyncope, and respective contributions of the four countries from which most cases were reported**



*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

Syncope is listed as a warning in the Infanrix hexa reference safety information.

GSK will continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

APPENDIX 7B : SAFETY EVALUATIONS

APPENDIX 7B.1 : Literature Review Pertussis effectiveness studies

A summary of literature related to pertussis vaccines effectiveness/duration of protection (updated in September 2014) *The review captures data on GSK vaccines (Infanrix and Boostrix), as well as other acellular vaccines in studies including GSK vaccines*

Contents

1. METHODS AND LIMITATIONS

Vaccine effectiveness (VE) studies provide information on how well licensed vaccines work when used in routine circumstances in the community. In an attempt to assess the impact of time since vaccination on vaccine effectiveness, the tables in Appendix present an overview of epidemiological studies reporting vaccine effectivenesss of acellular Pertussis vaccines and including GSK 3-component vaccine. In most studies, there was a mix of different acellular vaccines. Data on the effectiveness of maternal immunisation are not included here, and data on the impact of vaccination are not included either. The review is organised firstly by vaccine type, with the studies on reduced dose vaccines (Tdap) and then the studies with full dose DTPa vaccines, and a further classification by study design. In an attempt to capture most recently available data as exhaustively as possible, studies that are not yet published but presented in congresses/scientific meetings are also included, although the data might be incomplete. A key limitation is that different case definitions have been used in different studies, which may greatly hamper any comparisons between studies, since effectiveness may depend on case definition [Cherry, 1999]. Furthermore, some of the studies are retrospective data base analyses with possible information, selection and confounding bias. Most of our discussion here is focused on the impact of time since vaccination (waning immunity) and therefore not all aspects of every study are discussed here. Such is the case with the recently published effectiveness data from the UK related to maternal immunization aimed to assess the vaccine effectiveness and the overall effect of the vaccine programme in preventing pertussis in infants. (Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014 July 15, pii: S0140-6736(14)60686-3. doi: 10.1016/S0140-6736(14)60686-3.

2. SUMMARY OF MAIN RESULTS

2.1. Vaccine effectiveness following Tdap boosters with reduced antigen content (see also Appendix Table 1)

Vaccine effectiveness of the adolescent boosters with reduced-antigen content acellular vaccines has been assessed so far in several published studies, including: i) a study in Australia, in a region using Boostrix GSK vaccine [Rank, 2009] and three studies in the US, a country using both GSK and Sanofi-Pasteur vaccines: ii) in one school [Wei, 2010] , iii) in California via retrospective database analyses led by Kaiser [Baxter 2013] and iv) the Wisconsin birth cohort [Koepke, 2014] . Based on different study designs, the screening method, an outbreak investigation and a retrospective database analysis with a matched case-control design, vaccine effectiveness estimates for the 1st three studies were respectively 85.4% (95%CI: 83, 87.5) , 70.6% (-110.3, 95.9), and 64.0% (55.5, 70.9) in the comparison with Kaiser Permanente Northern California controls. For the Wisconsin study, Tdap VE decreased with increasing time after vaccination from 75.3% (95% CI, 55.2-86.5%) for those vaccinated in 2012 to 11.9% (95% CI, -11.1-30.1%) for receipt in 2009/2008. The first two studies followed the recent introduction of adolescent vaccination, with a sub-optimal vaccination coverage of the population (not allowing for

herd protection), and due to the relatively short time since implementation of the adolescent dose there was no possibility to assess waning immunity (statistical power was also limited). Although the third study covered the period from January 2006 to December 2011, 75% of the cases were observed during the Californian outbreak between January 2010 and June 2011, and time since vaccination was still relatively short (among the recipients of Tdap vaccines, 91.6% were vaccinated within 2 years of their PCR test in the group who received only acellular vaccines, 61.7% in the group who received whole cell vaccines in early childhood, and 57.9% in the oldest group born before pertussis vaccines were widely available). The first two studies involved adolescents primed with whole cell vaccines only, whereas the third and fourth studies also included adolescents primed with acellular vaccines.
The Wisconsin study published in June 2014, was performed during a state wide pertussis outbreak in Wisconsin with a total of 6264 reported cases; 25% of cases occurred among adolescents aged 11-14 years, 76% of whom had previously received Tdap. A cohort of residents born during 1998-2000 with Tdap vaccine history (Boostrix/Adacel) was constructed using the Wisconsin Immunization Resgistry (WIR). Laboratory confirmed pertussis cases (940) were matched to WIR clients and Tdap vaccine effectiveness (VE), by brand and year of receipt, for preventing pertussis during 2012, were estimated using Poisson regression. This data, consistent with the data reported by the CDC on Washington state outbreak [Acosta 2013] and the Oregon study (Liko 2014], confirms that Tdap VE decreases with increasing time since vaccination. See table 1. This study also presented brand-specific VE data indicating that Boostrix was more effective than Adacel in preventing pertussis in their cohort. This result should be handled with caution considering that the study design is not adapted to provide conclusive comparisons between brands. So far, there are no other data available that would suggest any potential difference by brand. It is worth noting that the results are specific to an outbreak setting.

In addition, two studies have also been published more recently: a very small outbreak investigation in Italy, and a study in the French Armed Forces (see Appendix Table 1).

Then, two US outbreak investigations are not yet published (congress presentations) are also reported in Table 1 [Skoff, 2011; Terranella, 2012], with vaccine effectiveness estimates of 72% (95%CI: 38.0, 87.3), 76% and 71%, respectively.

A more recent vaccine effectiveness study on the adolescent booster is not yet published but has been presented at the ACIP in June 2013. It is a very large case-control study led by the US CDC based on recent outbreaks in Washington State in January-June 2012. By contrast with the previous studies, this study has sufficient power to assess vaccine effectiveness according to time since vaccination, at least for the first few years after vaccination. Indeed the adolescent booster was introduced in the US in 2005 with progressively increasing vaccine coverage (about 11% in 2006, 41% in 2008, 69% in 2010, 78% in 2011 and 83% in 2012). The overall vaccine effectiveness during the first four years following the adolescent booster was estimated at 63.9% (95%CI: 49.7, 74.1), with estimates of 73.1% (95%CI: 60.3, 81.8) in the first year following vaccination, 54.9% (95%CI: 32.4, 70.0) in the second year following vaccination, and 34.2% (95%CI: -0.03, 58) in the third and fourth years following vaccination. These final numbers shared recently by the CDC are similar to those reported last year based on preliminary results, showing an overall vaccine effectiveness of 66% (95% CI: 52-76%), and an estimate of

75% (95% CI: 62-83%) within one year of Tdap vaccination, declining to 41% (95% CI: 7-63%) at 2 or more years post-vaccination [Acosta 2013]. Sensitivity analyses restricted to individuals who had confirmed receipt of 5 doses of DTaP, or 5 doses of DTaP plus confirmed case of Pertussis, led to a similar trend regarding the duration of protection as in the unrestricted population. When the analysis included adolescents aged 15-19 years, who received whole cell Pertussis vaccines in infancy and childhood, the overall vaccine effectiveness estimated in the first 8 years following Tdap vaccination was 51.5% (95% CI: 26.1, 68.1) (final results), which suggests that whole cell recipients may have greater durability of vaccine protection following Tdap compared to acellular-only vaccinees. Indeed, it is interesting to note that from the descriptive publication on the Washington state outbreak, there is a strong cohort effect. This was also described during the 2005 epidemic in the US, where the cohorts born in 1997-99, corresponding to the time of introduction of acellular vaccines in the primary vaccine schedule, appear to be at highest risk. In the 2005 epidemic, the 7 year-olds (first birth cohort which received acellular vaccines for their entire childhood series) also had an increased reported rate of pertussis and this was maintained in the following years (until the adolescent booster at 11 years of age). The cohorts born after 1998 also experienced a similar upward trend resulting in an increasing number of cases in 7 to 10 years olds [ACIP, 2013].

In Australia, the introduction of acellular vaccines in the primary schedule in 1998 led in that birth cohort to mixed sequences of different vaccines in a large proportion of the population [Sheridan, 2012]. The type of vaccines used in the primary schedule appears to have an impact on the risk of acquiring pertussis at the age of (pre-)adolescence, with potentially a higher risk in individuals who received acellular vaccines as compared to whole cell vaccines (may be outlining the importance of the first dose), and a higher risk in individuals who received mixed sequence of vaccines (acellular and whole cell) during their primary vaccine schedule as compared to those who received the same vaccine for subsequent doses. If the individuals who did not receive a toddler booster are excluded from the analysis, the results remain similar (communication from the authors). Similar findings were reported in the US [Liko, 2013], although the three transition cohorts were pooled together (1997-1999), ignoring the effect of age. Age is a key confounding factor, as there are age-specific incidence patterns and age-specific reporting levels, in particular the oldest cases are less likely to be reported – this may bias the results towards over-estimating the differences between the cohorts primed with whole cell vaccines and those primed with acellular vaccines, by contrast to the conclusions of Klein [Klein, 2012]). Similar findings as in Australia and the US have also been reported recently in England, in a retrospective case-control study based on Pertussis cases reported in 2011-2012, showing the impact of the type of vaccines received during the primary schedule, on the risk of Pertussis among children and teenagers born in 1997-2006 [Carvalho, 2013].

In the US, there is limited data on the extent to which mixed sequences took place in the transition phase from whole cell to acellular vaccines – moreover, at that time a number of different acellular vaccines were on the US market, some of which are not available anymore (as described in Bisgard [2005] and Cherry [1999]). Due to this marked cohort effect in the US (that appeared clearly during the 2005 epidemic, before adolescent vaccination), the recent US epidemics may not allow one to disentangle the waning of vaccine immunity after the adolescent booster from this cohort-specific effect, seen in particular in the transition cohorts born in 1997-1999 [CDC, 2012]. The risk of pertussis

in adolescents also depends on the primary schedule (as seen in Australian [Sheridan, 2012] and in the US [Liko, 2013]), and therefore the potential implications of the US case-control effectiveness study for other countries should be addressed with caution. Moreover, the recent US outbreaks largely involved Pertactin-negative isolates [Queenan 2013; Pawloski 2013]. This has also been reported in Australia, with a frequency of up to 80% [Lam 2014], but, the frequencies reported so far in other countries are not that high.

Another effectiveness study based on the 2012 US outbreak, in Oregon [Liko 2014], is aligned with the results reported in adolescents in Washington State and Wisconsin (see table 1). This database study also provides effectiveness estimates for DTPa vaccines in younger age groups, which are aligned with previously published data.

In addition, Oregon data indicate that Pertussis cases identified via enhanced Pertussis surveillance in 2010-2012 in vaccinated individuals aged 6 weeks to 18 years old are less severe than cases occurring in non-vaccinated individuals; in particular, vaccinated cases have a lower risk of hospitalisation and a reduced duration of illness [Barlow 2014].

2.2. Vaccine effectiveness following primary schedule or pre-school boosters based on full antigen content acellular vaccines (DTPa)

2.2.1. Case-control studies (see also Appendix Table 2)

Contrary to the studies mentioned in paragraphs 2.2.3 and 2.2.4 below, the advantage of case-control studies is that these studies are not biased by under-reporting of cases. A potential source of bias for case-control studies that is especially relevant for Pertussis would be the issues related to false positives, as this could lead to under-estimation of vaccine effectiveness. In Pertussis RT-PCR diagnostic, there are regularly issues linked to other *Bordetella* species or contaminations of the clinics or the laboratories, so this needs to be kept in mind. Another potential source of bias may come from the ascertainment of vaccination history (in case of missing data and misclassification).

So far, four case-control studies have been published, among which two studies have been conducted recently in the US in California in children aged 4 to 10 years old, the CA VE study led by the CDC and the one led by Klein [2012]. These two studies are based on different statistical methods (the Klein [2012] study assumed a linear decrease of vaccine effectiveness according to time since vaccination, whereas the CDC study estimated vaccine effectiveness independently each year following vaccination), but their results are consistent. Only the CDC study provided estimates of vaccine effectiveness, with an initial effectiveness of 98% (95% CI 96.1, 99.1) in the first year after vaccination, and a steady drop to 82.8 (95% CI 68.7-90.6) in the fifth year after vaccination, and 71% (95% CI 45.8, 84.8) during the sixth year and beyond.

For the primary schedule, a case-control study has been performed by Bisgard [2005] in the US, but there was not enough power to quantify the impact of time since vaccination. The fourth case-control study is from Australia [Quinn, 2014], confirming a high vaccine effectiveness of the primary schedule up to 2 years of age, and then showing a waning of

effectiveness and hence the need for a toddler booster in the second year of life (see table 2), which is not implemented in Australia (cf also serological data [Campbell 2012]).

Researchers from Germany presented effectiveness data from a stratified case-cohort study among children in schools and kindergarten born in 2005-2009 (aged 2 – 3 years), in 1995-2006 (aged 5-7 years) and in 1995- 1998 (aged 15-16 years), in the federal state of Brandenburg [Haller et al]. The VE for the 4 primary doses (3 + 1 at about 14months of age) decreased from 97% in 2-3year olds, 88% in 5 – 7year olds to 84% in 15 – 16 year olds. (Appendix Table 2). In addition, some data from a small German study based on laboratory data, with a case-negative design was recently published [Riffelmann, 2013] (see table 2).

An abstract from Stein-Zamir et al will be presented at the ESPID 2014 congress [Stein-Zamir 2014], based on a case-control study among infants less than one-year old in Israël (Jerusalem district), including 317 Pertussis cases (hospitalized and non-hospitalized) and 951 age-matched controls. They report a vaccine effectiveness of 84%, 71% and 67% for 3, 2 and 1 vaccine doses, respectively (GSK vaccines). More details should be available in the poster and in the publication -- this study is not yet listed in the appendix tables.

2.2.2. Outbreak investigations (see also Appendix Table 3)

Two outbreak investigations have been conducted, one in Israël in a day-care centre [Hochwald, 2010], and one in the US (California) by Witt [2012a]. The Witt [2012a] study has a number of caveats and has been heavily critiqued by the CDC [Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, Clark TA, Martin SW. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA. 2012a; 308(20): 2126-32.

Misegades, 2012b] and Nicole Guiso [Guiso, 2012] -- in their answers to these comments, the authors showed some more data with extremely large confidence intervals [Witt, 2012b]. The study from Israël, although of a limited size, is based on GSK vaccines only and showed a high vaccine effectiveness of 92% (40-98) from 2.5 years to 4 years after vaccination.

2.2.3. Screening method applied to passive national surveillance data (hospital and non-hospital cases) (see also Appendix Table 4)

The UK and the Netherlands used their national integrated surveillance to assess vaccine effectiveness, capturing both hospital and non-hospital cases across all age groups [Campbell 2012; van der Maas, 2013; de Greeff, 2008]. Their surveillance is passive and the levels of reporting might be relatively low, as indicated by serological data [Miller, 2000; de Melker, 2006]. These two countries introduced acellular vaccines in 2001 for the pre-school booster (full-dose), but for the primary schedule only in 2004 and 2005, respectively, which limits the time of follow-up for cohorts who received only acellular vaccines (as compared to other countries). The use of GSK vaccines was limited in the UK, where the vaccine schedule is atypical with no toddler booster in the second year of life, and in the Netherlands the market shares for GSK vaccines rose only since 2008.

After the primary schedule, the estimated vaccine effectiveness was 96.6% (95% CI 90.2-98.7) in the UK, based on culture-PCR confirmation (serology is not be used in the year following vaccination).

After the pre-school booster, the estimated vaccine effectiveness was 95.3% (95% CI 91.9-97.2) in the UK [Campbell, 2012], and 79% (95% CI 71-85) in the Netherlands [de Greeff, 2008]. Only the recent publication from the Netherlands [van der Maas, 2013] mentions waning of vaccine effectiveness in the years following the pre-school booster.

Another study based on the screening method was done by Sheridan [2014] in Australia, in Queensland region in 2009 and 2010. Here mostly GSK vaccines were used. Vaccine effectiveness was calculated for 3 doses in children aged 1-<4 years (no toddler booster), and for 4 or 5-doses of pertussis vaccine in children aged 5-<12 years, for each year of birth (from 1999 to 2008). Vaccine effectiveness estimates in children 1-<4 years old ranged from 83.5% (95% CI 73.9-89.5) to 89.4% (95% CI 82.6-93.5). In children 5-<12 years old, vaccine effectiveness estimates were between 71.2% (95% CI 49.9-83.4) and 87.7% (95% CI 80.1-92.3) in 2009, and between 34.7% (95% CI -7.2-60.3) and 70.3% (95% CI 53.0-81.3) in 2010, when reporting rates were possibly higher.

2.2.4. Studies based on active national surveillance, including only hospital cases (see also Appendix Table 5)

Two relatively old studies have assessed the vaccine effectiveness based on national hospital surveillance, one in Austria (at a time where different vaccines were used) [Rendi-Wagner; 2007] and one in Germany (at a time where mostly GSK vaccines were used) [Juretzko, 2002]. The estimated vaccine effectiveness was high in both studies, 92%, and 98.6% (91.5-99.9), respectively, with some protection seen already after the first dose (as confirmed recently in an impact study in Sweden [Nilsson, 2012]). The strength of these studies is the large population size. The main limitations of these studies are: i) unknown and potentially low levels of reporting (as shown in the same ESPED hospital network in Germany for varicella and intussusception, via capture-recapture studies), ii) the vaccination history was reported by the parents (and not validated), and iii) hospitalisation rates decrease with age as the disease is less severe in older children, with country-specific patterns (potentially linked to medical practices). These two studies can't measure the waning of vaccine immunity according to time since vaccination.

3. CONCLUSIONS

Following vaccination after DTPa vaccines, there are a number of different studies measuring the effectiveness of acellular vaccines and, despite different limitations for some studies, there has been so far no evidence of an unexpected lack of effectiveness within the first 5 to 6 years – in other words, the decrease in effectiveness according to time since vaccination reported in recent studies was in line with previous knowledge. Indeed, there are two recent studies in the US with enough power to specifically assess the impact of time since vaccination, based on a case-control design (not affected by under-ascertainment of the cases): the CA VE study by the US [Misegades 2012a] and the recently published study by Klein [2012]. Both studies show consistent results in 4 to

10 year old children in California regarding the impact of time since vaccination. Vaccine effectiveness is not measured in the Klein [2012] study, where the impact of time since vaccination depends on the assumed value in the first year after vaccination (by design, due to assumptions on which is based the statistical model). However, based on the vaccine effectiveness estimated in the CA VE study for the first year after vaccination, the impact of time since vaccination measured in both studies is consistent (from CA VE study, vaccine effectiveness was 98% (96.1, 99.1) in the first year after vaccination, with a drop to 71% (45.8, 84.8) during the sixth and following years). These two recent US studies may not however fully reflect the potential impact of the increased circulation of Prn-negative isolates in the US (as seen in Washington state outbreak for example).

Regarding Tdap vaccines, the case-control vaccine effectiveness study in adolescents currently led by the US CDC indicated a waning of effectiveness according to time since vaccination within the first 3-4 years after vaccination, which was not reported previously in the literature (there were so far few studies on Tdap vaccine effectiveness, with limited power to assess the impact of time since vaccination). The Tdap data from Washington State and Wisconsin are specific to birth cohorts who received only acellular vaccines (born in 1998-2002) and to a period of high circulation of Prn-negative isolates.

The relatively rapid waning of vaccine immunity according to time since vaccination contributed to the outbreaks in the US, as shown by the clusters of cases in specific birth cohorts, with an impact of the primary schedule (in particular the first dose) on Pertussis incidence. The use of acellular vaccines in the primary schedule and in particular for the first dose led to a higher incidence later in life (in >= 10 years old) both in Australia and the US (and in the UK). However, whether or not similar outbreaks as seen in these countries can be predicted in the future in other countries is difficult to understand, for the following reasons: **a)** in the US vaccination coverage and timeliness of vaccination are sub-optimal (including primary schedule), and Australia and the UK do not give the toddler booster, **b)** acellular vaccines used in 1998-2002 in the US included vaccines that were not used after 2002, **c)** the progressive implementation of Tdap since 2006 involved at the beginning cohorts primed with whole cell vaccines, and then, cohorts primed with acellular vaccines. This means that due to a different duration of protection (depending on the type of vaccine used in the primary schedule) several cohorts lost their vaccine protection at about the same moment, which may facilitate outbreaks. These specificities do not impact the conclusions of Washington state study, but make it difficult to assess the risk of similar outbreaks in the future in other places. For instance, in Australia, Tdap vaccines were introduced at about 15-17 years of age, with regional differences (cohorts born from 1998 start receiving Tdap now), and there is no adolescent booster in the UK.

There are gaps in the available data so far, for instance, there are no published data on Tdap effectiveness at pre-school age, when the effectiveness could be higher owing to the fact that pre-school children received already 3-4 doses within the past 4-6 years, whereas most of the US adolescents had not received any Pertussis vaccine in the past 7-8 years. There are also limited data on Tdap effectiveness in the adults or elderly [Baxter 2013].

Regarding the outbreaks of Pertussis, it is difficult to assess the impact of a decrease in Tdap vaccine effectiveness, because Pertussis outbreaks are multifactorial. Other factors also contributing to the reported outbreaks are: i) the temporal changes in surveillance

and diagnostic methods, disease awareness and reporting [Fisman, 2011; He, 2012] ii) a suboptimal vaccine coverage, or delayed vaccination (especially for the first dose), or missing one dose (especially the toddler dose), as shown in the US [Omer, 2008; Omer 2006], France [Grimprel, 1999], Sweden [Nilsson, 2012], Australia [Campbell, 2012], and in several other countries [Gangarosa, 1998]. In addition, new isolates such as Prn negative isolates are now becoming more frequent in several countries including the US and Australia, and the role of these isolates with respect to the outbreaks is unknown.

Some publications indicate a lower incidence of Pertussis in cohorts primed with whole cell vaccines. One should also be careful before extrapolating from country to country any data involving whole cell vaccines: there are different whole cell vaccines, and for some vaccines the characteristics changed over time (lot to lot inconsistency). In Latin America for instance there are also outbreaks despite the high coverage and use of whole cell vaccines. In Sweden and France, where there are robust long-term surveillance data, the 2012 peak is either small or undetected, although, these countries are not comparable to the US, Canada, Australia or the UK for several reasons such as vaccine coverage and vaccination schedule.

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5. APPENDICES

Appendix Table 1 Summary of published data on vaccine effectiveness studies on Tdap vaccination (reduced antigen content acellular GSK vaccines and other vaccines)

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
Rank [2009]								
Screening method, with cases being identified through surveillance based on mandatory notification (passive surveillance)	All high schools in New South Wales, Australia	Jan 1-Dec 31 2005	167 confirmed or suspected cases	GSK-vaccine (Boostrix)	Estimated population VC for the adolescent booster (Tdap) was 62% in 12-15 years old and 41% in 16-19 years old. Among the cases, 43 cases (26%) received the Tdap vaccine during the mass immunization school program	Adolescents from 12-19 years old. Time since vaccination not reported, but was <= 20 months as cases were collected from Jan to Dec 2005, and vaccination in the mass immunization school program took place from May to Dec 2004	78% (60.7, 87.6) for all study cases (167), and 85.4% (83.0, 87.5) for laboratory confirmed cases (155)	Unclear definition for breakthrough cases (what delay after vaccination was used?). Among the 43 vaccinated cases, 31 cases were confirmed by serology, whereas within one year of vaccination the serology used in this study may not differentiate the immune response to vaccination from that to infection. Both clinically and serologically diagnosed cases are likely to have included false positives and VE may therefore be underestimated. However, under-reporting was not considered as an issue.

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
Wei [2010]								
Outbreak investigation in a school including 499 students	Nursery to twelfth grade students in a school on St. Croix Island, USA Virgin Islands	30 Sep-19 Dec 2007	51 confirmed or probable cases (attack rate 10%)	GSK and Sanofi-Pasteur vaccines	Within the studied school, 98% of the students of >= 11 years had received at least 4 doses of Pertussis vaccines, and VC for the adolescent booster (Tdap) was 12% for students aged >= 11 years and 15-21% for 12-14 year old students	Disease clustered in grades 6-12 (11-18 years old), with a mean attack rate of 10%, and a 38% peak attack rate in tenth grade students (15-16 years old, i.e. born in 1991-1992) Time since vaccination was not reported in the article, but was likely <3 years as adolescent booster vaccination in the US started in 2005	65.6% (-35.8, 91.3) for all study cases (51), and 70.6% (-110.3, 95.9) for laboratory confirmed cases (25)	Small study with limited power (wide confidence intervals), in a population with low vaccine coverage. The vaccines received in the primary schedule in the studied cohorts are not specified (probably whole cell vaccines)

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
Baxter [2013]								
Retrospective database analysis based on a matched case-control design	Kaiser Permanente Northern California, USA	January 2006-December 2011	668 PCR positive cases	GSK and Sanofi-Pasteur vaccines	Tdap vaccination rates steadily increased over time, from near 0% in early 2006 to 25-30% in early 2010 when the outbreak started	69.8% of the cases were 11-19 years old. 91.6% of Tdap recipients were vaccinated within 2 years of their PCR test in the group who received only acellular vaccines, 61.7% in the group who received whole cell vaccines in early childhood, and 57.9% in the oldest group born before pertussis vaccines were widely available	64.0% (55.5, 70.9) in the comparison with Kaiser Permanente Northern California controls; 53.0% (41.9, 62.0) in comparison with PCR negative controls	Matching with PCR negative controls intended to control for different health-seeking behaviours, but then the matching was less precise than with the other control group and this would impact VE estimates (some of the covariates being important confounders) -- this is well discussed in the article. Limitations of the PCR test (lack of sensitivity and/or lack of specificity) would also lead to under-estimate VE.

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
Sicard [2013]								
Surveillance based on mandatory reporting within the French armed forces. Screening method.	French armed forces	From 2007 to 2012	458 reported cases, including 176 cases confirmed by serology, 20 by PCR, 262 with non-interpretable or negative laboratory results (102 epidemiologically confirmed cases and 160 suspected cases)	dTap-IPV (Boostrix Polio from GSK and Repevax from Sanofi)	The number of dTap-IPV doses delivered in the armed forces increased from 2008 to 2010 up to about 32000 doses per year, and remained stable since 2010	Adult population. The mean age of the cases was 31 years. A dTap vaccination history was reported for 79 cases, with a mean time since vaccination of 13 years (median 12 years, range 0.3-30.9 years), including 52 subjects vaccinated over 5 years earlier.	VE was 83.7% (72-90.5%) and a comparable value of 88.4% (73.6-94.9%) after exclusion of suspected cases from the analysis. VE in 2011-2012 was 93.5% (79.4-98%) and 73.5% (51.4-85.5%) in 2008-2010.	Limitations of the study are related to the fact that aggregated data (number of vaccines delivered) were used as a proxy to estimate the population size of vaccinated and non-vaccinated persons, and some vaccination events in the cases might have been underreported. However, the vaccination campaign was followed by a significant decrease in the incidence, showing the impact of vaccination in the French armed forces population.

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
Tafuri [2013]								
Outbreak investigation	Students of local elementary and middle schools and some adults in the small town of Puglia (Italy)	2009	16 children and 4 adults	In 2001-2005, Hexavac (SPMSD) and Infanrix Hexa (GSK), had about 50/50 market share. From 2005, only Infanrix Hexa is used. For the preschool booster, Tdap vaccines are used.	Vaccine coverage is high in Italy for the primary schedule but vaccine coverage for the 5th-6th year and at 13th-14th year are not available	Children and adults. A cluster occurred in the elementary class of the index case, who was 9-years old. Time since vaccination documented for each case.	Overall attack rate was 15.8%: 20% in children who did not receive booster doses at 5-6 years old and 14.3% in children who received the booster. The VE was estimated at 28.5%. In the cluster, the attack rate was 12/27: 10/20 in children who had not received a preschool booster and 2/7 in children who had not received it. The VE was 42.8% in this setting.	Very small outbreak, with no confidence intervals provided for the estimations of VE. An interesting observation is the fact that the vaccinated cases were mild, only the index case developed a persistent cough..

Terranella et al, 61st Annual Epidemic Intelligence Service Conference, 2012								
Retrospective cohort studies (school A and B)	high schools in one county in Maine (2 outbreak schools with the highest attack rate)	August-Dec 2011	13 cases among 120 students in School A, and 13 cases among 206 students in School B	Acellular pertussis vaccines (Boostrix and Adacel)	In School A Tdap coverage among eligible students was 65% At School B Tdap coverage was 39% among eligible students	Adolescents from 11-19 years old Time since vaccination not reported	76% for School A and 71% for School B	Tdap was effective in preventing disease among vaccinated students; however suboptimal coverage of 65% or less may have contributed to these outbreaks.
Skoff et al, 45th National Immunization Conference, CDC, 2011								
Case-Control Study	Cases and controls from 36 high schools in Minnesota	October 2007-December 2008	99 cases and 187 controls were included in the analysis	Tdap acellular vaccines available in the USA (Boostrix and Adacel)	9.1% of cases and 31.6% of controls received Tdap	Adolescents from 11-17 years old Median age for cases and controls was 15 and 14 years, respectively Time since vaccination not reported	Overall VE against laboratory-confirmed pertussis for adolescents receiving Tdap was 72.0% (38.0, 87.3). VE was higher but not significantly when vaccination occurred in the previous year compared with a year or more: 75% (24.2, 91.8) vs. 68.9% (13.9, 88.8) respectively	This study suggests that Tdap is effective at preventing disease among adolescents 11-17 years of age

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
Liko, 2014								
Retrospective database analysis Screening method	Oregon residents aged 2 months to 19 years old during the year 2012	2012	617 laboratory confirmed Pertussis cases	DTPa and Tdap acellular vaccines available in the USA (GSK and Sanofi). The 17-19 years old, and some of the 13-16 years old, were primed with whole cell vaccines.	Vaccination coverage obtained from the "ALERT" population-based immunisation information system which began in 1996. VC presented by age group, eg for Tdap 45% in 11-12 years old, 85% in 13-16 years old and 73% in 17-19 years old	Population aged 2 months to 19 years old. Results presented by age group and not according to time since vaccination; definition of "up to date" vaccination status for preschool and adolescent boosters did not consider timeliness of vaccination	Primary schedule: 73% (43-87) and 72% (6-91) at 2-3 months and 4-5 months, raising to 86% (72-93) at 6-14 months and 95% (92-97) at 15-47 months. Preschool DTPa booster: 89% (81-94) at 4-6 years and 83% (72-90) at 7-10 years Tdap adolescent booster: 65% (46-78) at 11-12 years, 47% (19-65) at 13-16 years and 66% (30-84) at 17-19 years	The results are aligned with previous studies for the primary schedule, and with the CAVE study in preschool children in California (Misegades 2012), and with recent US data in adolescents from Washington state and from Wisconsin (Acosta 2013; Koepke 2013)

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
CDC case-control study, ACIP June 2013 and Acosta 2013								
Matched Case-Control Study	Cases and controls from Washington state (from 7 counties with highest incidence)	January-June 2012	826 cases and 2306 controls included in the analysis	Tdap acellular vaccines available in the USA (Boostrix and Adacel)	For the 11-14 years old adolescents, VC was 88% among the controls and 77% among the cases	Adolescents from 11-19 years old, born in 1993-2000 Median time since vaccination among the 11-19 years old: 32 months. Median time since vaccination among the 11-14 years old: 20 months. Median time since Tdap vaccination among the 15-19 years old: 44 months.	In adolescents aged 11-14 years, VE was 65% (50, 75), with estimates of 75% (62, 83) in the first year following vaccination, 56% (34, 71) in the second year, and 39% (4, 61) in the third and fourth years following vaccination. If adolescents aged 15-19 years are included, VE was 41% (4, 63)	This study indicated a relatively rapid waning of vaccine protection during the first 4 years following vaccination, in adolescents who received acellular vaccines in the primary schedule in the years 1998-2001 (when different vaccines were used, including vaccines that were not used anymore since 2002).

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
Koepke et al, 2014								

Study type = study design to assess vaccine effectiveness	Study population	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC)	Age of the population/Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals (CI) in parentheses	Comments
Retrospective database analysis Screening method	Wisconsin residents born during 1998-2000 with client records in the Wisconsin Immunisation Registry	July 2011-Dec. 2012 outbreak (vaccination data back to 2008)	959 cases reported among 223959 members, among which 940 were matched to the immunisation registry client records	Tdap acellular vaccines available in the USA (Boostrix and Adacel)	Tdap receipt increased with increasing age to 91.6% among the population members aged 14 years old in 2012 (born in 1998).	Adolescents born in 1998-2000 Among the cases, time since vaccination was 1.9 years.	Tdap age-adjusted VE decreased significantly from 75% (55 – 87%) to 68% (61-74%) to 35% (20-46%) to 12% (-11-30%) among those with Tdap immunity dates in 2012, 2011, 2010, and 2009/2008 respectively. Among the members who had Tdap immunity date before 2012, the VE was greater among Boostrix recipients than among Adacel recipients, with estimates of 80%, 53% and 31%, versus 59%, 14% and -2%, in 2011, 2010 and 2009/2008 respectively.	The results are consistent with the CDC case-control study in Washington state, and the Oregon data. The brand-specific VE data should be handled with caution because the design does not permit any comparative conclusions to be drawn. However, the results showed a good VE for the Tdap vaccine.

Note: Only effectiveness studies were included, therefore the APERT efficacy clinical trial is not included [Efficacy of 92% (95% CI: 32.0-99.0) [Ward, 2005].

Appendix Table 2 Summary of published data or abstract available on vaccine effectiveness studies on DTPa vaccination (Infanrix and other acellular vaccines) – Case-Control Studies

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage	Age of the population /Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals in parentheses	Comments
Misegades [2012a] - Preschool vaccination								
Case control study with 3 controls for 1 case	15 counties of California, USA	2010 Outbreak	>1000 cases	Both GSK and Sanofi-Pasteur (5 component) pertussis vaccines	65% of the cases and 68% of the controls received the 5th dose of DTPa at 4 years of age	Cases 4 to 10 years old. Up to 5-6 years after vaccination	Overall VE was 88.7% (79.4, 93.8); with a steady drop from 98% (96.1, 99.1) during the first year following the 5th dose to 71% (45.8, 84.8) during the sixth and following years after the 5th dose of DTPa (overall 27% drop)	With estimates for each year following vaccination independent from each other, and a sufficient power (small confidence intervals), the study measures precisely the waning of VE according to time since vaccination
Klein [2012] - Preschool vaccination								
Retrospective case–control database study. Two sets of controls: i) 3318 controls who were PCR-negative for pertussis ii) 6086 matched controls from the population of health-plan members. Logistic regression to assess the odds ratio according to time since vaccination (linear relation assumed in the proportions)	Kaiser Permanente Northern California, USA	2006-2011	277 cases	Both GSK and Sanofi-Pasteur (5 component) pertussis vaccines	Not reported	Children 4-12 years of age that received the 5th DTPa dose at 47 to 84 months of age	The risk of pertussis increased by 42% each year after the fifth DTPa dose. Thus, if the VE of DTPa was 95% or 90% in the first year after vaccination, it would drop to 71% or 42% after 5 years, respectively	Protection against pertussis waned during the 5 years after the fifth dose of DTPa. Based on these statistical methods (assuming a proportional drop in VE), the remaining amount of protection after 5 years depends heavily on the initial effectiveness

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage	Age of the population /Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals in parentheses	Comments
Bisgard [2005] - Primary vaccination								
Case-control study For each case, 5 control children were matched from birth certified records according to date of birth and place of residence	Cincinnati, Ohio, metropolitan area of Colorado, Idaho and Minnesota, USA	1998-2001	184 confirmed cases in children aged 6-59 months	From 1998-2001, 4 different acellular pertussis vaccines were used: i) Mono–component Baxter vaccine; ii) Two component Sanofi vaccine; iii) Three component GSK vaccine; iv) Four component Wyeth vaccine	One quarter of reported cases were unvaccinated from 6 to 59 months (no more details in the publication)	Cases aged from 6 months to 59 months Time since the last dose <= 41 months	Combined VE for 3 doses of the different DTPa vaccines: 95.4% (88.7, 98.2); Combined VE for 4 doses of the different DTPa vaccines: 96.7% (90.8, 98.8)	Any combination of >3DTP/DTPa vaccine doses for children was highly protective against pertussis, with an effectiveness of 98% (95.0-99.2)

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage	Age of the population /Time since vaccination	Vaccine Effectiveness (%) with 95% confidence intervals in parentheses	Comments
Quinn [2014] - Primary vaccination								
Retrospective matched case-control database study (hospitalised and non-hospitalized cases)	All regions of Australia. Cases from notification data; control subjects selected from the national database of immunizatio n in children	2005-2009	4584 cases, and 20 controls matched to each case	the majority of these children should have received Infanrix	VC for 3 doses or more: 92% at 12 months and 95% at 24 months. Toddler booster removed since 2003 ("3+0" vaccine schedule)	Cases aged from 2 months to 3 years old (<4 years old) Time since vaccination not reported (<4 years)	VE against all reported cases increased from 53.7% (43.8, 61.9) for 1 dose before 4 months of age to 75.3% (65.7, 82.3) for 2 doses before 6 months of age. VE of 3 doses against all reported cases was: - 83.5% (79.1, 87.8) between 6 and 11 months of age - 79.2% (75.0, 82.8) in one-year old children, - 70.7% (64.5, 75.8) in 2 years old children, - 59.2% (51.0, 66.0) in 3 years old children.	Decreased VE for all notified cases of pertussis during the first four years of life was consistent with waning of immunity, prior to the first booster of DTPa scheduled at 4 years of age in Australia (where there is no toddler booster).

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage (VC)/ vaccine schedule	Age of the population/Time since vaccination	Vaccine Effectiveness (VE) (%) with 95% confidence intervals in parentheses	Comments
Riffelmann [2013] - Primary vaccination								
Laboratory data from 3 paediatric offices with 7 paediatricians (passive surveillance). Case-negative design.	Germany, non-hospitalized cases, laboratory data	June 2005-January 2006	262 consecutive nasopharyngeal swabs from children with symptoms compatible with Pertussis	In Germany, hexavalent vaccines were introduced in 2000 and then quickly replaced previously used vaccines, with a balanced market share between Infanrix Hexa (GSK) and Hexavac (SPMSD) up to 2005 (Von Kries 2009)	In 2005, acellular vaccines were recommended at 2, 3, and 4 months of age, 11-14 months of age and 9-17 years of age for the adolescent booster. Among all cases, only one had more than 4 doses and therefore the results relate here to the primary schedule. From 2003 to 2006, vaccine coverage with >=4 doses was 94%-95.8% in different age groups between 15 months and 10 years old.	Age of the population: 0–15 years Time since vaccination was 6.05 years among PCR-positive cases and 2.22 years among PCR-negative cases	Taking as a reference the group with >8 years since vaccination (as a proxy for unvaccinated reference), the VE was estimated at 98% (87-100%) from 0 to <2 years after vaccination, 96% (74-100%) from 2 to <4 years after vaccination, 64% (-243-97%) from 4 to <6 years after vaccination, and 53% (-272-95%) from 6 to <8 years after vaccination	Small population size. Short article with a good discussion, presenting an original and very interesting method for assessing vaccine effectiveness

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage (VC)/ vaccine schedule	Age of the population/Time since vaccination	Vaccine Effectiveness (VE) (%) with 95% confidence intervals in parentheses	Comments
Haller et al, ESCAIDE reference number: 20131579								
Stratified case-cohort analysis in 3 different age groups.	Germany (Brandenburg). Children in schools and kindergarten born in: 2005 – 2009: aged 2/3 yrs 1995 – 2006: aged 5/7yrs 1995 – 1998: aged 15/16yrs	1995 - 2012	2-3yrs: 19 cases 5-7yrs: 271 cases 15-16yrs: 96 cases	In Germany, high concentration acellular pertussis vaccines replaced whole cell vaccines in 1995	VC: 2-3yrs: 94% 5-7yrs: 96% 15-16yrs: 97% Vaccine schedule: 3 +1 (by 14 months of age). Tdap boosters recommended for 9-17yr olds in 2000 and for 5-6yr olds in 2006.	2005 – 2009: 2-3 yrs old 1995 – 2006: 5-7 yrs old 1995 – 1998: 15- 16 yrs old Time since vaccination not mentioned in the abstract	VE for 4 doses: 2-3yrs: 97% 5-7yrs: 88% 15-16yrs: 84%. VE was higher among children 5-7years (93%) and 15-16 years (97%) of age who had received a booster.	This is one of the few studies with age stratified data. The importance of boosters and vaccine coverage in modifying pertussis incidence was highlighted

Appendix Table 3 Summary of published data on vaccine effectiveness studies on DTPa vaccination (Infanrix and other acellular vaccines) - Outbreak Investigations

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage	Age of the population/Time since vaccination	Vaccine Effectiveness (VE) (%) with 95% confidence intervals in parentheses	Comments
Witt [2012a] - Mostly preschool vaccination								
Case-based study (outbreak investigation)	Kaiser Medical center, Marin County, California, USA	Outbreak in 2010	132 cases	Not reported in the publication. Both GSK and Sanofi–Pasteur acellular pertussis vaccines are used	Vaccination rates across age groups were 88% to 94%. Among the study cases (<18 years), 81% were fully vaccinated, 11% under vaccinated and 8% never vaccinated	Cases aged from 2 years to 18 years. The incidence rose in patients 8 to 12 years old. Time since vaccination not reported	41% for children aged 2-7 years; 24% for children aged 8-12 years; 79% for children aged 13-18 years; 51% for children aged 2-18 years	Methodology not robust and results not reliable, due to methodological issues, as reported in the comments by Guiso and Misegades [Witt, 2012b; Misegades LK, Winter K, Harriman K, Talarico J, Messonnier NE, Clark TA, Martin SW. Association of childhood pertussis with receipt of 5 doses of pertussis vaccine by time since last vaccine dose, California, 2010. JAMA. 2012a; 308(20): 2126-32. Misegades, 2012b; Guiso, 2012]
Hochwald [2010] - Primary vaccination								
Case-based study (outbreak investigation)	Day-care center in Israel	Outbreak from Dec 2005 to Jan 2006	6 cases among a population of 31 children in	Infanrix	4 out of the 31 children were not vaccinated; the remaining 27 children had all four doses of Infanrix	In the 31 children, the time from the last dose of pertussis vaccine to the current outbreak	92.5% (40, 98)	All non-vaccinated children got pertussis in this outbreak. Only two cases were vaccinated, and for these two

			the day care center			ranged from 2.5 to 4 years		children, one was PCR-culture negative, and got the disease later with milder symptoms

Appendix Table 4 Summary of published data on vaccine effectiveness studies on DTPa vaccination (Infanrix and other vaccines) – Screening method based on passive surveillance data (hospital and non-hospital cases)

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage (VC)/ vaccine schedule	Age of the population/Time since vaccination	Vaccine Effectiveness (VE) (%) with 95% confidence intervals in parentheses	Comments
Campbell [2012] - Primary and preschool vaccination								
National surveillance bases on mandatory reporting, including hospital cases (passive surveillance) Screening method	England and Wales, hospitalized and non-hospitalized cases, laboratory notifications to the Health Protection Agency, and deaths (registry, National Office of Statistics)	2002-2009	Hospitalized cases from 2002-2009: 1695 cases in <3 month old children; 464 cases in 3-5 month old children; 179 cases in 6-11 month old children; 298 cases in 1-4 year old children; 113 cases in 5-9 year old children; 82 cases in 10-14 year old children; 43 cases in >15 year old children	In 2001, acellular vaccines were introduced for the preschool booster at 3 years of age, using both GSK and Sanofi-Pasteur (5 components) vaccines In 2004, acellular vaccines were introduced for the primary vaccination (first year of life). Since 2004, only Sanofi-Pasteur vaccine was used (5 components)	In 2009, VC for primary vaccination (3 doses) in England was 95.3%, and 79% for 4 doses "3+0" schedule, i.e. 3 doses in the first year of life, no toddler booster in the second year of life, and first booster in the third year of life	Age of the population: 0–16 years Time since vaccination not reported	VE for 4 doses: 95.3% (91.9, 97.2) In children 12-39 months old who received only DTPa: the VE for 3 doses was 69% (-24.2, 89.5) with serology confirmation and 96.6% (90.2, 98.7) with culture-PCR confirmation	Large population size, but passive surveillance with unknown under-reporting

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage (VC)/ vaccine schedule	Age of the population/Time since vaccination	Vaccine Effectiveness (VE) (%) with 95% confidence intervals in parentheses	Comments
Van der Maas [2013] - Primary and preschool vaccination								
National surveillance, based on mandatory reporting, including hospital cases (passive surveillance) Screening method	The Netherlands hospitalized and non-hospitalized cases, and laboratory notifications to the RIVM, and deaths (registry)	1996-2012	Although the measures taken resulted in decreased IRs among the targeted age groups after implementation, the overall mean IRs of notifications increased over the study period. During the 2011-2012 outbreak, young infants not yet vaccinated had an IR of 259.6/100000 in 0-2 months old.	For the preschool booster, acellular vaccines were introduced in 2001, with a recent switch from a full-dose booster to Tdap For the primary vaccination, a whole cell vaccine was replaced by GSK vaccine in 2005 (Infanrix-IPV-HIB), and then by Sanofi-Pasteur 5-component vaccine in 2006. Then, market shares for GSK vaccines rose since 2008. All details are provided in the article (Box 1).	VC for primary and booster dose at 4 years of age was about 96% and 92% respectively	VE provided for the preschool booster for 6-11 years old per year.	VE of the booster dose decreased with time since vaccination, being 82%, 76%, 63%, 59% and 52% for 5, 6, 7, 8 and 9-years old, respectively. After introduction of the acellular vaccines, the VE per 3-years-period of the primary series increased, ranging from 33-73%, 27-48% and 24-51% for the 1-, 2- and 3-years old before introduction, to 86-92%, 75-91% and 65-85% for the respective ages after implementation of acellular vaccines.	This article presents both extensive VE data, and incidence and impact data, by age group and period. VE estimates by age and calendar time (table 3) are based on small numbers in each age and period, and the confidence intervals are not available.

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of cases	Vaccines used	Vaccine coverage (VC)/ vaccine schedule	Age of the population/Time since vaccination	Vaccine Effectiveness (VE) (%) with 95% confidence intervals in parentheses	Comments
de Greeff [2008] - Primary and preschool vaccination								
National surveillance, based on mandatory reporting, including hospital cases (passive surveillance) Screening method	The Netherlands hospitalized and non-hospitalized cases, and laboratory notifications to the RIVM, and deaths (registry)	1998-2001 (without pre-school booster) and 2002-2005 (with pre-school booster)	During the 2002-2005 period (as compared to 1998-2001), the incidence of hospitalizations drop by 40% in infants aged 0-6 months, by 48% in 1-4 year old children, and by 32% in 5-9 year old children Whereas, in the 10-19, 20-59 and >60 years age groups, the incidence rose by 60%, 44% and 68%, respectively	For the preschool booster, acellular vaccines were introduced in 2001, with a recent switch from a full-dose booster to Tdap For primary vaccination, a whole cell vaccine was replaced by GSK vaccine in 2005 (Infanrix-IPV-HIB), and then by Sanofi-Pasteur 5-component vaccine in 2006. Then, market shares for GSK vaccines rose since 2008	VC >96% in infants	All ages (including >60 years old)	VE for the preschool booster was 79% (71, 85) in cohorts born in 1998-2000	No evidence was found for waning of immunity up to 4 years after the preschool booster as the estimated VE remained high, 73-84% in the vaccinated cohorts
Sheridan [2014]- Primary and preschool vaccination								
National surveillance based on mandatory reporting including hospital cases (passive surveillance) Screening method	Queensland region in Australia	2009-2010 epidemic	599 notified cases and 20 hospitalised cases in 2009, 1362 notified cases and 9 hospitalized cases in 2010	Infanrix and Boostrix were used since 1999, except from Nov 2005 to June 2006 when Quadracel was used for the primary schedule	Ranging from 94.5% to 96.1% depending on the birth cohort (cohorts included in the study: 1999 to 2008)	Children aged 1-<4 years and 5-<12 years	In children 1-<4 years old, VE point estimates (by age) against notification and hospitalisation ranged from 83.5% to 89.4%. In children 5-<12 years old VE point estimates against notification were between 71.2% and 87.7% in 2009 and between 34.7% and 70.3% in 2010.	Waning VE by age is reflected in the results (cf table 3), with wide CI in older age groups. Laboratory data indicates higher reporting in 2010 than 2009 (more negative tests in 2010)

Appendix Table 5 Summary of published data on vaccine effectiveness studies on DTPa vaccination (Infanrix and other pertussis vaccines) – Studies based on hospital surveillance (active surveillance)

Study type = study design to assess vaccine effectiveness	Study setting	Study period	Number of pertussis cases	Vaccines used	Vaccine coverage (VC) / vaccine schedule	Age of the population/ Time since vaccination	Vaccine Effectiveness (VE) (%) with 95% confidence intervals in parentheses	Comments
Rendi-Wagner [2007] - Primary vaccination								
National surveillance of hospitalized patients (active surveillance)	All paediatric departments in Austria	Jan 1996-Dec 2003	1441 hospitalized pertussis cases <15 years old	1998-1999: both acellular and whole cell vaccines were used 2000-2003: acellular vaccines from GSK and Sanofi-Pasteur (Tetravac, Hexavac Infanrix, Infanrix-Hexa)	88-97% in 2000-2003 ("acellular era")	The median age of all reported cases since 1998 was 3.6 years (range: 0-14 years). Time since vaccination not reported (median around 2 years)	92% in children vaccinated with acellular vaccines with 3 doses (no confidence intervals reported) VE with acellular vaccine is higher in children up to 24 months as compared to older children	Large population size. There is a no capture-recapture study. Some cases may have been missed, leading to an under-estimated vaccine effectiveness
Juretzko [2002] - Primary vaccination								
National surveillance of hospitalized patients (active surveillance)	All hospitals in Germany (ESPED network)	June 1996-Dec 1998	529 hospitalized pertussis cases <16 years old	From a vaccine coverage phone survey done in 1999: 1559 doses of acellular vaccine were received by 503 children, of which 89% of the doses were Infanrix.	In 1997 the VC for 24 months old children was 91% In the 1999 phone survey, by 12 months of age 84.1% of children had completed primary vaccination (schedule 3+1)	Most of the cases were unvaccinated The age of the hospitalized cases ranged from 0-32 months Time since vaccination not reported (maximum <32 months)	VE for 3 doses of acellular vaccine was 99.8% (98.9-100) After the toddler booster, VE for 4 doses was 98.6% (91.5-99.9)	Large population size. There is a no capture-recapture study. Some cases may have been missed, leading to an under-estimated vaccine effectiveness

APPENDIX 7B.2 : Infanrix hexa - Prevenar 13 co-administration

Vaccines Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Infanrix hexa - Prevenar 13 co-administration: Convulsions with or without fever and Hypotonic-hyporesponsive episode

Date of review	20 February 2013
Vaccine terms included	• Infanrix hexa (IGA182) • Pneumococcal vaccine (IGB047)
Adverse events included	• Convulsions (narrow SMQ) • Hypotonic-hyporesponsive episode (PT), Hypotonia, Hypotonia neonatal (PT)
Authors	• [redacted] Safety Scientist • [redacted] Safety Physician

[redacted]

LIST OF ABBREVIATIONS

CHMP	Committee for Medicinal Products for Human Use
DTP	Diphtheria, Tetanus, Pertussis
EMA	European's Medicines Agency
EU	European Union
GSK	GlaxoSmithKline
HHE	Hypotonic-Hyporesponsive Episode
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
PCV	Pneumococcal Conjugate Vaccine
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PI	Product Information
PT	Preferred Term
RSI	Reference Safety Information
SAE	Serious Adverse Event
SMQ	Standard MedDRA Query

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1. BACKGROUND

On 21 January 2014 GlaxoSmithKline (GSK) was informed by the European's Medicines Agency (EMA) about the fact that, on 19 September 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted Opinion on the periodic safety update report (PSUR) of Prevenar 13 (pneumococcal polysaccharide conjugate vaccine, 13-valent, adsorbed). This Opinion was based on a recommendation from the Pharmacovigilance Risk Assessment Committee (PRAC) and recommended that the Product Information (PI) for Prevenar 13 be updated with a warning on the observed increased reporting rates of convulsions (with or without fever) and hypotonic hyporesponsive episode (HHE) following concomitant administration of Prevenar 13 and Infanrix hexa.

The PRAC was of the opinion that the identified safety information and corresponding PI changes are also relevant for Infanrix hexa. Therefore, as Marketing Authorization Holder (MAH) of Infanrix hexa, GSK was requested to assess the need to update the PI of Infanrix hexa.

GSK hereby provides a recent (data lock point 26 January 2014) assessment of spontaneous data for convulsions with fever, convulsions without fever and HHE following:

- Infanrix hexa without concomitant administration of any pneumococcal vaccine
- Infanrix hexa concomitantly administered with Prevenar 13

2. POST-MARKETING EXPOSURE

Since market launch over 107 million doses of Infanrix hexa have been distributed worldwide. Sales data for Prevenar 13 and the number of Infanrix hexa doses co-administered with Prevenar 13 are unknown to GSK.

3. SAFETY DATA REVIEWED

3.1. Database Search Strategy

Convulsions (with or without fever) and HHE are known side effects listed in the Infanrix hexa reference safety information (RSI). The present evaluation primarily intends to assess whether concomitant administration of Infanrix hexa with Prevenar 13 tends to trigger these side effects more frequently compared to administration of Infanrix hexa without concomitant administration of any pneumococcal vaccine.

A direct comparison of spontaneous reporting rates[1] is not feasible because post-marketing exposure data of concomitant administration of Infanrix hexa with Prevenar 13 is unavailable. Therefore the methodology chosen consisted of comparison of the proportion (percentage) of an event of interest among all cases spontaneously reported to the GSK global safety database where Infanrix hexa was not reported as co-administered with any pneumococcal vaccine, to the proportion of that event among all cases spontaneously reported to GSK where Infanrix hexa was reported as co-administered with Prevenar 13.

3.1.1. Initial query

Two separate searches were performed in the GSK worldwide safety database on 27 January 2014, one for each of the following '**Vaccine names**':

i. Infanrix hexa (drug code IGA182)

ii. Pneumococcal vaccine (Non-GSK) (drug code IGB047)

Further search criteria were as follows:

- **Report types**: All spontaneous reports
- **Data lock point:** since first case reported until 26 January 2014
- **MedDRA preferred terms:** None (i.e. *at this stage* all cases/SAEs are retrieved for the queried vaccines)
- **Vaccine type:** Suspect

[1] A spontaneous reporting rate or frequency is the number of spontaneously reported cases/SAEs divided by a number of doses distributed.

3.1.2. Overall number of cases

The two queries described above respectively retrieved 16925 cases where Infanrix hexa was the suspect drug, and 7839 cases/SAEs where a 'Pneumococcal vaccine (Non-GSK)' was reported as the suspect drug.

3.1.3. Identification of Prevenar 13 cases/SAEs among 'Pneumococcal vaccine (Non-GSK)' cases/SAEs

In the GSK global safety database, the vaccine name 'Pneumococcal vaccine (Non-GSK)' includes different non-GSK pneumococcal vaccines. To distinguish Prevenar 13 from other non-GSK pneumococcal vaccines, the field 'Associations - Drug IT' was used. Results are shown in Table 1. Prevenar 13 was the second most frequent non-GSK pneumococcal vaccine spontaneously reported to GSK, preceded by Prevenar (PCV7). There were 2746 spontaneous cases/SAEs where Prevenar 13 was reported as suspect drug.

Table 1 Non-GSK pneumococcal vaccine brands among spontaneous cases where the suspect drug is Pneumococcal vaccine (Non-GSK)

Included term (IT)	Number of cases (%)	
Prevnar	4672	(59.60%)
Prevenar 13	2746	(35.03%)
Unkown	330	(4.21%)
Pneumovax	63	(0.80%)
Pneumovax II	27	(0.34%)
Pneumopur	1	(0.01%)
TOTAL	**7839**	**(100.00%)**

3.1.4. Identification of cases/SAEs where Infanrix hexa was not reported as co-administered with any pneumococcal vaccine

Cases/SAEs where Infanrix hexa was not reported as co-administered with a pneumococcal vaccine (regardless of brand) were identified as a subset of the total cases/SAEs where Infanrix hexa was reported as suspect drug. This subset was built by removing all cases/SAEs where co-administration of Infanrix hexa with a pneumococcal vaccine (regardless of brand) was reported from the total Infanrix hexa set of cases/SAEs. The number of cases/SAEs remaining in this subset was 10155 (see Table 2).

3.1.5. Identification of co-administration cases/SAEs

Cases/SAEs where Infanrix hexa and Prevenar 13 were reported as concomitantly administered (regardless of events) were defined as those present in both the set of cases/SAEs where Infanrix hexa is the suspect drug and the set of cases/SAEs where Prevenar 13 is the suspect drug.

An overview of the outcomes of the datasets operations described above is provided in Table 2.

Table 2 Overview of numbers of cases worldwide since 2000

	Infanrix hexa	Pneumococcal vaccine (Non-GSK)	Infanrix hexa & Prevenar 13 co-administration
Total number of spontaneous cases/SAEs reported by the query described in Section 3.1.1	16925	7839	-
Subset of Prevenar 13 cases/SAEs among 'Pneumococcal vaccine (Non-GSK)' cases/SAEs	-	2746	-
Cases common to both Infanrix hexa cases (16925) and the Prevenar 13 subset (2746)	-	-	2244
Subset of Infanrix hexa cases/SAEs reported without any pneumococcal vaccine among all 'Infanrix hexa' cases	10155	-	-
Number of cases in final datasets	10155	-	2244

3.2. Spontaneous data

3.2.1. General trends

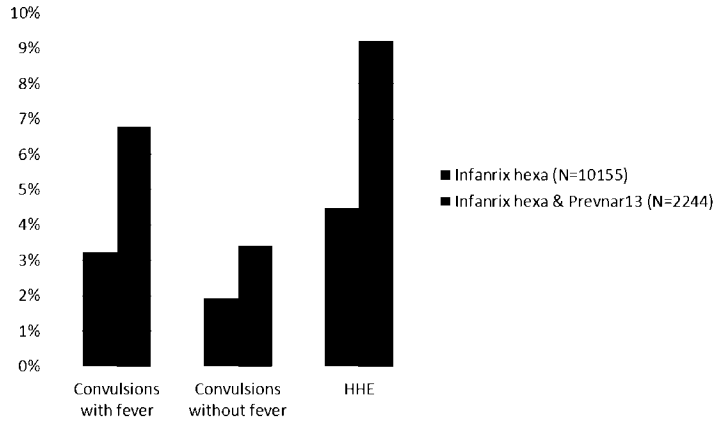
The 'Infanrix hexa' subset and the co-administration subset (see Table 2) were further queried to identify those cases/SAEs for which convulsions (with or without fever)[2] or HHE[3] were reported. Among the convulsion cases/SAEs, those that were reported with fever were distinguished from those reported without fever by the presence/absence of the following preferred terms (PTs): Pyrexia, Hyperpyrexia, Hyperthermia, Body temperature increased, Febrile convulsion and Febrile infection.

Figure 1 shows the worldwide proportion (%) of cases/SAEs since launch of Infanrix hexa (2000) for each of the three events of interest among all cases/SAEs in the 'Infanrix hexa' and 'Infanrix hexa & Prevenar 13' subsets. All three events of interest displayed higher reporting proportions in the 'Infanrix hexa & Prevenar 13' co-administration subset.

[2] Using the narrow SMQ 'Convulsions'

[3] Using the PTs 'Hypotonic-hyporesponsive episode', 'Hypotonia' and 'Hypotonia neonatal'.

Figure 1 Worldwide spontaneous proportions since 2000



The Y-axis represents the % of cases including the event of interest among all cases in a given subset. The denominator of each subset of cases is provided between brackets next to the subset name in the graph's legend.

3.2.2. Specific trends by calendar time, country and age at event onset

In order to limit confounding by calendar time, country and subject's age, specific sub-analyses were performed for these parameters.

A potential bias in Figure 1 might be the fact that cases in the 'Infanrix hexa' subset were received in the period between and including 2000-2014, while those in the 'Infanrix hexa & Prevenar 13' subset were received between and including 2010-2014. Given that, in theory, specific national reporting of convulsions and HHE can change over time as compared to other events, sub-analyses were performed for two **time periods**: 2000-2014 and 2010-2014.

Spontaneous cases in the 'Infanrix hexa' and 'Infanrix hexa & Prevenar 13' subsets were mainly received from Germany (29.5% and 21.3%, respectively) and from Italy (29.0% and 69.4%, respectively) (see Table 3). Therefore, **country** sub-analyses were performed separately for these 2 countries which together represent between 58.5% (for the 'Infanrix hexa' subset) and 90.7% (for the 'Infanrix hexa & Prevenar 13' subset) of available spontaneous data.

Measles-mumps-rubella (MMR) and especially measles-mumps-rubella-varicella (MMRV) vaccination are also triggers of fever and febrile convulsion. The national MMR(V) vaccination schedules in the two countries from which most cases analysed herein were reported recommend the first MMR(V) dose at 11-14 months of age (Germany) and 12-14 months of age (Italy). In order to limit confounding by potential (not reported) MMR(V) vaccinations, two age groups were separately assessed: 0-9 months of age (which should include subjects not receiving MMR(V) vaccination) and 10-24 months (which might include subjects potentially receiving MMR(V) vaccination).

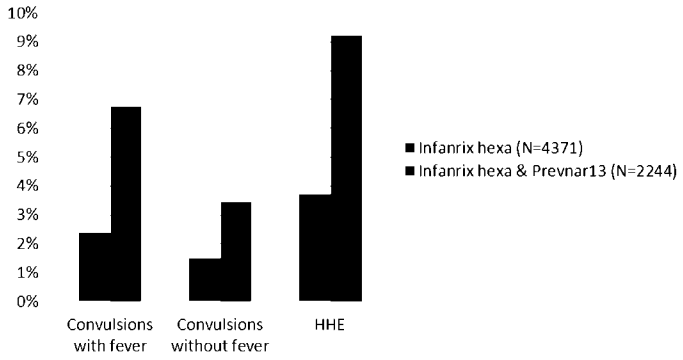
Table 3 Country distribution of cases/SAEs in the 'Infanrix hexa' and 'Infanrix hexa & Prevenar 13' subsets

Subset of Infanrix hexa cases/SAEs reported without any pneumococcal vaccine			Infanrix hexa & Prevenar 13 co-administration cases/SAEs		
Country	Number of cases/SAEs (%)		Country	Number of cases/SAEs (%)	
Germany	2991	29.5%	Italy	1558	69.4%
Italy	2943	29.0%	Germany	479	21.3%
France	1661	16.4%	France	54	2.4%
Poland	479	4.7%	Poland	52	2.3%
Austria	175	1.7%	Czech Republic	16	0.7%
Spain	163	1.6%	Sweden	15	0.7%
Australia	156	1.5%	Spain	13	0.6%
Belgium	153	1.5%	Australia	11	0.5%
South Africa	134	1.3%	Argentina	10	0.4%
Sweden	132	1.3%	Ireland	10	0.4%
Czech Republic	122	1.2%	Slovakia	5	0.2%
Netherlands	106	1.0%	Belgium	4	0.2%
Ireland	98	1.0%	South Africa	3	0.1%
Greece	84	0.8%	Switzerland	3	0.1%
Brazil	77	0.8%	Brazil	2	0.1%
Switzerland	69	0.7%	Greece	2	0.1%
Canada	64	0.6%	Kenya	2	0.1%
Philippines	46	0.5%	Austria	1	0.0%
Kenya	40	0.4%	Colombia	1	0.0%
Slovakia	38	0.4%	Singapore	1	0.0%
Thailand	36	0.4%	Thailand	1	0.0%
Viet Nam	34	0.3%	United Arab Emirates	1	0.0%
Peru	29	0.3%			
Singapore	29	0.3%			
New Zealand	25	0.2%			
Sri Lanka	25	0.2%			
Argentina	23	0.2%			
Ukraine	22	0.2%			
Romania	20	0.2%			
Cyprus	18	0.2%			
Hong Kong	18	0.2%			
Chile	16	0.2%			
Pakistan	15	0.1%			
Malaysia	11	0.1%			
Mexico	11	0.1%			
Colombia	10	0.1%			
Latvia	8	0.1%			
Taiwan, ROC	6	0.1%			
Jamaica	5	0.0%			
Costa Rica	4	0.0%			
Ecuador	4	0.0%			
Lebanon	4	0.0%			
Russian Federation	4	0.0%			
Venezuela	4	0.0%			
Belarus	3	0.0%			
Cayman Islands	3	0.0%			
Croatia	3	0.0%			
Kazakhstan	3	0.0%			

Malta	3	0.0%			
Turkey	3	0.0%			
Andorra	2	0.0%			
El Salvador	2	0.0%			
Myanmar	2	0.0%			
Saudia Arabia	2	0.0%			
United Arab Emirates	2	0.0%			
Congo, The Democratic Republic of the	1	0.0%			
Estonia	1	0.0%			
Guatemala	1	0.0%			
India	1	0.0%			
Lithuania	1	0.0%			
Luxembourg	1	0.0%			
Mauritius	1	0.0%			
Nicaraqua	1	0.0%			
Panama	1	0.0%			
Serbia	1	0.0%			
Slovenia	1	0.0%			
Trinidad and Tobago	1	0.0%			
United Kingdom	1	0.0%			
Zambia	1	0.0%			
Unknown	1	0.0%			
Total	**10155**	**100.0%**		**2244**	**100.0%**

Restricting the worldwide proportions (as shown in Figure 1) to data as of 2010 (specifically as of the point in time when the first co-administration case/SAE was received by GSK, see Figure 2) generated results consistent with Figure 1: All three events of interest displayed higher reporting proportions in the 'Infanrix hexa & Prevenar 13' co-administration subset.

Figure 2 Worldwide spontaneous proportions since 2010



The Y-axis represents the % of cases including the event of interest among all cases in a given subset. The denominator of each subset of cases is provided between brackets next to the subset name in the graph's legend.

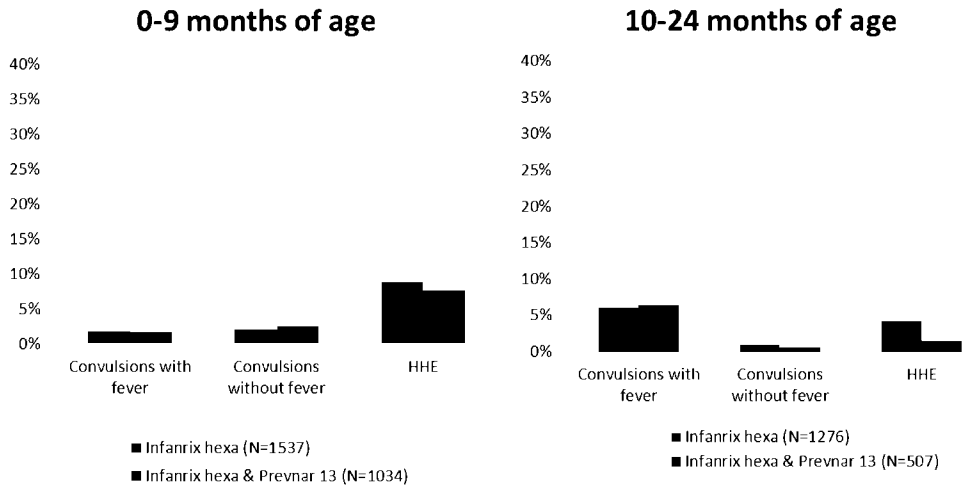
According to the spontaneous data from **Italy** in Figure 3, all three events of interest displayed comparable proportions in both age groups following administration of Infanrix hexa without any pneumococcal vaccine and concomitant administration of Infanrix hexa and Prevenar 13. Among convulsion cases (with or without fever) in both

age groups, MMR(V) co-administration, time to convulsion onset after the last dose (within 3 days) and pre-existing convulsion risk factors (history of convulsion, infections) were reported at similar proportions following administration of Infanrix hexa without any pneumococcal vaccine and concomitant administration of Infanrix hexa and Prevenar 13 (data not shown).

The spontaneous data from **Germany** in Figure 4 displayed a trend in both age groups towards increased proportions of all three events of interest following concomitant administration of Infanrix hexa and Prevenar 13. As in Italy, convulsion cases (with or without fever) in both age groups from Germany had similar rates of MMR(V) co-administration, similar time to convulsion onset after the last dose (within 3 days) and similar pre-existing convulsion risk factor rates (history of convulsion, infections).

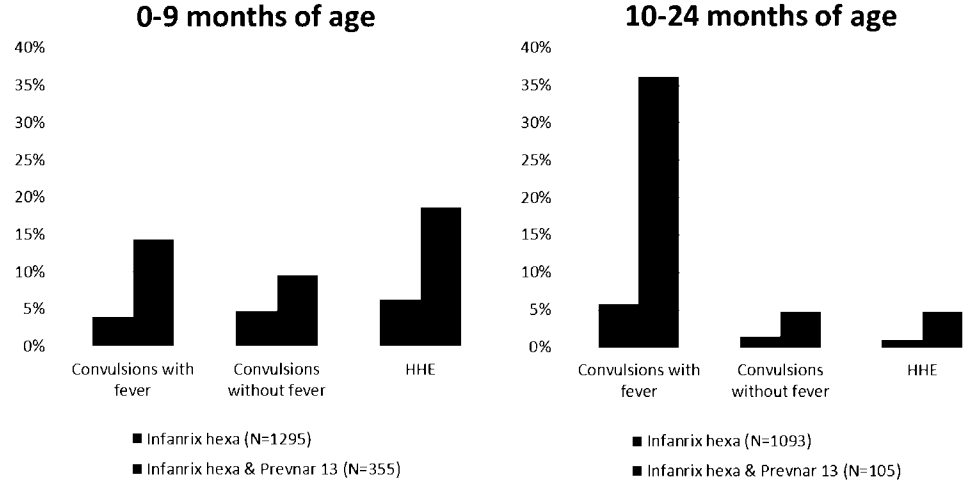
Restricting the spontaneous data to the 2010-2014 calendar period resulted in comparable observations, i.e. no increased reporting proportions in Italy and increased proportions in Germany of all three invents of interest following concomitant administration of Infanrix hexa and Prevenar 13 (see Figure 5 and Figure 6).

Figure 3 Spontaneous SAEs/cases from Italy by age group since 2000



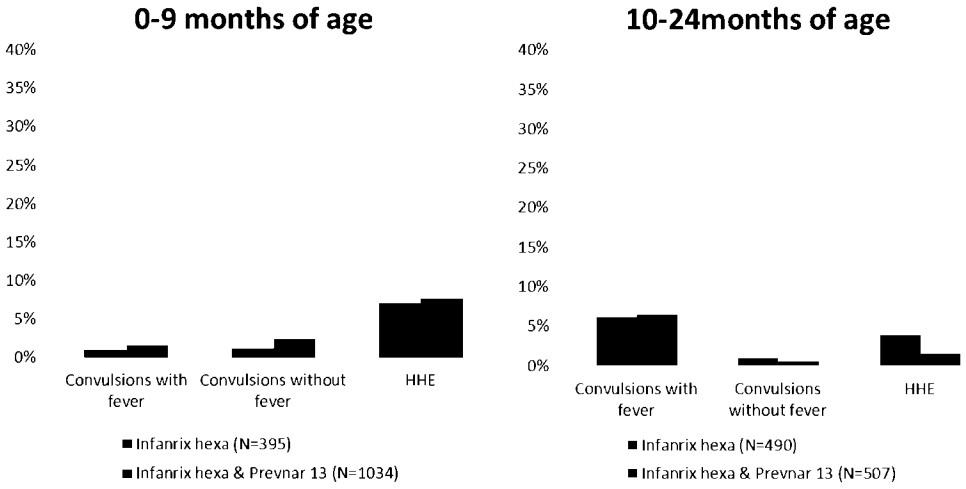
The Y-axis represents the % of cases including the event of interest among all cases in a given subset. The denominator of each subset of cases is provided between brackets next to the subset name in the graph's legend.

Figure 4 Spontaneous SAEs/cases from Germany by age group since 2000



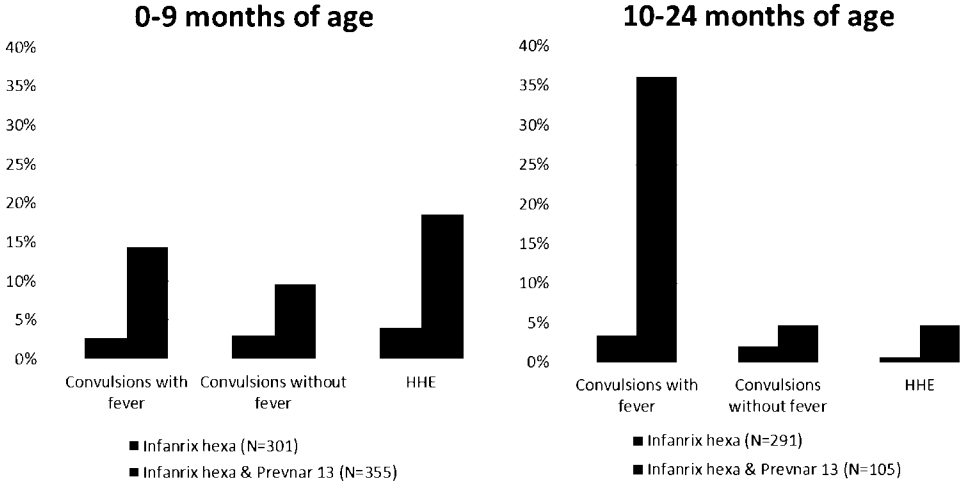
The Y-axis represents the % of cases including the event of interest among all cases in a given subset. The denominator of each subset of cases is provided between brackets next to the subset name in the graph's legend.

Figure 5 Spontaneous SAEs/cases from Italy by age group since 2010



The Y-axis represents the % of cases including the event of interest among all cases in a given subset. The denominator of each subset of cases is provided between brackets next to the subset name in the graph's legend.

Figure 6 Spontaneous SAEs/cases from Germany by age group since 2010



The Y-axis represents the % of cases including the event of interest among all cases in a given subset. The denominator of each subset of cases is provided between brackets next to the subset name in the graph's legend.

4. DISCUSSION

Infanrix hexa has a well-established safety profiles and a high number of doses have been distributed worldwide. Convulsions (with or without fever) and HHE are known side effects listed in the Infanrix hexa reference safety information (RSI) and in the Prevenar 13 EU SmPC. The evaluation of spontaneous data reported to the GSK global safety

database showed an increased reporting of each of these events following concomitant administration of Infanrix hexa with Prevenar 13. This observation is mainly driven by spontaneous cases reported from Germany, despite the fact that most (69.4%) cases/SAEs in the Infanrix hexa & Prevenar 13 co-administration subset come from Italy (Table 3).

Post-marketing surveillance (PMS) reflects the safety profile of a medicinal product in a large population not exclusively composed of healthy subjects, which is an advantage compared to clinical trial data. However, spontaneous data might provide invalid information because of:

- **reporting being biased** by calendar time, country[4], media effects, underlying diseases, unknown factors
- **underreporting**
- **missing or limited information**, e.g. uncertainty about the number of exposed subjects, unmeasured time lag[5] between sales and actual use of vaccines and adverse event reporting, uncertainty about single *vs.* concomitant administration[6], absence of case validation, absence of adequate comparator group.

Most of these shortcomings were limited by the use of proportions of events (see Section 3.1). The denominator being a total amount of cases/SAEs for a given vaccine setting (i.e. Infanrix hexa with or without pneumococcal vaccine co-administration) allowed correcting for changes in overall and event-specific reporting frequencies as well as for unknown factors impacting spontaneous reporting. Furthermore, country-specific confounding was reduced by country-specific sub-analyses; and uncertainty about actual vaccine administration was limited by analysing different time periods (taking into account the receipt date of the first case/SAE involving Infanrix hexa and Prevenar 13 co-administration, thus indirectly marketing of Prevenar 13) and different age groups, including the 0-9 months of age group where absence of MMR(V) vaccination was indeed not reported.

5. CONCLUSION

Data currently available to GSK, including the limitations of this evaluation, suggest an increased risk of convulsions (with or without fever) and HHE following co-administration of Infanrix hexa with Prevenar 13.

The possibility of concomitant administration of vaccines containing multiple antigens remains a critical strategy to ensure high coverage and protection against disease. The potential and known risks identified in association with Infanrix hexa are justified by the

[4] Differing national/local reporting systems, health authorities encouraging increased reporting overall or of specific events in certain countries as of a certain date.

[5] Sales data and adverse event data do not necessarily coincide temporally. The reporting rate of more recent periods (i.e. here the period with Prevnar 13) may be underestimated since an unknown proportion of doses sold may not have been yet administered or triggered a spontaneous report.

[6] Not all administered vaccines might actually be reported to GSK.

anticipated benefits afforded by Infanrix hexa vaccination, including co-administration with pneumococcal conjugate vaccines.

The benefit/risk profile of Infanrix hexa for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b continues to be favourable.

APPENDIX 7B.3 : Infanrix Hexa Signal Review Guillain-Barré syndrome

Following review of a case of GBS following vaccination with Infanrix-IPV-Hib reported spontaneously to GSK in November 2013, an evaluation of GBS following DTPa-containing vaccines was carried out. Around the same time, a request was received from Health Canada to review the labels for Boostrix and Boostrix Polio with regard to GBS, following its inclusion in the label of a competitor. A separate review for TdaP vaccines has been conducted. As GBS does occur in the background population, an observed:expected analysis was undertaken.

1. LITERATURE REVIEW

The article quoted by Sanofi-Pasteur regarding an association of their TdaP vaccine with GBS is an Institute of Medicine publication from 1994 entitled 'Adverse Events Associated With Childhood Vaccines: Evidence Bearing on Causality.' This report found there to be a causative association between vaccines containing tetanus toxoid and GBS. The theoretical mechanism for which is induction of an auto-immune response to a glycoside moiety residing on the myelin sheath surrounding peripheral nerves, leading to demyelination and impaired or absent peripheral nerve conduction [Israeli, 2012]. This correlates with increased levels of anti-glycoside antibodies in GBS patients and electromyography showing impaired conduction. However, it has not been shown how tetanus toxoid or other components of TdaP-containing vaccines resemble this glycoside, nor how they direct this auto-immune response. These are not the only antigens which have been implicated in the genesis of GBS [Souayah, 2007] – there has been a focus on influenza vaccines given a large increase in GBS diagnosis following the 1976 influenza vaccination campaign in the US [Randall, 2010]. More recently, a large case-controlled study with over 30 million person-years of data was carried out on a Healthcare Provider database in the US. The results were published in 2013 and no association between GBS and any of the influenza, TdaP or pneumococcal vaccines was found [Baxter, 2013]. The Institute of Medicine published a report in 2011 [Institute of Medicine , 2011] which concluded that the evidence is inadequate to accept or reject a causal relationship between DTPa-containing vaccines and GBS. However, case reports with a temporal relationship between vaccination and GBS are well described with all types of vaccine [Bakshi, 1997; Hussam A , 2011].

2. CASE REVIEW FROM GSK'S DATABASE

A search of the GSK's worldwide safety database from 01 June 1980 to 14 January 2014 was carried out using the narrow MedDRA standard query for GBS with *Infanrix,* Infanrix-IPV, Infanrix-Hib, Infanrix IPV-Hib, Infanrix hexa, and Infanrix penta as administered vaccines, for cases from any source – from clinical trials, spontaneously reported, or post-marketing surveillance. The narrow query was chosen so as to avoid ambiguous cases which describe only symptoms or signs, and where the patient may not have been tested for GBS. This search found 26 case reports detailing 27 episodes from 26 subjects, however 1 case report ([redacted]) appeared to be a duplicate, and 1 case report [redacted] described below) contained 2 episodes of GBS. The other case reports were then reviewed according to the Brighton Collaboration Criteria [Sejvar, 2011] which examine the diagnostic and temporal information provided in a case report, where level 1 provides the greatest detail, and level 4 may merely state a diagnosis of GBS without diagnostic information being included. Seventeen of these episodes were

level 4; one was level 3; two were level 2; four were level 1; and two case reports were of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) rather than GBS. Of the 4 episodes at level 1, one patient appeared to experience GBS twice – after exposure to *Infanrix* vaccines many years apart. Narratives for this and the other level 1 episodes appear below.

- **Case [redacted] ([redacted] Regulatory Authority). MedDRA PT: Guillain-Barré Syndrome**

At the age of 6, a boy received a dose of Infanrix quinta (Diphtheria, Tetanus toxoid, acellular Pertussis, *Haemophilus influenzae* type B, and inactivated Poliomeylitis vaccine). Within a month, he developed a left hemiparesis with lower limb areflexia. Raised CRP, and elevated CSF protein were found, as were low conduction speeds in all 4 limbs on electromyography. He received one course of immunoglobulin. Within 15 further days he had become tetraplegic and required feeding assistance. He received another course of immunoglobulin and by two months after vaccination, he was partially walking, and had fully recovered several months later. In 2013, at the age of 12, he received a dose of Infanrix tetra (Diphtheria, Tetanus toxoid, acellular Pertussis and inactivated Poliomyelitis vaccine). Sixteen days later he developed a severe headache and blurred vision. At 20 days post-vaccine, he had paraesthesia in hands and legs, and a bilateral reduction of lower limb strength. Bilateral areflexia was present. Again, CSF protein was elevated, and nerve conduction in lower limbs was reduced on electromyography. Cerebral MRI showed a white matter signal (no further information about this given in the report). Upper limb testing then also showed a reduction in nerve conduction velocity, with a mild loss in power, and reduced reflexes. GBS was diagnosed and he received several courses of immunoglobulin. At 1 month after vaccination, at the time of reporting, there had been a mild improvement in the overall picture. Therefore this single report contains two instances of GBS, both at Brighton Collaboration Level 1.

Company Comment: The report does not contain information regarding assessment of immunocompetence, therefore a full assessment of causality cannot be made. However, a causal role for either vaccine cannot be excluded.

- **Case [redacted] ([redacted] Regulatory Authority). MedDRA PT: Guillain-Barré Syndrome**

An 11 month old female received a dose of Infanrix hexa (Diphtheria, Tetanus toxoid, acellular Pertussis, Hepatitis B, Inactivated Poliomyelitis and *Haemophilus influenzae* vaccine). The next day she experienced cough, fever and pharyngitis. Seven days after vaccination she was hypotonic, less responsive to stimuli, and was irritable. She had a slightly raised serum white cell count. Cerebral CT and EEG were negative. A rash also developed at her neck and trunk. Reflexes were not present and electromyography was positive, and CSF cell/protein levels were consistent with GBS. She was treated with ibuprofen and immunoglobulin. Improvement was gradual over the next month and she was discharged at 33 days post vaccination.

Company comments: An acute pharyngitis and fever were reported seven days before manifestation of GBS, suggesting a pre-existing infection as possible contributor to the GBS.

- **Case [redacted] ([redacted] Regulatory Authority). MedDRA PT: Guillain-Barré Syndrome**

A 6 year old female received a dose of Infanrix tetra (Diphtheria, Tetanus toxoid, acellular Pertussis, Hepatitis B, inactivated Poliomyelitis vaccine). Within 4 days she had inflammation at the injection site, fever, and cough and was being treated with clarithromycin. At 15 days post-vaccination, she had myalgia in both legs. At 19 days post-vaccination, she had bilateral lower limb paralysis and facial paralysis mainly on the left. She was found to be areflexic in the lower limbs, and had reduced nerve conduction speed on electromyography. CSF had an elevated protein level without cells. She was treated with immunoglobulin and was completely recovered within 28 days from vaccination.

Company's comments: *Cough and fever were reported 11 days before manifestation of GBS, suggesting a pre-existing infection as possible contributor to the GBS.*

Narratives for the 2 episodes at Level 2 appear below.

- **Case [redacted] ([redacted] Regulatory Authority). MedDRA PT: Guillain-Barré Syndrome**

A 15 month old boy received a dose of Infanrix hexa and a dose of Prevenar (anti pneumococcus vaccine). Within 2 days he experienced fever, restlessness, reduced appetite and asthenia. Fourteen days after vaccination he was having difficulty standing. He was found to have a hyperaemic pharynx, dyspnoea, and was globally hypotonic and areflexic. Blood tests showed a raised white cell count and raised platelet level. A microbiological sreen from swabs of nasopharynx, urine culture and serology were all negative. CSF showed raised protein levels in the absence of a raised cellular level, and negative CSF microbiological culture. EEG was normal. Specialist evaluation noted peripheral neuropathy with global asthenia. He was treated with co-amoxiclav antibiotics and showed some general improvement. At follow-up visits his neurological state had not sufficiently improved. At 1 month post-vaccination his lab tests continued to show a raised white cell count and slightly raised platelet count. MRI of brain and spinal cord were negative. GBS was diagnosed, and he was treated with anti-histamine and immunoglobulin and some improvement in the upper limbs was noted.

- **Case [redacted] [redacted] Regulatory Authority). MedDRA PT: Miller Fisher Syndrome**

A 5 year old boy received a dose of *Infanrix* as well as a dose of a non-GSK Measles, Mumps and Rubella vaccine. He had a concurrent cough and fever. Eighteen days after vaccination he presented with ophthalmoplegia, ptosis, diplopia, lower limb areflexia, ataxia and dysphonia. Electromyography did show abnormalities but these were not consistent with a diagnosis of GBS. Infection screen was negative, as were MRI, CSF examination, and ultrasound. A diagnosis of Miller-Fisher Syndrome was made. He was treated with steroids and immunoglobulin and began to improve. He was discharged at 1 month post-vaccination with continuing steroids.

3. Observed:Expected Analysis

As many other papers [Baxter, 2013; Souayah, 2007] have taken a 6 week interval between vaccination and onset of GBS as the period of interest when looking for a causal association, so the same time period was used in our analysis as the 'time at risk'. Note that this is different from the Brighton Collaboration Criteria which only include episodes which begin between 12 hours after vaccination and 28 days after vaccination. The background incidence of GBS increases with increasing age, therefore a straight comparison of total numbers of cases was not appropriate. Case reports from GSK's worldwide safety database were re-assessed to include those with the appropriate 'time at risk' (regardless of Brighton Collaboration Criteria) and then separated by age group. The reference incidence was taken from a 1991 study of data from Finland [Rantala, 1991]. An incidence rate for infants of 2 years or below could not be found, although it is described as rare [Orlik, 2014]. Therefore the incidence rate for childhood was reduced slightly to 0.3 to account for this. This has the effect of reducing the number of expected cases, therefore potentially making the observed:expected analysis more sensitive. Although few of the GBS case reports found in this search came from Finland, we assumed that the reference incidence was relevant for other countries in Europe. Since *Infanrix* products were not used in Finland during that study period, this is relevant as an unvaccinated population. The small number of case reports (3) from outside Europe was therefore excluded from analysis. Two further case reports were not within the appropriate 'time at risk'. The 2 case reports of CIDP were excluded. This left 19 of the 26 episodes for the analysis for the observed:expected analysis restricted to the European cases.

The denominator was taken from cumulative (to January 2014) sales data of all *Infanrix* family vaccines, only in those countries whose case reports were included in the analysis. It is not possible for GSK to know the number or age of every person vaccinated with either vaccine. In the main analysis, the unit used is the number of doses, not the number of subjects since each dose/vaccination contributes to a fixed time at risk. The immunisation schedule for *Infanrix* vaccines was assumed to be 3 doses given one month apart within the first year of life, one further dose in year 2, and one dose later in childhood. Therefore the time at risk of 6 weeks overlaps during the first 3 doses. Therefore the risk period is therefore 42 days from dose 3, 72 days from dose 2 and 102 days from dose 1, assuming that all infants receive all 3 doses. Although it is unlikely that all infants receive all 3 doses, this results in lowering the expected number of cases, thereby increasing the sensitivity of the analysis. Also the number of doses received is not known for all of the *Infanrix* cases in the GSK global safety database. Although an average could be calculated where this is known, reducing the person time at risk to the same 42 days as in single doses would again reduce the number of expected cases and therefore increase the sensitivity of the analysis. Beyond the age of 2, since the vaccine is given once only, each dose can be considered as contributing independently to the total risk period for a given individual and thus the risk period here is 42 days. It was assumed that the risk is identical at each dose and does not increase with each additional dose.

Since the distribution of the age at which subjects are vaccinated is unknown, it was assumed that the frequency distribution of the age at vaccination in spontaneous cases reported to GSK is representative of the actual age distribution at vaccination. The highest proportion of all *Infanrix* family of vaccine cases were from patients aged 0-2 years which is not surprising given the vaccines' use at very young infancy timepoints.

However, there are several limitations inherent to observed:expected analyses, and several levels of uncertainty due to:

- Underreporting, reporting biases, and incomplete case details.
- Uncertainty on the number of subjects actually vaccinated.
- Uncertainty on the distribution of the age at which subjects are vaccinated.
- Lack of background incidence rate from all Europe.
- Lack of background incidence rate in largest age group vaccinated.

Table 11 Observed and Expected cases of GBS by age group in Europe

Age (years)	Doses sold	Age distribution, % (GSK Safety Database)	Time at risk (42 days risk period, single dose)	Incidence rate per 100,000 P-Y (Rantala, 1991)	Expected number of cases with onset within 42 days of vaccination	Observed number of cases with diagnosis Level 1-4, 42 days risk period (95% CI*)
<2 years	93458839	69.12	10754168	0.3	32.26	7
2-5 years	23215976	17.17	2671427	0.38	10.15	3
>5 years	13588850	10.05	1563648	0.38	5.94	9
Unknown	4948775	3.66	569448	0.38	2.16	0
TOTAL	135212442				50.52	19

Although overall there are less cases than would be expected by this analysis (19 v 50.52 cases), the age group >5 years has more than the expected number of cases, however the age group with the greatest exposure (<2 years old) has a much lower observed number compared to the expected number of cases. Of these 19 observed cases, 11 were of Brighton Collaboration Criteria level 4.

Summary and Conclusion

Review of recent literature found case reports or case series describing at least a temporal association between GBS and immunization for various vaccines, however large epidemiological studies have not been able to conclusively prove a causal link. Review of GBS case reports after vaccination with the *Infanrix* family of vaccines within GSK's database found generally poor documentation of diagnosis or reasonable alternative causes for most cases, however some cases with reasonable documentation do not have an alternative explanation. One case report would appear to show a positive rechallenge to *Infanrix* antigens. An internal observed to expected ratio analysis found no overall excess of cases, but an excess of cases within a certain age group, but many fewer cases than expected in the age group most represented. The majority of case reports used for this analysis had incomplete assessments of GBS. In addition, the observed:expected analysis was undertaken without a precise incidence rate for the largest group vaccinated.

It is GSK's position that there is currently insufficient evidence of a causal link between the *Infanrix* family of vaccines and Guillain-Barré Syndrome. GSK will continue to monitor all case reports of GBS through routine pharmacovigilance.

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Case Listing

Table 12 Case Listing from GSK Safety Database meeting narrow MedDRA query for GBS with DTPa-containing vaccines to 14 January 2014

Case ID	Age	Gender	Country	Vaccine	Dose	Brighton Collaboration category	Time To Onset
[redacted]	18m	m	[redacted]	Inf IPV Hib	4	4	10w
[redacted]	16y	f		Inf IPV	?	4	<1d
[redacted]	17y	m		Inf tetra	?	4	32d
[redacted]	13m	f		Inf hexa	1	4	3w
[redacted]	57y	f		DTPa-IPV	?	4	24d
[redacted]*	*57Y*	*F*		*DTPa-IPV*	*?*	*4*	*24d*
[redacted]	6y	m		Infanrix	?	4	27d
[redacted]	11m	f		Inf hexa	3	1	7d
[redacted]	4m	f		Inf quinta	3	4	3d
[redacted]	6y	f		Inf tetra	?	1	15d
[redacted]	8y	m		Inf tetra	?	4	1m
[redacted]	5y	m		Infanrix	?	2	18d
[redacted]	?	?		DTPa	?	4	2d
[redacted]	18m	m		Inf IPV Hib	?	4	4d
[redacted]	15m	m		Inf hexa	?	2	14d
[redacted]	13m	f		Inf IPV Hib	3	4	1d
[redacted]	61y	f		DTPa	?	4	25d
[redacted]	6y	m		Inf quinta	?	1	1m
[redacted]	12y	m		Inf tetra	?	1	1m
[redacted]	11y	m		Inf tetra	6	4	31d
[redacted]	7m	m		Inf Hib	?	4	4w
[redacted]	2y	m		Inf IPV Hib	1	3	<1d
[redacted]	3m	m		Inf hexa	3	4	2m
[redacted]	4y	m		Inf IPV Hib	3	4	U
[redacted]	2y	m		Inf hexa	4	4	3d

*likely duplicate case
Infanrix = Diphtheria, Tetanus, acellular Pertussis
Infanrix-IPV = as Infanrix + Inactivated Poliomyelitis Virus (aka Infanrix tetra)
Infanrix-Hib = as Infanrix + Haemophilus influenzae type B
Infanrix-IPV-Hib = all of the above
Infanrix quinta = Infanrix-IPV + Hepatitis B Virus
Infanrix hexa = Infanrix-IPV-HBV-Hib
Boostrix = low antigen content Diphtheria, Tetanus, acellular Pertussis
Boostrix polio = Boostrix + IPV

APPENDIX 7B.4 : GSK DTPa vaccines extensive swelling of vaccinated limb

Vaccines' Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

GSK DTPa vaccines: Extensive swelling of vaccinated limb

Date of completion of evaluation	29 October 2014
Vaccine terms included	GSK DTPa- and Tdap-combination vaccines
Adverse events (MedDRA preferred terms) included	- Extensive swelling of vaccinated limb - Injection site swelling - Injection site joint swelling - Injection site inflammation
Authors	[redacted] (Safety Scientist) [redacted] (Safety Physician) [redacted] (Safety Analyst)

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LIST OF ABBREVIATIONS

AE	Adverse event
ap	acellular pertussis (reduced antigen content)
aP	acellular pertussis
AERS	(FDA) Adverse Event Reporting System
CMG	Case Management Group
DPA	Disproportionality analysis
DTPa	diphtheria, tetanus, acellular pertussis
DTPw	diphtheria, tetanus, whole-cell pertussis
LLT	Lower Level Term
LOC	Local Operating Company
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred term
wP	whole-cell pertussis

1. BACKGROUND

1.1. Trigger and Scope

As of 2011 an increased reporting of spontaneous cases of extensive limb swelling (ELS) was observed for Infanrix and Infanrix-IPV. GSK conducted a first safety evaluation (dated 28 September 2012, data lock point 30 June 2012) covering several diphtheria-tetanus-acellular pertussis (DTPa) combination vaccines. The outcome was that, at that time, other DTPa vaccines were not impacted by this signal. This was expected in view of the fact that:

- ELS incidence and severity are known to increase with each successive DTPa dose
- Both Infanrix and Infanrix-IPV vaccines are indicated as booster dose in children ≥ 4 years of age, i.e. 'pre-school booster' (fifth dose), while other DTPa vaccines are indicated up to four doses and do not have this fifth dose indication. ELS is therefore expected to occur less frequently with other DTPa vaccines compared to Infanrix and Infanrix-IPV.

Countries involved were the Netherlands, Belgium and Sweden. The following were identified as the most likely root causes of the increased ELS reporting observed in these three countries:

- pre-school boosting following switch from diphtheria-tetanus-whole cell pertussis (DTPw) priming to DTPa priming,
- local pertussis vaccination schedules
- introduction of GSK vaccines in local national immunization programmes
- local studies and communications related to ELS

GSK considered that the identified ELS safety signal did not indicate a new safety concern, that ELS was appropriately reflected in the applicable product labels and closed the signal.

In 2013 and 2014, increased ELS reporting was observed again for Infanrix and Infanrix-IPV, but this time in other countries, and also following other DTP-lifecycle vaccines. The ELS signal was therefore re-opened and its new aspects are addressed in the present safety evaluation. The following DTPa-containing vaccines were included in this evaluation: Infanrix, Infanrix-IPV, Infanrix-IPV/Hib, Infanrix/Hib, Infanrix Penta, Infanrix hexa, Boostrix and Boostrix Polio. Note that Infanrix-HepB was excluded since this vaccine is not marketed anymore since 2007. This evaluation covers the time period between 2003 (i.e. the first year when an ELS cases was reported for the vaccines in scope of the present evaluation) and 25 September 2014.

1.2. Current Global Prescriber Information of DTPa-containing vaccines

Extensive swelling reactions are listed in the global prescriber information (GPI) of all DTPa and Tdap vaccines.

1.2.1. Infanrix, Infanrix-IPV, Infanrix-IPV/Hib, Infanrix Penta and Infanrix hexa

The GPIs of Infanrix, Infanrix-IPV, Infanrix-IPV/Hib, Infanrix Penta and Infanrix hexa mention the following frequencies as assessed in clinical trials:

- **very common** (≥ 10%): local swelling at the injection site (≤50 mm)
- **common** (1% and < 10%): local swelling at the injection site (>50 mm)*
- **uncommon** (≥ 0.1% and < 1%): diffuse swelling of the injected limb, sometimes involving the adjacent joint*

The post-marketing sub-section of these GPIs refers to 'Swelling of the entire injected limb*', except the Infanrix hexa GPI which reads 'Extensive swelling reactions, swelling of the entire injected limb*'.

All DTPa-containing vaccines in scope of the present evaluation are indicated for primary vaccination during the first year of life, as well as for booster vaccination (toddler booster) during the second year of life. In addition to this, Infanrix and Infanrix-IPV are both indicated as booster dose in children ≥ 4 years of age, i.e. 'pre-school booster' (fifth dose), while Infanrix/Hib, Infanrix-IPV/Hib, Infanrix Penta and Infanrix hexa do not have this extra indication.

The GPIs of DTPa vaccines include footnotes for large swelling reactions referred to by an asterisk (*). The footnotes differ depending on the product and whether or not a given country has a booster indication in children ≥ 4 years of age. Footnotes ***a*** and ***b*** are both included in the GPI of Infanrix and Infanrix-IPV, while the GPIs of Infanrix/Hib, Infanrix-IPV/Hib, Infanrix Penta and Infanrix hexa do not include footnote ***b***, they only include footnote ***a***.

Footnote (a) is in the Infanrix, Infanrix-IPV, Infanrix-IPV/Hib, Infanrix Penta and Infanrix hexa GPIs
**Wording for countries that do not have a booster indication in children ≥ 4 years of age:*
Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. These reactions resolve over an average of 4 days.

Footnote (b) in the Infanrix and Infanrix-IPV GPIs, in addition to footnote (a)
**Wording for countries having a booster indication in children ≥ 4 years of age:*
Children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. Local swelling at the injection site (>50 mm) and diffuse swelling may be more frequent (very common and common, respectively) when the booster dose is administered between 4 and 6 years. These reactions resolve over an average of 4 days.

1.2.2. Infanrix/Hib

The global prescriber information (GPI) of Infanrix/Hib mentions the following frequencies as assessed in clinical trials:

Primary vaccination:

- **very common** (≥ 10%): Application site swelling (<2 cm)
- **uncommon** (≥ 0.1% and < 1%): Application site swelling (>2 cm)

Booster vaccination:

- **very common** (≥ 10%): Application site swelling (<2 cm)
- **common** (1% and < 10%): Application site swelling (>2 cm), local swelling at the injection site (> 50 mm)*
- **uncommon** (≥ 0.1% and < 1%): diffuse swelling of the injected limb, sometimes involving the adjacent joint*

The post-marketing sub-section of the GPI refers to 'Swelling of the entire injected limb*'.

Asterisks (*) refer to footnote (a) described in Section 1.2.1.

1.2.3. Boostrix and Boostrix Polio

The global prescriber information (GPI) of Boostrix and Boostrix Polio mention the following frequencies as assessed in clinical trials:

Children from 4 to 9 years of age:

- **Very common (≥ 10%)**: injection site reactions (including pain, redness and swelling)

Adults, adolescents and children from the age of 10 years onwards

- **Very common (≥ 10%)**: injection site reactions (including pain, redness and swelling)

Post-marketing data:

- **Rare (≥0.01% and <0.1%)**: extensive swelling of the vaccinated limb

Additional wording in the Boostrix GPI: *Data on 146 subjects suggests a small increase in local reactogenicity (pain, redness, swelling) with repeated vaccination according to a 0, 1, 6 months schedule in adults (> 40 years of age).*

Subjects fully primed with 4 doses of DTPw followed by a Boostrix dose around 10 years of age show an increase of local reactogenicity after an additional Boostrix dose administered 10 years later.

2. LITERATURE

2.1. Whole-cell and acellular pertussis vaccines

Whole-cell pertussis vaccines, prepared from inactivated *Bordetella pertussis* organisms, were first introduced in the first half of the 20st century. They were highly efficacious against disease and their widespread use caused the incidence of whooping cough to rapidly fall. Despite this, the use of these vaccines remained problematic due to the fact that they induced fever and injection site reactions in a high percentage of recipients. In addition, the rare occurrence of more severe reactions, in conjunction with anecdotal reports of neurological complications, led to the search for less reactogenic vaccines against pertussis. The second generation of pertussis vaccines, acellular pertussis vaccines, were formulated to contain a limited number of well-defined and highly purified *B. pertussis* antigens, selected on the basis of their contribution to the pathogenicity of *B. pertussis* in *in vitro* and *in vivo* models. Six different combined DTPa vaccines were initially licensed in Japan in 1981. Licensure was based on the demonstration of diminished local and systemic reactogenicity, and equal or superior immunogenicity, with respect to whole-cell vaccines. Following licensure, routine vaccination was initiated in children from two years of age.

2.2. Reactogenicity as assessed in clinical trials

The success of vaccination with acellular pertussis vaccines in Japan stimulated efforts to develop other, similar vaccines to replace whole-cell vaccines in Western schedules, i.e. primary vaccination during the first year of life, followed by one or more booster doses. Several candidate vaccines were evaluated in clinical trials and subsequently licensed, first for booster use then for primary immunisation, once efficacy had been established. One of the first vaccines licensed was GlaxoSmithKline Biologicals' DTPa vaccine, Infanrix. Early trials showed a marked decrease in reactogenicity for DTPa vaccines with respect to diphtheria-tetanus-whole-cell pertussis vaccines (DTPw) when they were used as booster doses following priming with DTPw. In 1995, the first data from longitudinal studies of children who had been both primed and boosted with DTPa became available. These trials indicated that the incidence of local reactions increased significantly upon boosting, although they remained below the level seen after a fourth or fifth dose of

DTPw (Halperin, 1995; Halperin, 1996; Halperin, 1999; Pichichero, 1997; Schmitt, 1996; Schmitt, 1997a).

2.3. Large local reactions following DTPa

The most unexpected event after boosting was the occurrence of particular large local redness and/or swelling reactions, reported as involving the whole injected thigh. In fact, swelling reactions "with swelling of the arm down to the elbow or the wrist" had been previously described in Japanese children administered DTPa vaccines but had been considered as "extremely rare" (Noble, 1987). These large swelling reactions have been shown to begin generally within 48 hours of vaccination and to resolve spontaneously without sequelae.

Data from the Multicenter Acellular Pertussis Trial (MAPT), sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), showed that swelling of the entire thigh occurred with the DTPa vaccines from different manufacturers administered as a fourth dose in the second year of life (Rennels, 2000). The number of subjects administered a fifth dose in this trial was limited and large swelling reactions were not observed in any vaccinee; however, entire upper arm swelling has been reported after a fifth dose of DTPa in other trials (Liese, 2001).

Comparison of data across these and other published trials is made difficult by the lack of a standard definition and terminology. In published reports, the terms "extensive" or "large" have been used to describe reactions which are greater than a certain diameter (usually 5 cm), in addition to reactions which lead to a noticeable increase in limb circumference and/or extend to adjacent joints. In some trials, redness, rather than swelling, has been the parameter evaluated.

Large local injection site reactions have been documented with booster doses of aP vaccines, and the highest rates are reported after the fourth and fifth doses Pichichero, 2000; Liese, 2001; Rennels, 2000; Woo, 2003; Rennels, 2003; Skowronski, 2003). Retrospective evaluations suggest that ELS occurs in about 2% of the children given a fourth consecutive dose of DTPa vaccines, with the incidence and severity increasing with each successive DTaP dose (Rennels, 2000).

Local reactions, such as redness and swelling, occur more frequently after booster doses of DTPa in children primed with DTPa vaccine with respect to children primed with DTPw (Halperin, 1995; Halperin, 1999; Pichichero, 1997). Large local reactions, usually defined as either redness and/or swelling $\geq$50 mm in diameter, have been reported following booster doses of licensed vaccines from different manufacturers including GSK (Liese, 2001; Halperin, 1999; Halperin, 2003; Pichichero, 1997; Pichichero, 2000; Scheifele, 2001; Schmitt, 1997a; Skowronski, 2003), and should thus be considered a class-effect of DTPa-combination vaccines. These reactions are especially frequent in DTPa-primed children after booster doses of DTPa; indeed, they have been observed in approximately 20-50% of children administered a fifth dose of DTPa (Halperin, 1999; Halperin, 2003; Liese, 2001; Scheifele, 2001; Skowronski, 2003). Two types of large swelling reactions have been described. The first, reactions which involve a delimited

area around the injection site, are the most frequent; the second, reactions which extend diffusely over the injected thigh/upper arm and sometimes the entire limb, are more rare.

It should be stressed that, although these reactions are described after DTPa-containing vaccines, they are observed but much less frequently after administration of other vaccines. Indeed, in the US, extensive limb swelling has been reported through the Vaccine Adverse Event Reporting System for a total of 23 different vaccine types (Woo, 2003). However, extensive limb swelling in the 0-7 year age group was, in 43% of all cases, due to DTPa vaccine, which represented the largest proportion observed for any vaccine.

2.4. Mechanism

Attempts to elucidate the mechanisms responsible for large local swelling reactions have been made. A relationship between diffuse swelling reactions of the entire thigh and vaccine antigen content and/or excipients (Rennels, 2000) was postulated. Rates of entire thigh swelling was shown to be correlated with diphtheria toxoid content ($p = 0.02$); swelling > 50 mm but not involving the entire thigh was, however, shown to correlate with pertussis toxoid content after dose 4 ($p = 0.03$) and aluminium content after dose 5 ($p = 0.02$). Potential relationships of redness/swelling $\geq$50 mm to antibody levels pre- and post-boost were also examined, with several statistically significant correlations between individual local symptoms and antibody titre being observed (Halperin, 2003). However, as no consistent pattern could be developed from these analyses, the role of these factors in the induction of large swelling reactions remains doubtful. Immunologic pathways have also been explored. The fact that diffuse reactions onset hours, and not minutes after vaccination, argues strongly for a mechamism related to a delayed hypersensitivity response. Early and persistent Th2 responses are elicited after primary vaccination with DTPa vaccine (Rowe, 2000), with higher levels of IgE induced with respect to DTPw (Mascart, 2004). However, there has been no association found between levels of circulating IgE and booster reactogenicity despite increases in IgE levels after the booster dose (Holt, personal communication). Moreover, prophylactic treatment with antihistamines has been shown to have no effect on the frequencies of local redness or swelling (Tam, 1996). Skin tests have shown a correlation between redness $\geq$50 mm and test positivity for DT and Pa antigens, but no such correlation was found for swelling $\geq$50 mm (Scheifele, 2001). In addition, in this same trial, rates of swelling or redness were not influenced by a history of allergy/atopy. One evident intrinsic factor which would predispose the vaccinee towards large local reactions has therefore not been determined at present. Pragmatically, large local reactions after a fourth dose of DTPa would not appear to be predictive of reactions after a fifth dose. Clinical data indicates that children who had larger local redness or swelling after a fourth dose at 1-2 years were no more likely to have redness or swelling $\geq$50 mm after a fifth dose at 4-6 years (Scheifele, 2001; and GSK studies 208355/118 and 208355/120). In the MAPT, none of three children who had swelling of the entire thigh after the fourth dose reported swelling of the entire thigh after the fifth dose (Rennels, 2000).

2.5. ELS in Infanrix-line products

Due to the frequency of large swelling reactions, and their potential as a source of concern for the parents of the vaccinees, GSK amended the reference safety information (RSI) of all Infanrix-line products to include information on these reactions in 2005 (see Sections 1.2.1 and 1.2.2). It is important to stress that, despite the occurrence of large local reactions, acellular pertussis vaccines induce overall far fewer adverse events than whole-cell vaccines (reviewed in Decker, 2000; Jefferson, 2003). This is particularly true for common events, such as fever, which occur at much lower frequencies in acellular vaccine recipients.

2.6. Literature published after the RSI update with ELS information of the Infanrix line in 2005

Jacquet (2006) reported that local reactions following booster vaccination with DTPa-IPV vaccine appear more frequent after primary vaccination with an acellular pertussis priming than after a whole cell pertussis priming. They concluded that full DTPw series (primary and booster) are the most reactogenic; full DTPa series are intermediately reactogenic; and the DTPa booster after DTPw primary is the least reactogenic booster. This is in line with other studies, including the studies of Halperin (1999) and Gold (2003), which suggested that DTPa for primary vaccination may be a risk factor for local reactions with booster doses. However, for primary and booster vaccinations together, immunisation with acellular pertussis combination vaccines results in fewer adverse events than vaccination with whole cell combination vaccines (Kemmeren, 2011).

Onset of ELS was found not to be a reason for vaccination discontinuation (Rennels, 2000; Rennels, 2008; Huber, 2011; Jackson, 2011; Quinn, 2011). The use of vaccines with reduced or modified DTPa antigen content have been proposed to reduce the number of large injection site reactions at the preschool booster dose (Robbins, 2005; Scheifele, 2005).

Black (2008) found reporting of solicited local and systemic events was comparable when evaluating DTPa and IPV vaccines given separately or combined for booster dosing at 4–6 years of age. A study in the Netherlands found the addition of conjugated pneumococcal vaccine did not result in statistically significant increased rates of adverse events in children vaccinated with DTPa (David, 2008). And a shortening of the timeframe between two consecutive doses to one month was also shown not to exacerbate post-vaccination side-effects (Beytout, 2009).

3. CLINICAL TRIALS

3.1. Clinical trial data used to support the present ELS wording in Infanrix labels

Information on 18 clinical trials conducted by GSK is available. All enrolled subjects had previously received 3 or 4 doses of a DTPa-containing vaccine for primary/booster immunisation. Information from a total of 13604 doses of GSK vaccines has been analysed.

Data on the occurrence of large swelling reactions when DTPa or DTPa-containing combinations are used as a fourth dose in the second year of life have been obtained in 14 clinical trials. Large swelling reactions were a solicited adverse event in all trials.

The overall frequency of reports of large swelling reactions, and the frequencies for each of the individual vaccines administered for the booster dose are shown in Table 1. (An analysis of the frequency of reports as a function of both primary and booster vaccines administered was not performed, due to the relatively low number of subjects in some of the cohorts which would make the analysis meaningless.)

As shown in Table 1, reactions of this type were reported for all of the DTPa-combination vaccines evaluated as boosters in the clinical trial setting.

The frequencies for DTPa-HBV-IPV/Hib (obtained by pooling the results from 9 studies) and DTPa-IPV/Hib (pooled results from 5 studies) are similar, and indeed, were similar in both studies 217744/058 and 2117744/074 where the two vaccines were directly compared; incidences of 3.5% (95% CI: 2.0-5.6) and 1.9% (95% CI: 1.0-3.2) were observed for DTPa-IPV/Hib and DTPa-HBV-IPV/Hib, respectively, in study 217744/058, the respective incidences were 1.8% (95% CI: 1.4-2.3) and 2.6% (95% CI: 2.1-3.1) in study 217744/074.

For DTPa-HBV-IPV/Hib, the across-trial variablility was low, with frequencies ranging from 1.2% (in studies 217744/066 and 217744/095) to 3.4% (in study 217744/059). For DTPa-IPV/Hib, the frequencies across the 5 trials ranged from 1.8% (in study 1774/074) to 8.0% (in study 455697/001).

Importantly, there seems to be no correlation between the incidence of large swelling reactions and the number of antigenic components in the vaccine. Of note, relatively higher frequencies of these reports were observed for DTPa and DTPa/Hib. This higher frequency is probably exclusively due to the fact that all of the data for DTPa/Hib, and half of the data for DTPa, come from one clinical trial, 208108/076. In this trial, vaccine was administered in the deltoid region which is known to induce in a higher frequency of local reactions with respect to injection in the anterolateral thigh (Scheifele, 1992; Schmitt, 1997b). Indeed, the results from study 217744/061 show that the frequency of large swelling reaction reports was not different for DTPa with respect to DTPa-HBV-IPV, being approximately 1% for both vaccines when they were administered in the thigh.

Table 1 Frequency of reports of large swelling reactions, overall and by vaccine, in trials where these reactions were solicited – trials evaluating DTPa-containing vaccines as a fourth dose during the second year of life

Booster vaccine	N subjects	N reports	Frequency (%)
All	12306	326	2.6 (2.4-2.9)
DTPa-HBV-IPV/Hib	6641	157	2.4 (2.0-2.8)
DTPa-IPV/Hib	5181	137	2.6 (2.2-3.1)
DTPa-HBV-IPV	99	1	1.0 (0-5.5)
DTPa/Hib	219	18	8.2 (4.9-12.7)
DTPa	166	13	7.8 (4.2-13.0)

Of the GSK DTPa combination vaccines, only DTPa and DTPa-IPV are licensed for use in pre-school aged children in Europe. Data are available from four trials in which children of 4-6 years of age received either DTPa or DTPa-IPV.

In two trials, large swelling reactions were specifically solicited. In study 213503/045, children had been previously primed with DTPa according to a 3,5, 11/12 month schedule; in study 213503/046, children had previously been administered 4 doses of DTPa vaccines at approximately 2, 4, 6 and 18 months of age. The results from these two trials are given in Table 2 below. Within each trial, the frequencies of large swelling reaction reports were similar for the two vaccines tested (Table 2).

Table 2 Frequency of reports of large swelling reactions, overall and by vaccine, in trials where these reactions were solicited – trials evaluating DTPa-containing vaccines as a fourth or fifth dose at 4-6 years of age

	Booster vaccine	N subjects	n reports	Frequency (%)
4th dose	**All**	**416**	**63**	**15.1 (11.8-19.0)**
	DTPa-IPV	211	28	13.3 (9.0-18.6)
	DTPa	205	35	17.1 (12.2-22.9)
5th dose	**All**	**362**	**92**	**25.4 (21.0-30.2)**
	DTPa-IPV	181	43	23.8 (17.8-30.6)
	DTPa	181	49	27.1 (20.7-34.2)

Albeit difficult to quantify from the results obtained, available data support the conclusion that there is an increase in the incidence of large swelling reactions between the fourth dose given during the second year of life and the fifth dose given at 4-6 years of age. GSK-sponsored clinical trial data in children followed up for all 5 doses of the vaccination course are limited, with differences in methodology being additional confounding factors to analysis. This aside, the frequency of swelling reactions ≥50 mm after a fourth dose of DTPa in study APV-039B was 8.1% (95% CI: 6.9-9.4) and after a fifth dose in studies 208335/118 and 120 was 20.2% (95% CI: 16.6-24.1).

3.2. New clinical trials

New clinical trials assessing Infanrix combination vaccines not included in the pooling discussed in Section 3 showed similar ELS frequencies than those currently mentioned in the global prescriber information. In these trials, ELS frequency related to the 4th dose ranged between 0.4% and 8.7%, while ELS frequency related to the 5th dose ranged between 1.7% and 17.4% (see Table 3).

Table 3 Frequency of ELS observed in clinical trials not included in the 2005 safety pooling

Study eTrack number	Study abbreviated title	Study report date	Study population	Vaccine	DTPa Dose	Observed frequency of ELS
213503	DTPa-IPV-047	14 January 2005	Healthy children, 4 to 6 years of age	INFANRIX-IPV + M-M-R_{II}[a]	5	**4.5%** (9/200)
				INFANRIX + IPOL[b] + M-M-R_{II}*	5	**6.5%** (13/200)
102038	DTPa-130	11 August 2006	Healthy children, 4 to 6 years of age	INFANRIX administered to children born pre-term	5	**14.9%** (11/74)
				INFANRIX administered to children born full-term	5	**17.4%** (8/46)
213503	DTPa-IPV-048	March 2007	Healthy children, 4 to 6 years of age	INFANRIX-IPV + M-M-R_{II}[a]	5	**4.1%** (128/3156)
				INFANRIX + IPOL[b] + M-M-R_{II}[a]	5	**5.4%** (57/1053)
100917	DTPa-IPV-052	13 October 2008	Healthy children, 18 months of age	INFANRIX-IPV/Hib	4	**0.4%** (11/2540)
110478	DTPa-HBV-IPV-117	25 January 2010	Healthy children, 18 to 23 months of age	INFANRIX HEXA (new preservative-free formulation)	4	**4.5%** (5/111)
				INFANRIX HEXA (current preservative-containing formulation)	4	**8.7%** (10/115)
				INFANRIX PENTA (licensed preservative-free formulation)	4	**3.5%** (2/57)
111852	DTPa-IPV-055	31 March 2011	Healthy children, 4 to 6 years of age	KINRIX[c], VARIVAX[d] and M-M-R_{II}[a] on Day 0 or KINRIX[c] and M-M-R_{I}[a] on Day 0 and VARIVAX[d] at Month 1	5	**1.7%** (8/476)

[a] MMR, Merck and Company's Measles, mumps and rubella vaccine
[b] IPOL, Aventis Pasteur's IPV vaccine
[c] KINRIX, US brand name of INFANRIX-IPV
[d] VARIVAX, Merck and Company's varicella virus vaccine

4. POST-MARKETING EXPOSURE TO VACCINE

Information on the actual number of people exposed to GSK vaccines in the different countries is not directly available to the MAH. Therefore, the total patient exposure is approximated by the number of doses distributed which is the most reliable data available with regard to patient exposure for a vaccine in a post-marketing setting.

It is important to note that the sales database from which data are retrieved is an in-house 'living' database and is subject to updates and corrections depending on information provided by GSK local country subsidiaries (e.g. vaccine doses may be returned by subsidiaries to the central warehouse). These constant updates may result in discrepancies between consecutive queries of the database.

For this evaluation, the sales database was queried in September 2014. Table 4 provides the number of doses distributed for GSK DTPa-containing vaccines in scope of the present evaluation.

Table 4 Sales data for DTPa-combination vaccines included in the present analysis

Vaccine		Number of doses sold between, and including, January 2003 and September 2014
Infanrix	(DTPa)	75 106 037
Infanrix-IPV	(DTPa-IPV)	37 474 595
Infanrix-IPV/Hib	(DTPa-IPV+HIB)	64 230 025
Infanrix/Hib	(DTPa + HIB)	6 646 745
Infanrix Penta	(DTPa-HBV-IPV)	66 170 631
Infanrix hexa	(DTPa-HBV-IPV+HIB)	116 247 790
Boostrix	(Tdap)	100 362 146
Boostrix Polio	(Tdap-IPV)	15 477 054
TOTAL		**481 715 023**

5. SPONTANEOUS DATA

5.1. ELS definition

In the literature, various ELS definitions exist (Rennels, 2000; Woo, 2003; Gold, 2003; Marshall, 2006; Jacquet, 2006). Comparison of data across published trials and reviews is made difficult by the lack of a standard definition and terminology. In published reports, the terms "extensive" or "large" have been used to describe reactions which are greater than a certain diameter (usually 5 cm), in addition to reactions which lead to a noticeable increase in limb circumference and/or extend to adjacent joints. In some trials, redness, rather than swelling, has been the parameter evaluated.

The current definition used for coding into the GSK Worldwide Clinical Safety Database is (Argus Case Management Group Procedural Document Section 5.14.3):

1. Any local swelling/oedema with a diameter ≥50 mm for subject under 7 years and ≥100 mm for adults

2. Any noticeable increased circumference of the injected limb
3. Diffuse swelling/oedema involving the adjacent joint
4. A reporter's description of 'swelling of the injected limb' which describes a diffuse reaction of the whole injected limb.

5.2. Database Search Strategy for cases coded as 'Extensive swelling of vaccinated limb'

The GSK worldwide safety database was searched on 7 October 2014 using the following criteria:

- **Data lock points:** Cases having a GSK receipt date between 1 January 2003 and 25 September 2014.
- **Report types:** All spontaneous reports
- **Suspect vaccines:** Infanrix, Infanrix-IPV, Infanrix-IPV/Hib, Infanrix/Hib, Infanrix Penta, Infanrix hexa, Boostrix and/or Boostrix Polio.
- **MedDRA PT:** Extensive swelling of vaccinated limb

5.3. Summary of Overall Dataset

A total of 2626 reports were retrieved from the GSK worldwide safety database. For 108 (4.1%) of these cases the vaccination date was not reported. Since there might be a time lag between vaccination and, if any, event reporting to GSK, vaccination date (instead of GSK receipt date) was used to further assess ELS cases. Table 5 shows the number of cases retrieved for each of the vaccines in scope. Fifteen cases included more than one DTPa/Tdap vaccine, therefore the total in Table 5 is 2641 (2626+15).

Table 5 Number of cases retrieved from the safety database for the vaccines in scope between 2003 and September 2014

Vaccine	Total number of ELS cases	Subset for which vaccination date was unknown
Infanrix	685	14 (2.0%)
Infanrix-Hib	24	0 (0.0%)
Infanrix-IPV	622	43 (6.9%)
Infanrix-IPV-Hib	453	11 (2.4%)
Infanrix Penta	1	0 (0.0%)
Infanrix hexa	554	31 (5.6%)
Boostrix	266	8 (3.0%)
Boostrix Polio	36	1 (2.8%)
TOTAL	2641	108 (4.1%)

5.4. ELS reporting over time and by vaccine

Figure 1 shows the number of cases including the PT 'Extensive swelling of vaccinated limb' over time per calendar year. This PT started to appear in 2005. An increased

reporting trend was observed since 2011. As already shown in Table 5, few cases were reported for Infanrix/Hib, Infanrix Penta and Boostrix Polio. These 3 vaccines were not further evaluated due to lack of data.

Figure 1 Number of cases including the PT 'Extensive swelling of vaccinated limb' per 100 000 doses by DTPa/Tdap-containing vaccine over time

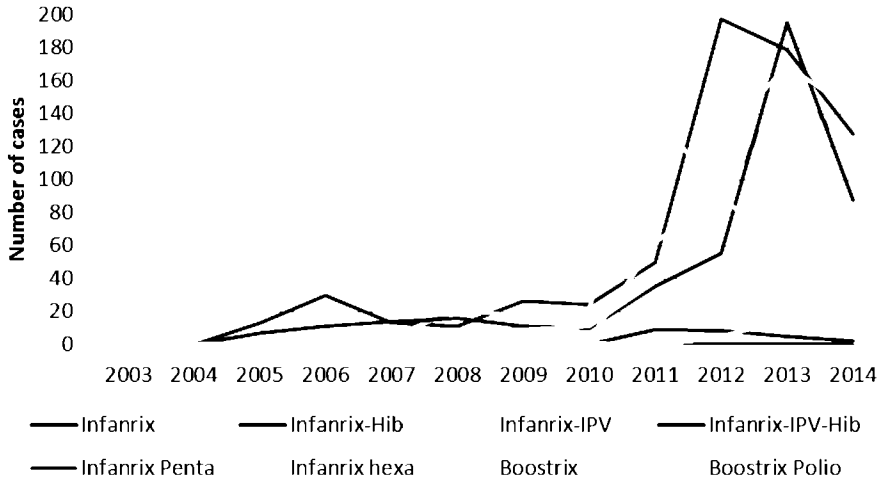
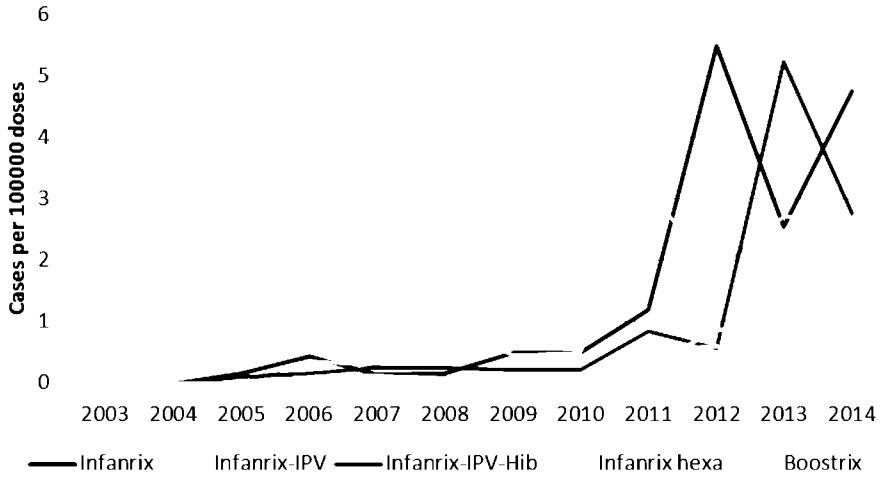


Figure 2 shows the global reporting frequency per 100 000 doses sold of the PT 'Extensive swelling of vaccinated limb' over time per calendar year. Until 2010, the reporting frequency varied between 0 and 1 case per 100 000 doses sold for all five vaccines considered. As of 2011, this reporting frequency increased up to 5-6 cases per 100 000 doses sold for Infanrix and Infanrix-IPV/Hib, up to 3 cases per 100 000 doses sold for Infanrix-IPV, and up to 1-2 cases per 100 000 doses sold for Infanrix hexa. The Boostrix reporting frequency increased from 0 to 0.6 cases per 100 000 doses sold in 2011 and 2012, and then decreased around 0.3 in 2013 and 2014.

Figure 2 **Reporting frequency of cases including the PT 'Extensive swelling of vaccinated limb' per 100 000 doses by DTPa/Tdap-containing vaccine over time**

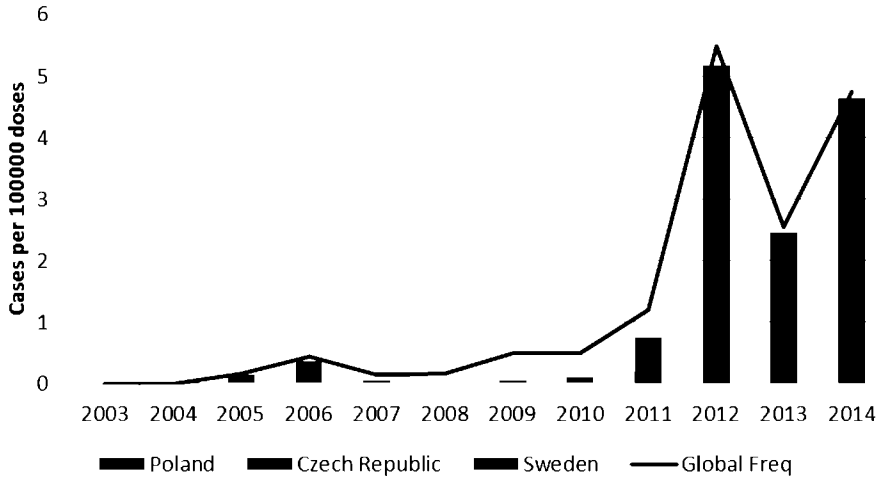


5.5. Country-specific trends by vaccine

5.5.1. Infanrix

Changes in the global ELS reporting frequency over time for Infanrix were mainly triggered by Poland, Czech Republic and Sweden (Figure 3).

Figure 3 **Countries that triggered changes in the global ELS reporting frequency for Infanrix**



5.5.1.1. Infanrix in Poland

Poland still uses whole cell pertussis vaccines. DTPa vaccines (Infanrix or Tripacel from Sanofi Pasteur) are available for special populations. DTPa is recommended as pre-school booster at six years of age since 2004, for infants with contraindications to DTPw since 2005 and for preterms (born before 37 weeks of gestation or with a birth weight <2500g) since 2013.

Poland has seen a sudden increase in pertussis incidence in 2012 which was about two-fold higher than seen in previous years and three-fold higher when compared with that in 2011 [Zawadka, 2014]. At the same time, Infanrix sales (Figure 4) and overall spontaneous reporting not restricted to ELS (Figure 5) both increased as of 2011. The age reported was children between 5 to 7 years (Figure 6), as expected in view of the Polish immunization schedule.

These elements indicate an increased use of Infanrix in Poland in children 5-7 years of age, as reflected by increased spontaneous reporting (including reporting of ELS), likely in response to the pertussis outbreaks between 2012 and 2014.

All (100%) Infanrix ELS cases from Poland were reported by Polish authorities. Also, ELS reporting in Poland increased at the same time for two other GSK vaccines: Infanrix-IPV/Hib (Figure 28) and Infanrix hexa (Figure 34). This is likely the result of increased attention, specifically to ELS, by local authorities, also possibly triggered by the Polish pertussis outbreaks between 2012 and 2014.

The highest yearly local reporting frequency was 1330 ELS cases per 100000 doses distributed in Poland (112 cases and 8417 doses sold, i.e. uncommon), which is 10-fold lower than the incidence currently mentioned in the Infanrix product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 4 Infanrix sales in Poland

Figure 5 **Proportion of ELS cases *versus* non-ELS cases reported for Infanrix over time in Poland**

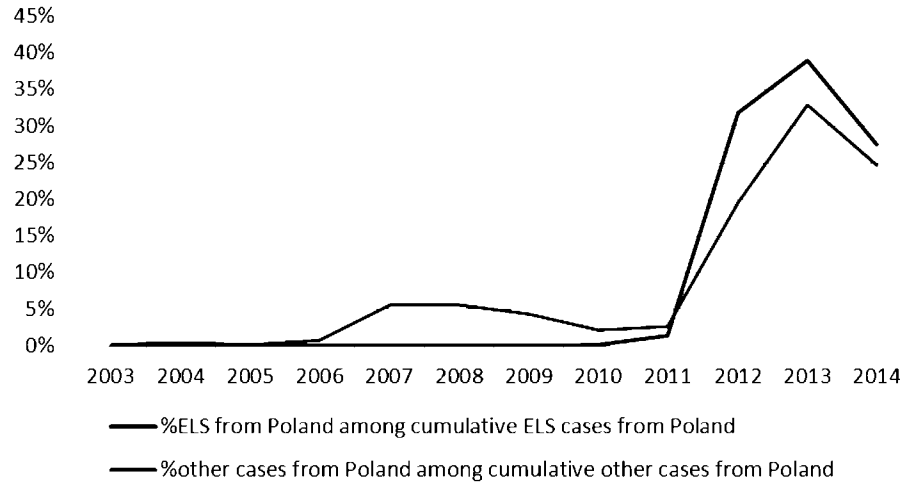


Figure 6 **Age reported in Infanrix ELS cases from Poland**

5.5.1.2. Infanrix in Czech Republic

In the Czech Republic, Infanrix is used as DTPa vaccine and is recommended as pre-school booster at five years of age since 2004.

Czech sales figures for Infanrix were constant over time (data not shown), and GSK is not aware of pertussis outbreaks having occurred in Czech Republic in recent years. However, overall spontaneous reporting not restricted to ELS started to increase as of 2012 (Figure 7). The age reported was children between 5 to 7 years (Figure 8), as expected in view of the Czech immunization schedule. 83% of cases were reported by the local regulatory authority. In the context of unchanged vaccine use/exposure, an increase

of overall spontaneous reporting not restricted to a given event/condition is likely the result of national/regulatory initiatives to increase local spontaneous reporting overall.

The highest yearly local reporting frequency was 52 ELS cases per 100000 doses distributed in Czech Republic (i.e. very rare), which is 1000-fold lower than the incidence currently mentioned in the Infanrix product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 7 Proportion of ELS cases *versus* non-ELS cases reported for Infanrix over time in Czech Republic

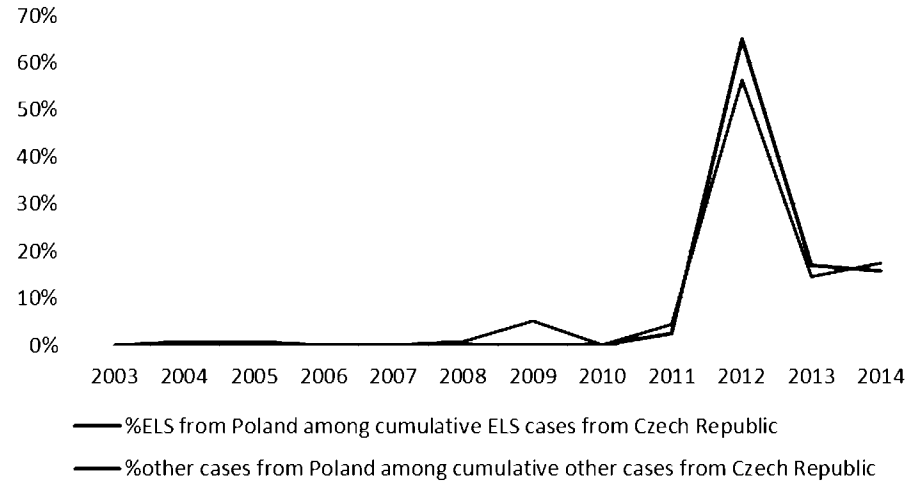


Figure 8 Age reported in Infanrix ELS cases from Czech Republic

5.5.1.3. Infanrix in Sweden

Sweden introduced acellular pertussis vaccines in the primary schedule in 1996, after a period of 17 years without any pertussis vaccination at all (Salmaso, 2004). The Swedish pertussis vaccination schedule consists of priming at 3-5-12 months. Children born before 2002 were boosted at 10 years (catch-up booster since 2005), while children born in 2002 or later were boosted at 5-6 years (with standard antigen content pertussis vaccine) since 2007 and will be boosted at 14-16 years of age (with reduced antigen content pertussis vaccine; ECDC, 2012). The catch-up booster at 10 years was recommended to start during the school year 2005/2006. In reality, only few schools started during (late) autumn of 2005 whereas the vast majority needed more time to prepare and waited until spring 2006. Some even waited until autumn 2006. Thus, the coverage rate was low in the school year 2005-2006. As a consequence of this catch-up, between 2007 and 2011, two cohorts of children were boosted simultaneously: those born before 2002 when they turn 10 years old, and those born after 2002 when they turn 5-7 years old.

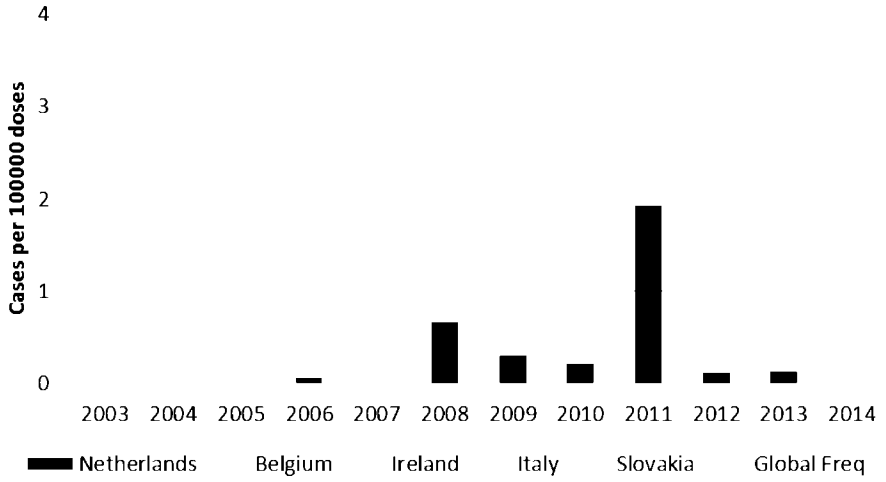
All cases reported from Sweden were related to the catch-up programme, i.e. only cases within the 8-13 years old age group were reported (no cases from the regular pre-school booster at 5-7 years - data not shown), with a peak at the start of the catch-up programme and then sporadic cases (and more recently a smaller peak, at the time when the catch-up programme was planned to end, see Figure 3). It is unclear whether or not this could be related to duplications in administration (e.g. if some children received two catch-up doses at the start of the programme, or if they changed school and lost track of it, or if they received a catch-up in 2011 after having received a pre-school booster in 2007).

The highest yearly local reporting frequency was 459 ELS cases per 100000 doses distributed in Sweden (i.e. rare), which is 100-fold lower than the incidence currently mentioned in the Infanrix product information (see Section 1.2.1). No new information was received with these ELS cases.

5.5.2. Infanrix-IPV

Changes in the global ELS reporting frequency over time for Infanrix-IPV were mainly triggered by the Netherlands, Belgium, Ireland, Italy and Slovakia (Figure 9).

Figure 9 **Countries that triggered changes in the global ELS reporting frequency for Infanrix-IPV**



5.5.2.1. Infanrix-IPV in the Netherlands

The Netherlands is one of the countries with late introduction of acellular pertussis vaccines in the primary schedule compared to other European countries. The preschool booster with acellular vaccines was introduced in 2001, while acellular vaccines were introduced in the primary schedule only in January 2005 (De Greef, 2008; Kemmeren, 2011). The Dutch schedule consists of priming at 2-3-4 months, followed by boosters at 11 months and 4 years of age.

As of 2008, the Dutch Infanrix-IPV sales increased (Figure 10) as a consequence of the switch from a competitor reduced antigen content DTPa-IPV vaccine to Infanrix-IPV. At the same time, in 2008-2009, a questionnaire study was performed to assess the tolerability (including local reactions) of Infanrix-IPV in aP-primed children versus wP-primed children [Kemmeren, 2011]. This was accompanied by an expected increase of overall case reporting, including ELS, as of 2008 (Figure 11). The age reported in Dutch ELS cases was children between 2 to 4 years (Figure 12), as expected in view of the Dutch immunization schedule for DTPa-IPV.

Also, 99% of cases were reported by the local regulatory authority. The Netherlands had a lot of communication around ELS in 2010 and 2011, which might have further stimulated ELS reporting to GSK and be the cause of the increase observed in 2011. Note that as a consequence a switch from DTPa to reduced antigen content acellular pertussis vaccine was recommended in the Netherlands.

Delayed ELS reporting compared to spontaneous reporting of other events was observed for Infanrix-IPV in Italy (see Section 5.5.2.4), Infanrix-IPV/Hib in Poland (see Section 5.5.3.2), for Infanrix hexa in Poland (see Section 5.5.4.2), for Infanrix hexa in France (see Section 5.5.4.3) and for Boostrix in Germany (see Section 5.5.5.2). The fact that spontaneous reporting of a listed event starts years after introduction of a vaccine, instead

of starting at the same time, can result from the fact that a certain threshold of subjects need to be vaccinated to detect the event in a spontaneous reporting setting. Also, most health care providers might not report the first ELS case(s) they observe and only start ELS reporting after having observed several ELS cases over time.

The highest yearly local reporting frequency was 48 ELS cases per 100000 doses distributed in the Netherlands (i.e. very rare), which is 1000-fold lower than the incidence currently mentioned in the Infanrix-IPV product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 10 Infanrix-IPV sales in the Netherlands

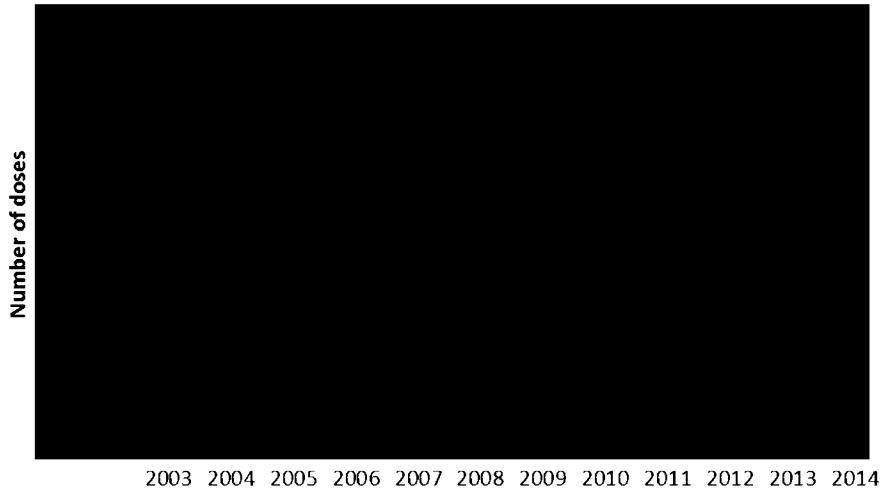


Figure 11 Proportion of ELS cases versus non-ELS cases reported for Infanrix-IPV over time in the Netherlands

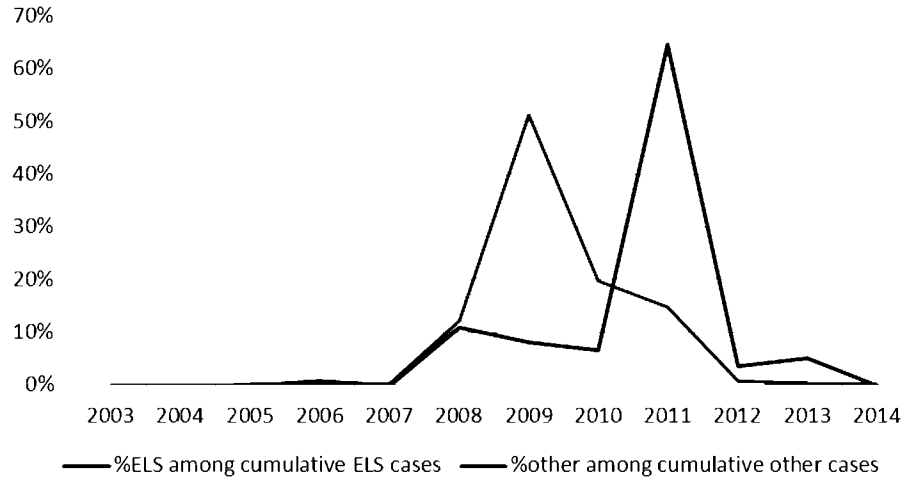
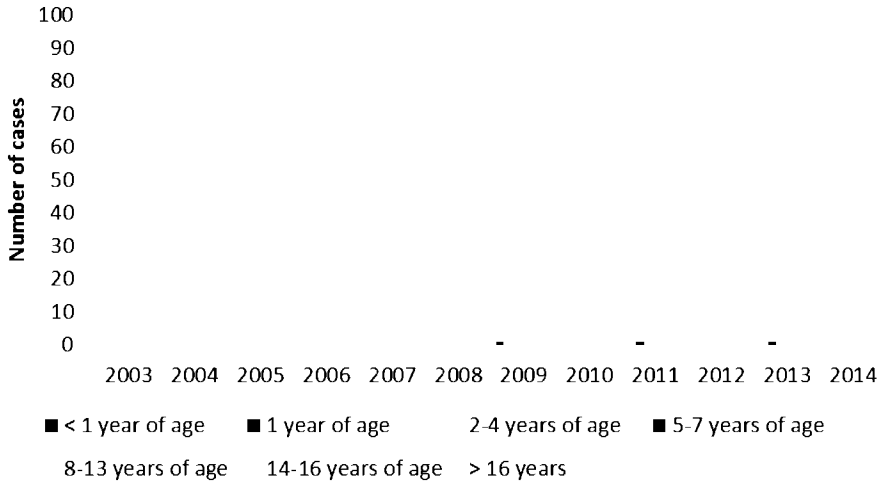


Figure 12 Age reported in Infanrix-IPV ELS cases from the Netherlands



5.5.2.2. Infanrix-IPV in Belgium

Belgium introduced acellular pertussis vaccines in the primary schedule in 2002 (Salmaso, 2004). The Belgian pertussis vaccination schedule consists of priming at 2-3-4 months, followed by boosters at 15 months and 5-7 years of age (ECDC, 2012).

As of 2009 Belgian Infanrix-IPV sales increased (Figure 13), accompanied by an expected increase of overall case reporting, including ELS, in the same year (Figure 14). The age reported in Belgian ELS cases was children between 5 to 7 years (Figure 15), as expected in view of the Belgian immunization schedule for DTPa-IPV.

Also, the first cohort primed with DTPa in Belgium got boosted with the fourth DTPa dose in 2003 (toddler booster, approximately 13 months after introduction of acellular pertussis vaccine), and with the fifth DTPa dose between 2007 and 2009 (pre-school booster, approximately 5-7 years after introduction of acellular pertussis vaccine). Considering that children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines (see Section 2.3), increased ELS reporting was expected in Belgium in 2003 and, especially, between 2007 and 2009. Also, the fifth dose is known to be more reactogenic than the fourth (see Section 2.3). Accordingly, an increase of the proportion of ELS cases reported from Belgium was expected and observed as of 2009 (see Figure 14).

Also, Belgium had a lot of communication in the health care community around ELS in 2012, and physicians were actively asked to report cases of ELS to local authorities (CEV, 2012; BCFI, 2012). 92% of Belgian ELS cases were reported by health care providers. This might have stimulated ELS reporting to GSK as of 2012, and most likely already in 2011.

The highest yearly local reporting frequency was 33 ELS cases per 100000 doses distributed in Belgium (i.e. very rare), which is 1000-fold lower than the incidence currently mentioned in the Infanrix-IPV product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 13 Infanrix-IPV sales in Belgium

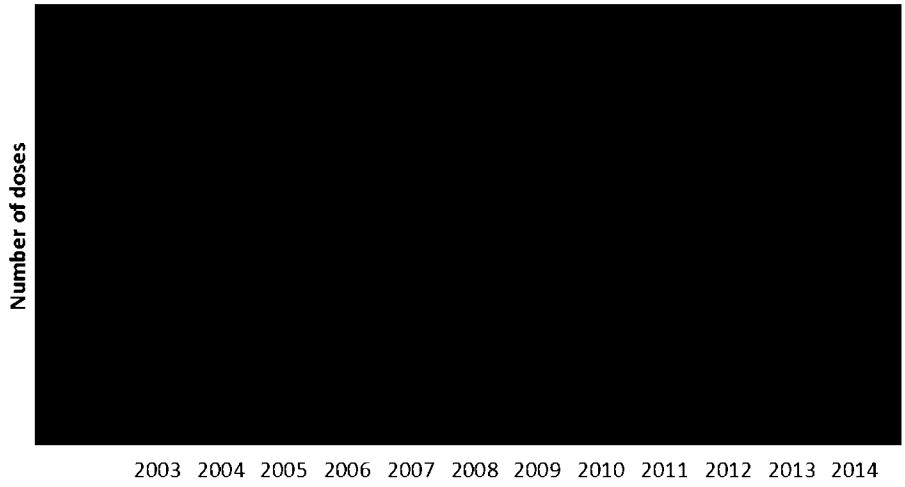


Figure 14 Proportion of ELS cases versus non-ELS cases reported for Infanrix-IPV over time in Belgium

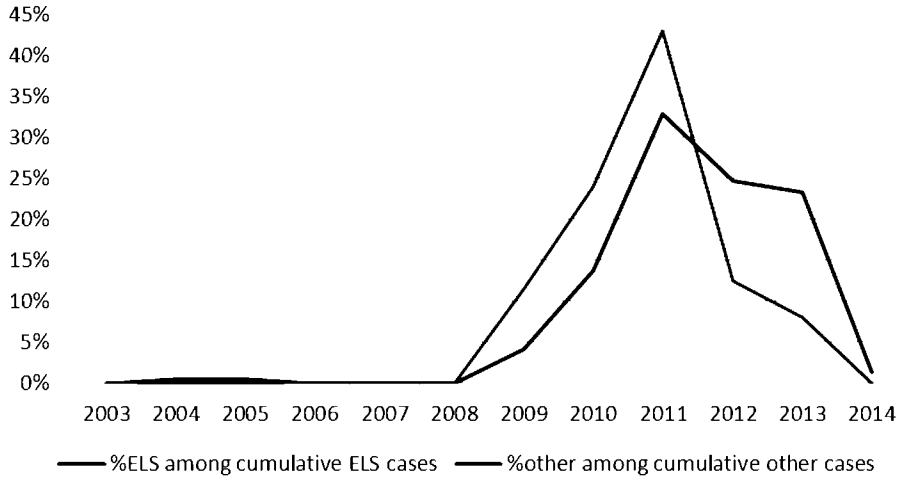
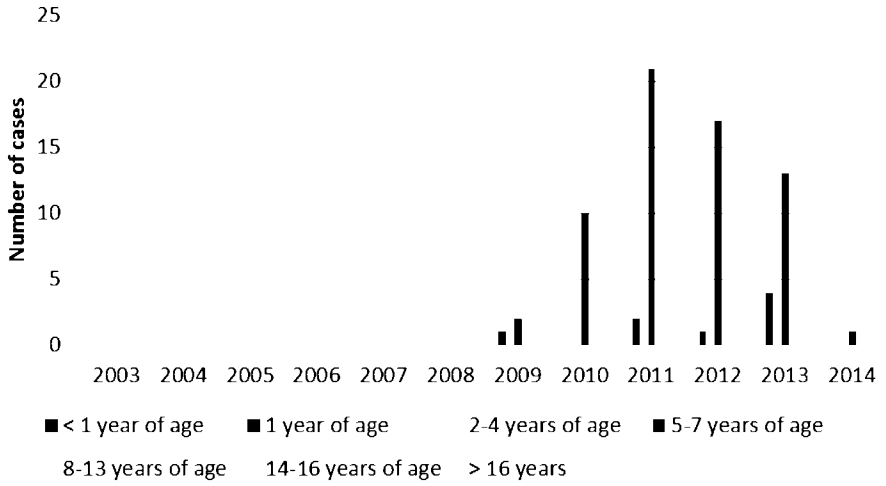


Figure 15 Age reported in Infanrix-IPV ELS cases from Belgium



5.5.2.3. Infanrix-IPV in Ireland

In Ireland, the whole cell pertussis vaccine (wP) was introduced in 1952/3 as part of the DTP vaccine (against diphtheria, tetanus & pertussis). The acellular pertussis vaccine (aP) was introduced in Ireland in 1996 as part of the DTaP vaccine. Children are vaccinated at 2, 4 and 6 months of age and are given a booster at 4-5 years. A further booster at 11-14 years is now recommended and implementation commenced in 2011 [PHMCDG, 2013].

As of 2012 sales increased (Figure 16) as a consequence of the switch from a competitor reduced antigen content DTPa-IPV vaccine (Tetravac from Sanofi Pasteur) to Infanrix-IPV in 2011. This was followed by an expected increase of overall case reporting, including ELS (Figure 17). This might also be due to increased regulatory attention as 90% of cases were reported by the local regulatory authority.

The highest yearly local reporting frequency was 79 ELS cases per 100000 doses distributed in Ireland (i.e. very rare), which is 1000-fold lower than the incidence currently mentioned in the Infanrix-IPV product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 16 Infanrix-IPV sales in Ireland

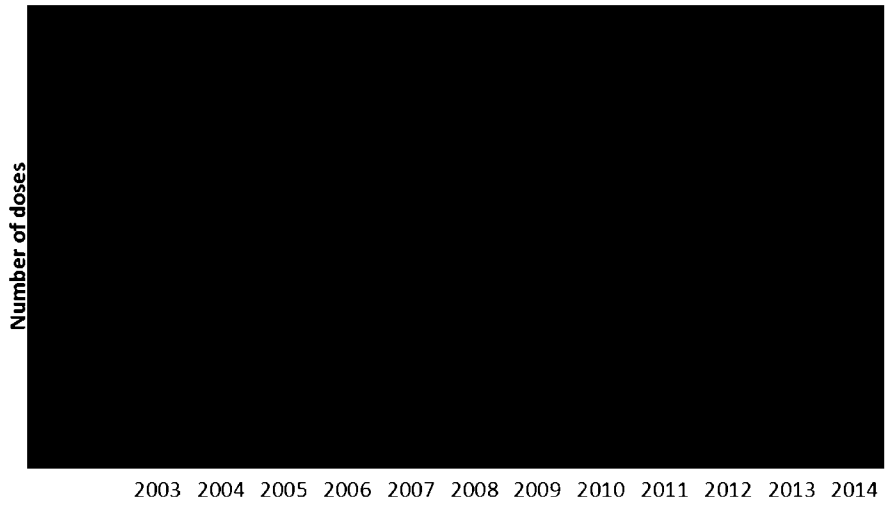
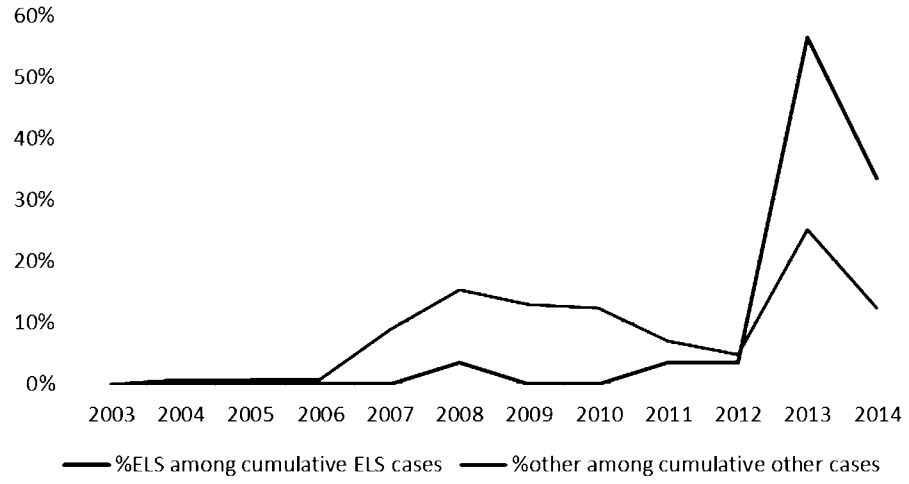


Figure 17 Proportion of ELS cases versus non-ELS cases reported for Infanrix-IPV over time in Ireland



5.5.2.4. Infanrix-IPV in Italy

In Italy, pertussis immunization of infants has been recommended since the 1960s. In 1995 acellular pertussis (aP) vaccines (one monovalent aP vaccine and two DtaP products) were introduced in Italy and three doses were recommended at 3, 5 and 11 months of age, respectively. Starting from 1999, a booster dose of pertussis vaccine was also recommended at 6 years of age [Rota, 2005].

Since 2009, Infanrix-IPV is used for this booster at 6 years of age. Accordingly, Figure 18) shows that Infanrix-IPV sales in Italy increased in 2009 and 2010. As expected, Italian spontaneous reporting for Infanrix-IPV also started to increase in 2009, however

ELS reporting only started in 2011 (2 years later, see Figure 19).The age reported in Italian ELS cases was children between 5 to 7 years (data no shown), as expected in view of the Italian immunization schedule for DTPa-IPV.

Delayed ELS reporting compared to spontaneous reporting of other events was observed for Infanrix-IPV in the Netherlands (see Section 5.5.2.1), Infanrix-IPV/Hib in Poland (see Section 5.5.3.2), for Infanrix hexa in Poland (see Section 5.5.4.2), for Infanrix hexa in France (see Section 5.5.4.3) and for Boostrix in Germany (see Section 5.5.5.2). The fact that spontaneous reporting of a listed event starts years after introduction of a vaccine, instead of starting at the same time, can result from the fact that a certain threshold of subjects need to be vaccinated to detect the event in a spontaneous reporting setting. Also, most health care providers might not report the first ELS case(s) they observe and only start ELS reporting after having observed several ELS cases over time.

All (100%) ELS cases were reported by health care providers. Increased attention of health care providers to report ELS as of a certain point in time, encouraged by local health authorities, might also have triggered overall reporting (including ELS). Since 2008 there has been a steady increase in the Italian case reporting frequency due to an increased attention of health care providers to report AEs as encouraged by the Italian Drug Agency (AIFA). AIFA also encouraged reporting an increasing level of detail. In March 2012, a new national vaccine plan for 2012 to 2015 was released [PNPV, 2012], although the pertussis vaccination schedule remained unchanged (vaccines impacted by the new plan were human papillomavirus, pneumococcal, meningococcal and varicella vaccines). Altogether, these events are likely to have contributed to the overall increase in case reporting as of 2009.

The highest yearly local reporting frequency was 18 ELS cases per 100000 doses distributed in Italy (i.e. very rare), which is 1000-fold lower than the incidence currently mentioned in the Infanrix-IPV product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 18 Infanrix-IPV sales in Italy

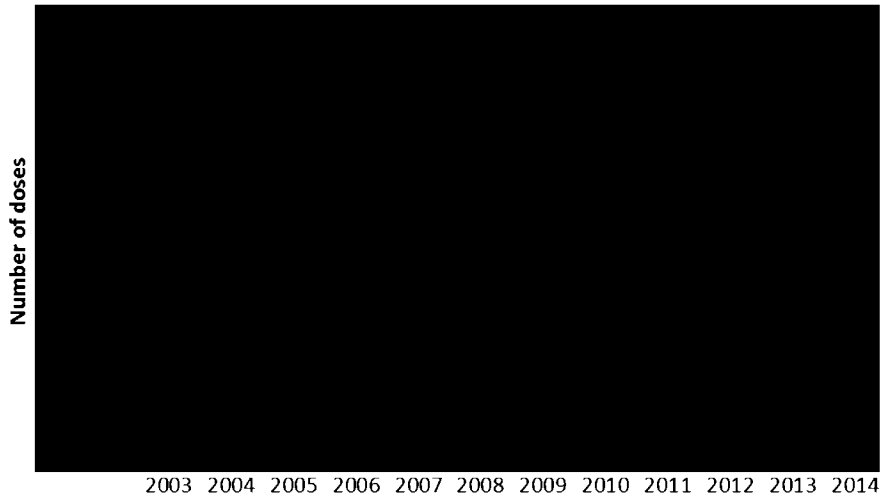
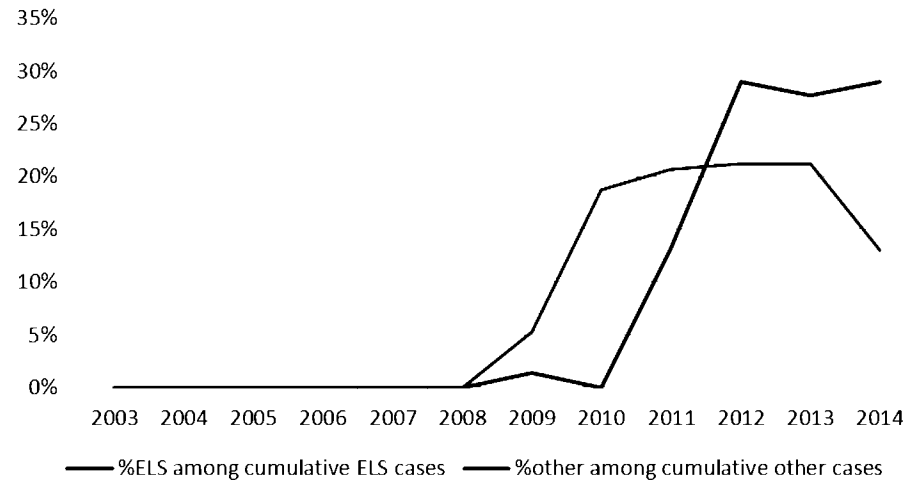


Figure 19 Proportion of ELS cases versus non-ELS cases reported for Infanrix-IPV over time in Italy



5.5.2.5. Infanrix-IPV in Slovakia

Slovakia is one of the countries with late introduction of acellular vaccines in the primary schedule compared to the other European countries. The preschool booster with acellular vaccines (in this case Infanrix-IPV) was introduced in 2009, while acellular vaccines were introduced in the primary schedule in 2008 [Kristufkoval, 2013]. The Slovakian childhood pertussis vaccination schedule consists of priming at 3-5 months, followed by boosters at 11 months and at 5 or 6 years of age.

As of 2009 Slovakian Infanrix-IPV sales increased (Figure 20) as a consequence of use of the vaccine as pre-school booster. As expected, this was accompanied by an increase of overall case reporting in the same year, however ELS reporting only started in 2011 (2 years later, see Figure 21). The age reported in Slovakian ELS cases was children between 5 to 7 years (Figure 22), as expected in view of the Slovakian immunization schedule for DTPa-IPV.

The first cohort primed with DTPa in Slovakia got boosted with the fourth DTPa dose in 2012-2013 (pre-school booster, approximately 4-5 years after introduction of acellular pertussis vaccine). Considering that children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines (see Section 2.3), increased ELS reporting was expected in Slovakia in 2012-2013. Also, the fourth dose is known to be more reactogenic than previous doses (see Section 2.3). Accordingly, an increase of the reporting frequency of ELS cases reported from Slovakia was observed in 2012 and 2013 (see Figure 21).

The highest yearly local reporting frequency was 63 ELS cases per 100000 doses distributed in Slovakia (i.e. very rare), which is 1000-fold lower than the incidence

currently mentioned in the Infanrix-IPV product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 20 Infanrix-IPV sales in Slovakia

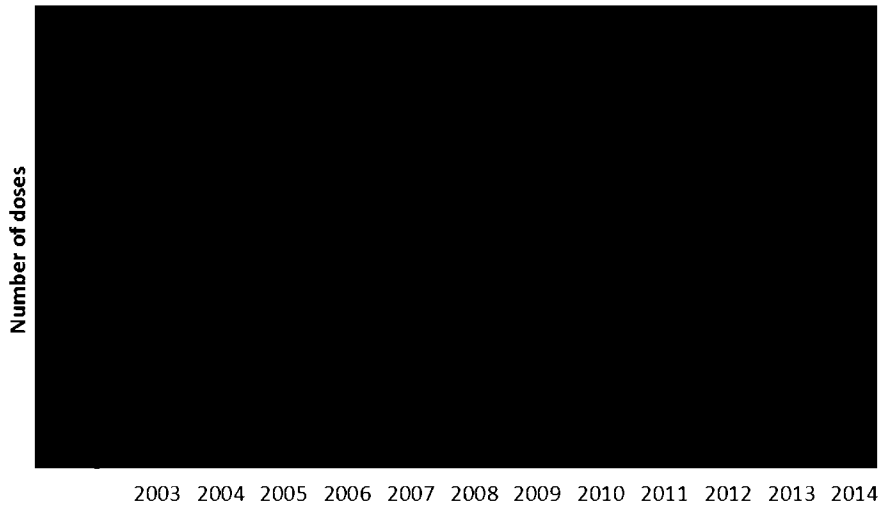


Figure 21 Proportion of ELS cases versus non-ELS cases reported for Infanrix-IPV over time in Slovakia

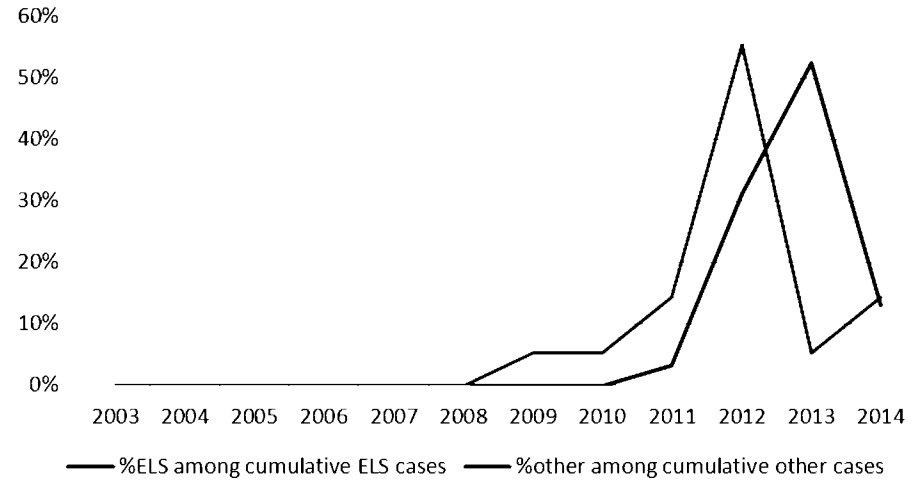
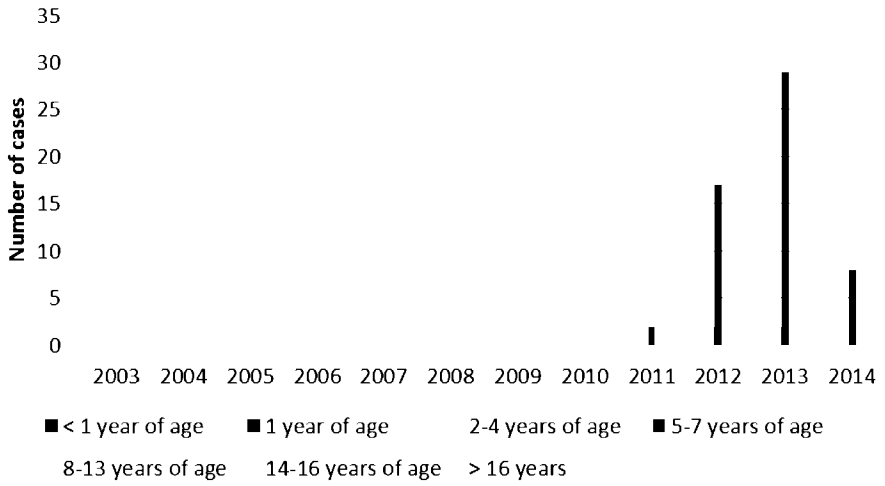


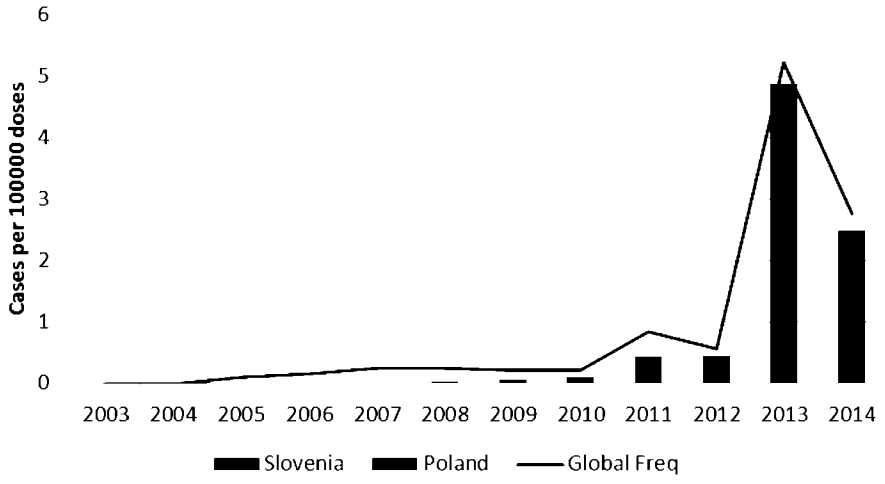
Figure 22 Age reported in Infanrix-IPV ELS cases from Slovakia



5.5.3. Infanrix-IPV/Hib

Changes in the global ELS reporting frequency over time for Infanrix-IPV/Hib were mainly triggered by Slovenia and Poland (Figure 23).

Figure 23 Countries that triggered changes in the global ELS reporting frequency for Infanrix-IPV



5.5.3.1. Infanrix-IPV/Hib in Slovenia

In Slovenia, pertussis immunization of infants has been recommended since 1959. In 1961 a booster in the second year was added. In 1969, the second booster was introduced at the age of 4. In 1990 the second booster was dropped, mainly to reduce the total number of doses against tetanus and diphtheria (from 8 to 7). In 1999, whole-cell

pertussis vaccine was replaced with acellular vaccine. The current Slovenian immunization programme recommends three doses of acellular pertussis vaccine in the first year (at 3, 4–5 and 6 months of age) followed by a booster in the second year of life [Grgič-Vitek, 2008] and 8 years of age (dTPa since 2009).

As of 2012 sales increased again after a two-year temporary interruption of Infanrix-IPV/Hib distribution in Slovenia (Figure 7). Simultaneously overall case reporting, including ELS, increased as well (Figure 25). The age reported was one year old children (Figure 26), as expected in view of the Slovenian immunization schedule. This might be due to increased regulatory attention as more than 99% of cases were reported by the local regulatory authority. Interestingly Slovenian authorities didn't perform any, or very little, spontaneous reporting before 2012 for Infanrix-IPV/Hib, although this vaccine was already distributed at that time.

The highest yearly local reporting frequency was 146 ELS cases per 100000 doses distributed in Slovenia (i.e. rare), which is 100 times lower than the incidence currently mentioned in the Infanrix-IPV/Hib product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 24 Infanrix-IPV/Hib sales in Slovenia

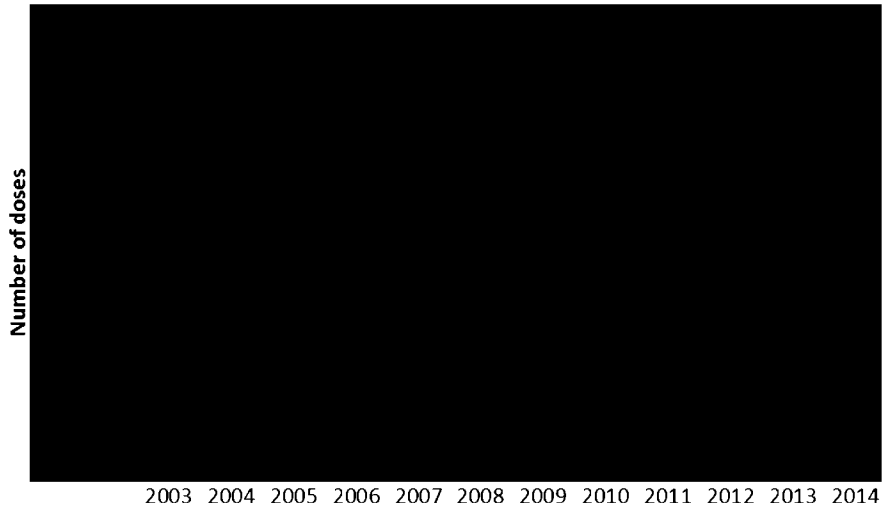


Figure 25 Proportion of ELS cases versus non-ELS cases reported for Infanrix-IPV/Hib over time in Slovenia

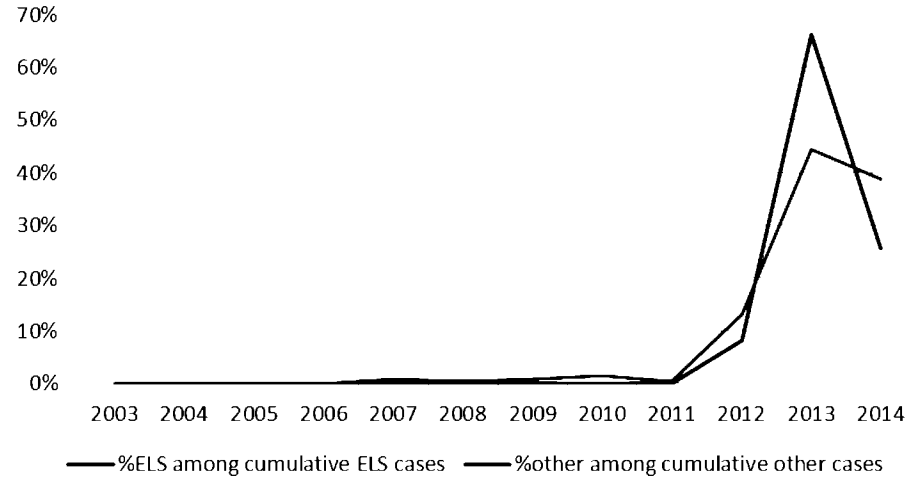
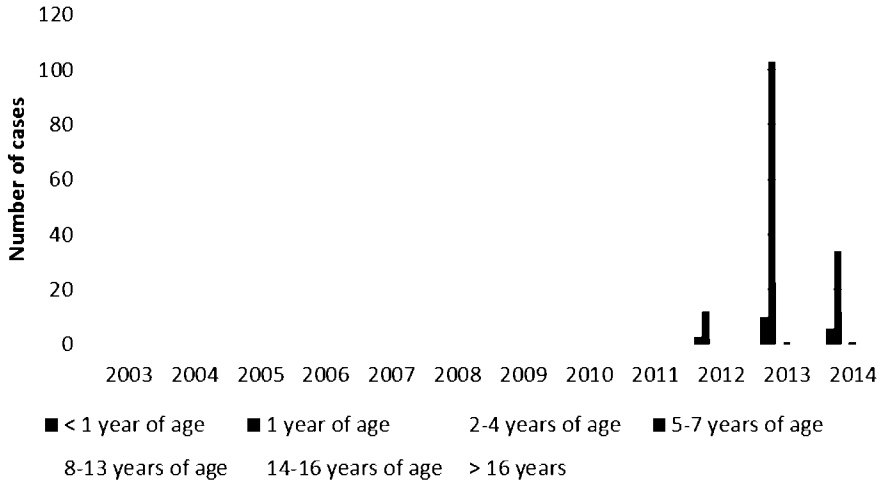


Figure 26 Age reported in Infanrix-IPV/Hib ELS cases from Slovenia



5.5.3.2. Infanrix-IPV/Hib in Poland

Poland still uses whole cell pertussis vaccines. DTPa-IPV/Hib vaccine (Infanrix-IPV/Hib) is available for special populations. It is recommended for primary vaccination in the first year of life and as booster in the second year of life only for:

- infants with contraindications to DTPw since 2005
- premature children born before 37 weeks of gestation or with a birth weight <2500g since 2013.

Poland has seen a sudden increase in pertussis in 2012 which was about two-fold higher than seen in previous years and three-fold higher when compared with that in 2011 [Zawadka, 2014]. However, Infanrix-IPV/Hib sales did not increase during that period, on the contrary, they decreased as of 2010 (Figure 27). Figure 28 shows that Polish spontaneous reporting for Infanrix-IPV/Hib started in 2007, however ELS reporting only started to increase in 2011 (4 years later).The age reported in Polish ELS cases was children one year of age (Figure 29), as expected in view of the Polish immunization schedule for DTPa-IPV/Hib. Note that in none of these cases prematurity or hypersensitivity to DTPw was reported.

Delayed ELS reporting compared to spontaneous reporting of other events was observed for Infanrix-IPV in the Netherlands (see Section 5.5.2.1), for Infanrix-IPV in Italy (see Section 5.5.2.4), for Infanrix hexa in Poland (see Section 5.5.4.2), for Infanrix hexa in France (see Section 5.5.4.3) and for Boostrix in Germany (see Section 5.5.5.2). The fact that spontaneous reporting of a listed event starts years after introduction of a vaccine, instead of starting at the same time, can result from the fact that a certain threshold of subjects need to be vaccinated to detect the event in a spontaneous reporting setting. However, Infanrix-IPV/Hib sales were decreasing in Poland when ELS reporting increased, therefore this cause is unlikely to be true.

Most (97%) ELS cases were reported by Polish authorities, as were non-ELS cases, although to a lesser extent (88%). Also, ELS reporting in Poland increased at the same time for two other GSK vaccines: Infanrix (Figure 5) and Infanrix hexa (Figure 34). This is likely to result from increased regulatory attention, specifically to ELS, by local authorities, possibly triggered by the Polish pertussis epidemic in 2012 (see Section 5.5.1.1).

The highest yearly local reporting frequency was 14 ELS cases per 100000 doses distributed in Poland (i.e. very rare), which is 1000-fold lower than the incidence currently mentioned in the Infanrix-IPV/Hib product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 27 Infanrix-IPV/Hib sales in Poland

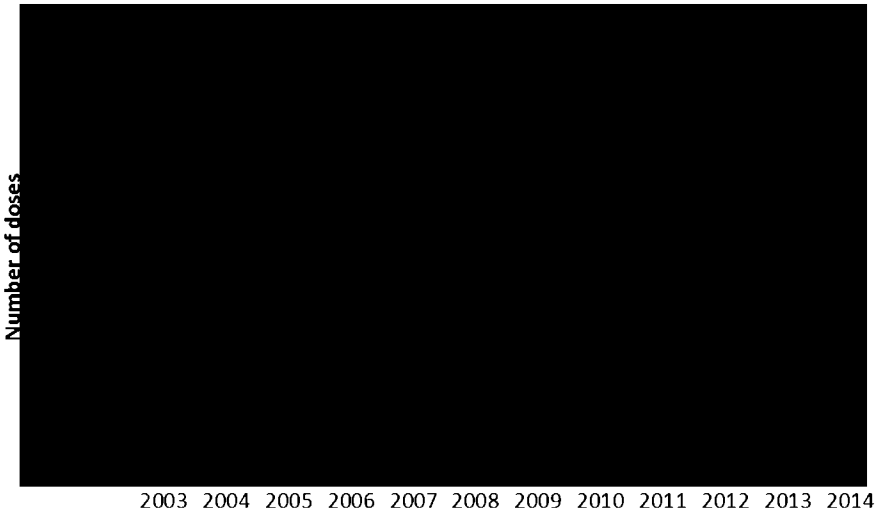


Figure 28 Proportion of ELS cases versus non-ELS cases reported for Infanrix-IPV/Hib over time in Poland

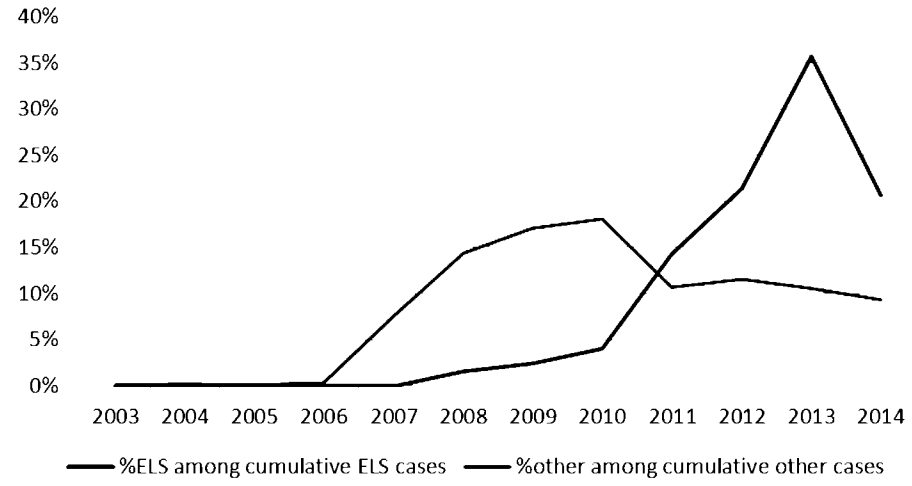
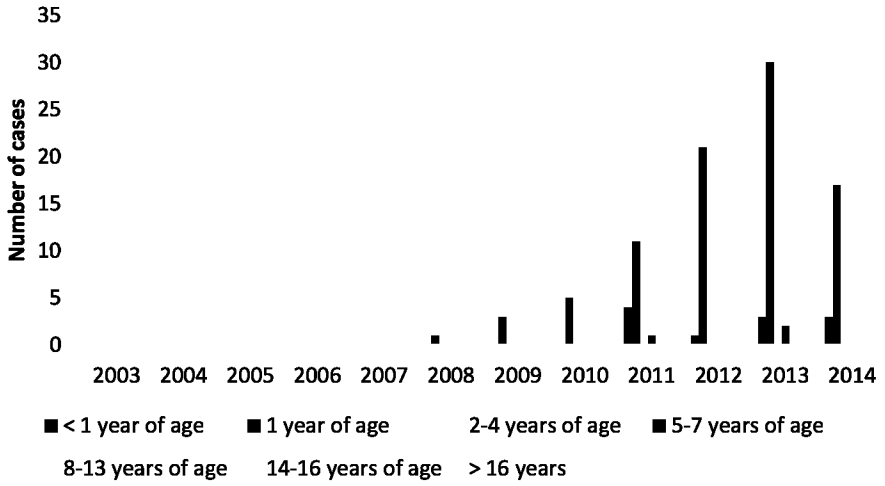


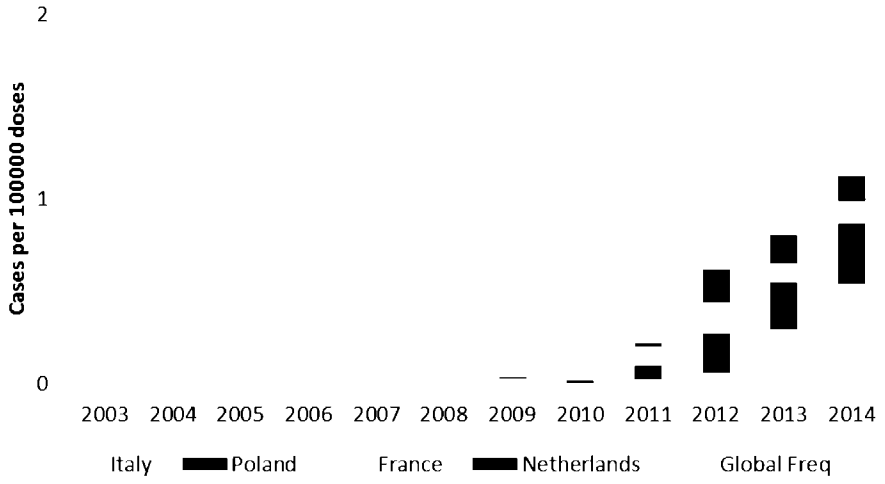
Figure 29 Age reported for Infanrix-IPV/Hib ELS cases from Poland



5.5.4. Infanrix hexa

Changes in the global ELS reporting frequency over time for Infanrix hexa were mainly triggered by Italy, Poland, France and the Netherlands (Figure 30).

Figure 30 Countries that triggered changes in the global ELS reporting frequency for Infanrix hexa



5.5.4.1. Infanrix hexa in Italy

In Italy, pertussis immunization of infants has been recommended since the 1960s. In 1995 acellular pertussis (aP) vaccines (one monovalent aP vaccine and two DtaP products) were introduced in Italy and three doses were recommended at 3, 5 and 11

months of age, respectively. Starting from 1999, a booster dose of pertussis vaccine was also recommended at 6 years of age [Rota, 2005].

Since 2000, Infanrix hexa is used for primary and booster vaccination in the first year of life, and there have been no significant changes in the number of doses distributed to Italy in the past 10 years (data not shown). The age reported in Italian Infanrix hexa ELS cases was children up to one year of age (Figure 31), as expected in view of the Italian immunization schedule for DTPa-HepB-IPV/Hib, and assuming that a certain proportion of children gets boosted when they are one year old instead of at 11 months.

Since 2008 there has been a steady increase in the Italian case reporting frequency due to an increased attention of health care providers to report AEs as encouraged by the Italian Drug Agency (AIFA). AIFA also encouraged reporting an increasing level of detail. In March 2012, a new national vaccine plan for 2012 to 2015 was released [PNPV, 2012], although the pertussis vaccination schedule remained unchanged (vaccines impacted by the new plan were human papillomavirus, pneumococcal, meningococcal and varicella vaccines). Altogether, these events are likely to have led to an overall increase in case reporting as of 2012, including ELS (Figure 32), more specifically reporting by regulatory authorities as 99% of ELS cases were reported by Italian authorities.

The highest yearly local reporting frequency was 5.2 ELS cases per 100000 doses distributed in Italy (i.e. very rare), which is 10000-fold lower than the incidence currently mentioned in the Infanrix-hexa product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 31 Age reported for Infanrix hexa ELS cases from Italy

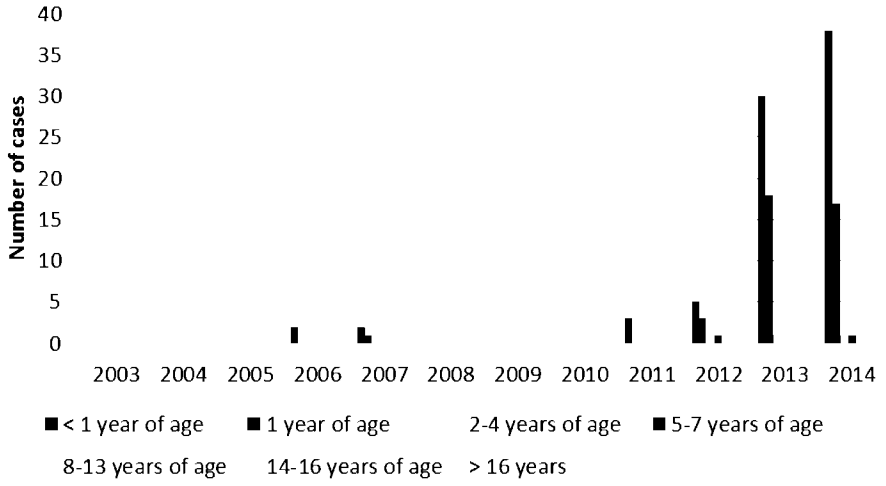
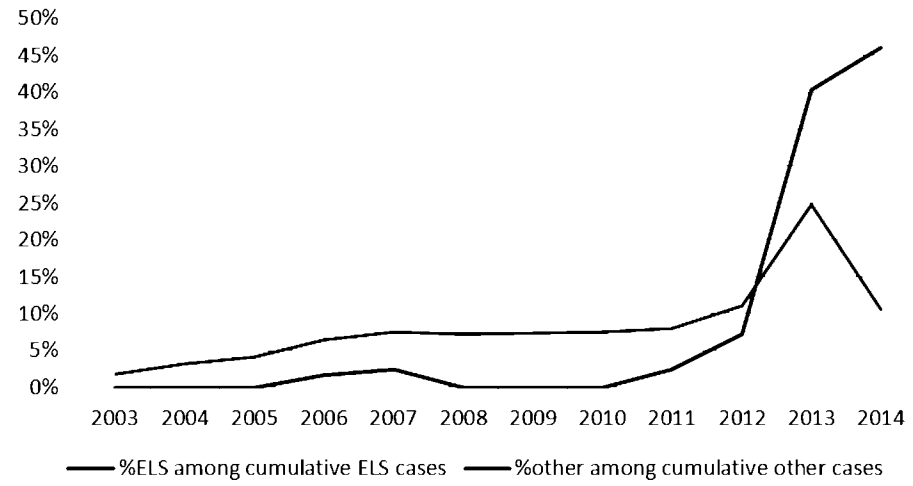


Figure 32 Proportion of ELS cases versus non-ELS cases reported for Infanrix hexa over time in Italy



5.5.4.2. Infanrix hexa in Poland

Poland has seen a sudden increase in pertussis in 2012 which was about two-fold higher than seen in previous years and three-fold higher when compared with that in 2011 [Zawadka, 2014]. Poland still uses whole cell pertussis vaccines and DTPa-IPV-HepB/Hib is not recommended by the Polish immunization schedule.

In line with sales in the private (non-reimbursed) market, Infanrix hexa sales in Poland increased between 2003 and 2010, and stabilized between 2010 and 2013 (Figure 33). Figure 34 shows that Polish spontaneous reporting for Infanrix hexa started in 2007, while ELS reporting only started in 2010 (3 years later). The age reported in ELS cases was one year old children (Figure 35).

Delayed ELS reporting compared to spontaneous reporting of other events was observed for Infanrix-IPV in the Netherlands (see Section 5.5.2.1), for Infanrix-IPV in Italy (see Section 5.5.2.4), for Infanrix-IPV/Hib in Poland (see Section 5.5.3.2), for Infanrix hexa in France (see Section 5.5.4.3) and for Boostrix in Germany (see Section 5.5.5.2). The fact that spontaneous reporting of a listed event starts years after introduction of a vaccine, instead of starting at the same time, can result from the fact that a certain threshold of subjects need to be vaccinated to detect the event in a spontaneous reporting setting. Also, most health care providers might not report the first ELS case(s) they observe and only start ELS reporting after having observed several ELS cases over time.

Most (96%) ELS cases were reported by Polish authorities. Also, ELS reporting in Poland increased at the same time for two other GSK vaccines: Infanrix (Figure 5) and Infanrix-IPV/Hib (Figure 28). This is likely to result from increased regulatory attention, specifically to ELS, by local authorities, possibly triggered by the Polish pertussis epidemic in 2012 (see Section 5.5.1.1).

The highest yearly local reporting frequency was 17 ELS cases per 100000 doses distributed in Poland (i.e. very rare), which is 1000-fold lower than the incidence currently mentioned in the Infanrix-hexa product information (see Section 1.2.1). Note that in none of these cases hypersensitivity to DTPw was reported, and prematurity was reported in only one of them. No new information was received with these ELS cases.

Figure 33 Infanrix hexa sales in Poland

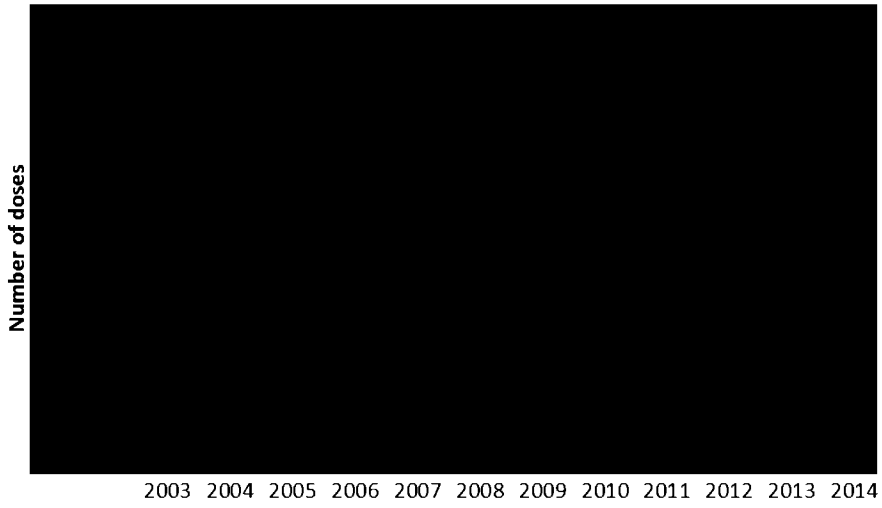


Figure 34 Proportion of ELS cases versus non-ELS cases reported for Infanrix hexa over time in Poland

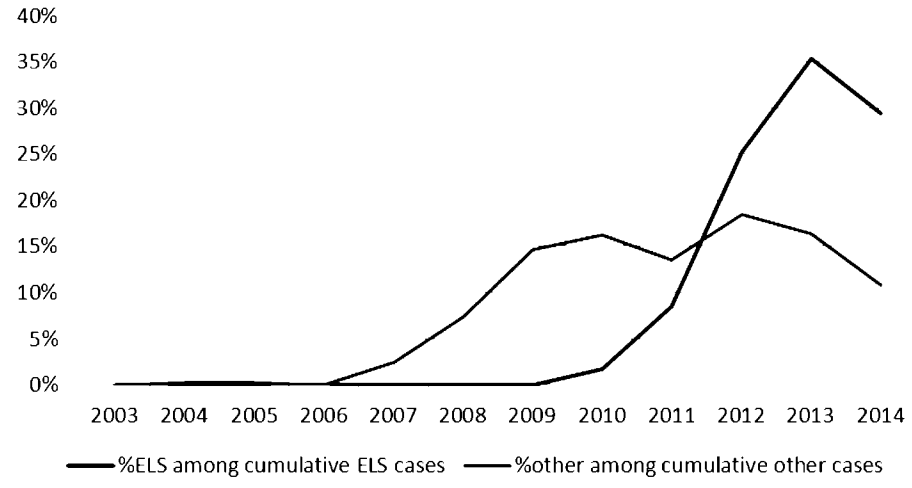
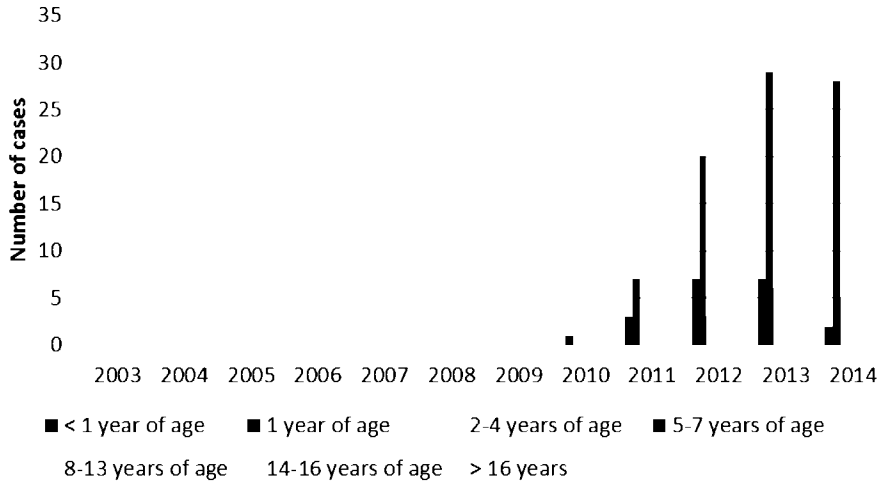


Figure 35 Age reported for Infanrix hexa ELS cases from Poland



5.5.4.3. Infanrix hexa in France

In France, pertussis immunization of infants has been recommended since 1959. In 1998 acellular pertussis (aP) vaccines were introduced in France and the whole cell vaccine was taken off the market in 2005. Initially, the childhood acellular pertussis vaccine schedule recommended a primary course at 2, 3 and 4 months and two boosters at 16-18 months and 11-13 years old [Bonmarin, 2007]. In April 2014, the 3+1 schedule was turned into a 2+1 schedule in France (at 2, 4 and 11 months), the booster at 11-13 months was maintained [INVS, 2014].

In line with the history of French pertussis vaccination recommendations, Infanrix hexa sales progressively increased between 2008 and 2013, and deceased in 2014 when the 3+1 schedule was replaced by the 2+1 schedule (Figure 36). Overall spontaneous reporting for Infanrix hexa started in 2008, soon after the vaccine was introduced in France, however ELS reporting only started in 2011 (three years later, see Figure 37). The age reported was one year old children (Figure 38), as expected in view of the French immunization schedule (booster at 16-18 months). Most (82%) ELS cases were reported by health care providers. GSK is not aware of pertussis outbreaks having occurred in France in recent years.

Delayed ELS reporting compared to spontaneous reporting of other events was observed for Infanrix-IPV in the Netherlands (see Section 5.5.2.1), for Infanrix-IPV in Italy (see Section 5.5.2.4), for Infanrix-IPV/Hib in Poland (see Section 5.5.3.2), for Infanrix hexa in Poland (see Section 5.5.4.2) and for Boostrix in Germany (see Section 5.5.5.2). The fact that spontaneous reporting of a listed event starts years after introduction of a vaccine, instead of starting at the same time, can result from the fact that a certain threshold of subjects need to be vaccinated to detect the event in a spontaneous reporting setting. Also, most health care providers might not report the first ELS case(s) they observe and only start ELS reporting after having observed several ELS cases over time.

The highest yearly local reporting frequency was 1.3 ELS case per 100000 doses distributed in France (i.e. very rare), which is 10000 times lower than the incidence currently mentioned in the Infanrix hexa product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 36 Infanrix hexa sales in France

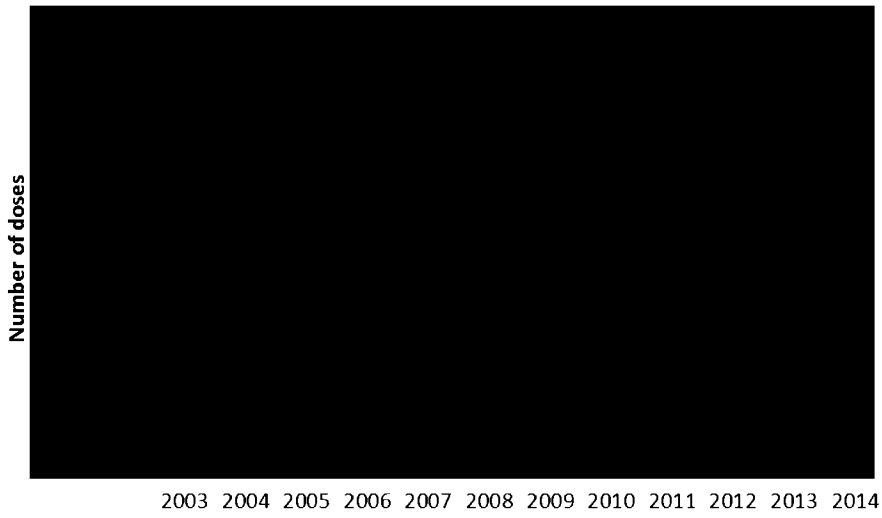


Figure 37 Proportion of ELS cases versus non-ELS cases reported for Infanrix hexa over time in France

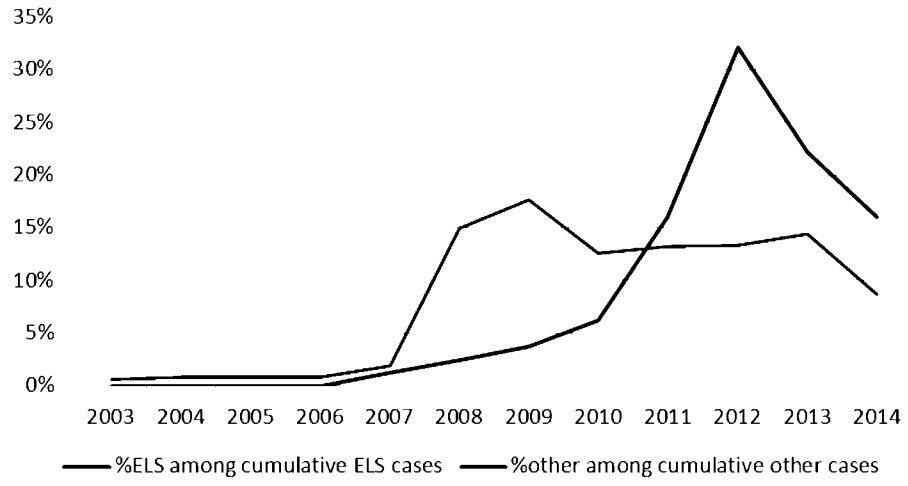
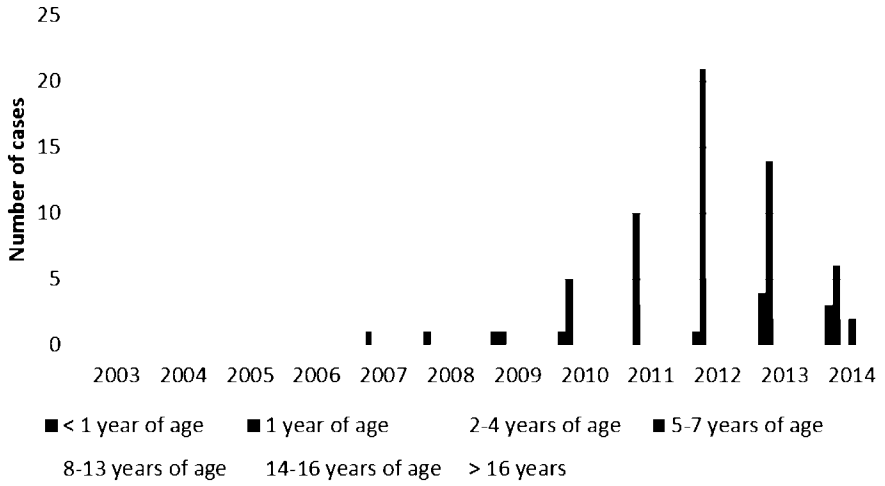


Figure 38 Age reported for Infanrix hexa ELS cases from France



5.5.4.4. Infanrix hexa in the Netherlands

In the Netherlands, the target population for Infanrix hexa vaccination was extended from only children at risk for hepatitis B infection in 2006, to children with Down syndrome as of 2008 and finally to all new-borns as of 2011. This is reflected by the sales data in Figure 39, as well as by spontaneous case reporting in Figure 40. The age reported in ELS cases was children less than one year old (data not shown), as expected in view of the Dutch immunization schedule (primary vaccination in the first year of life). All (but one) cases were received from Dutch regulatory authorities.

The highest yearly local reporting frequency was 3.6 ELS case per 100000 doses distributed in the Netherlands (i.e. very rare), which is 10000 times lower than the incidence currently mentioned in the Infanrix hexa product information (see Section 1.2.1). No new information was received with these ELS cases.

Figure 39 Infanrix hexa sales in the Netherlands

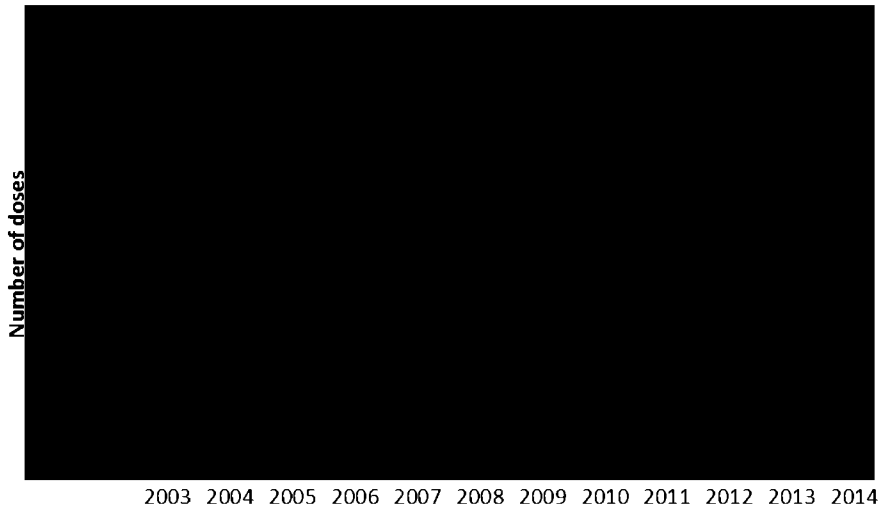
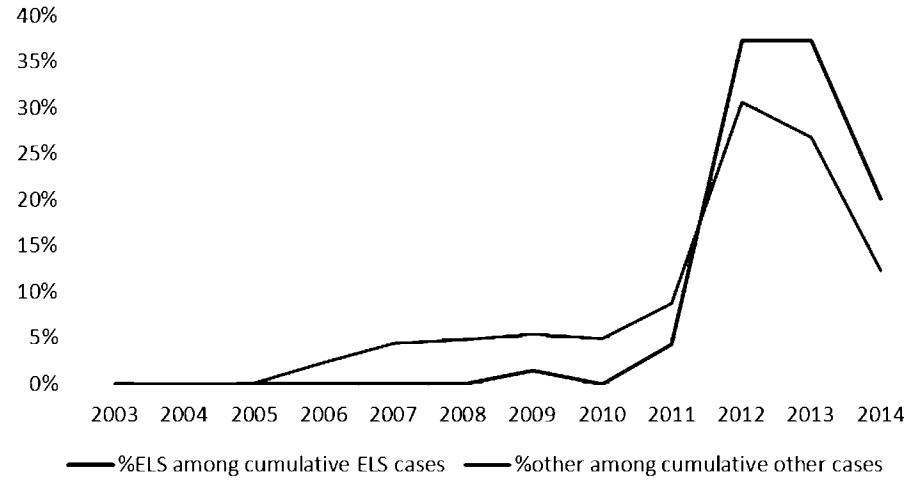


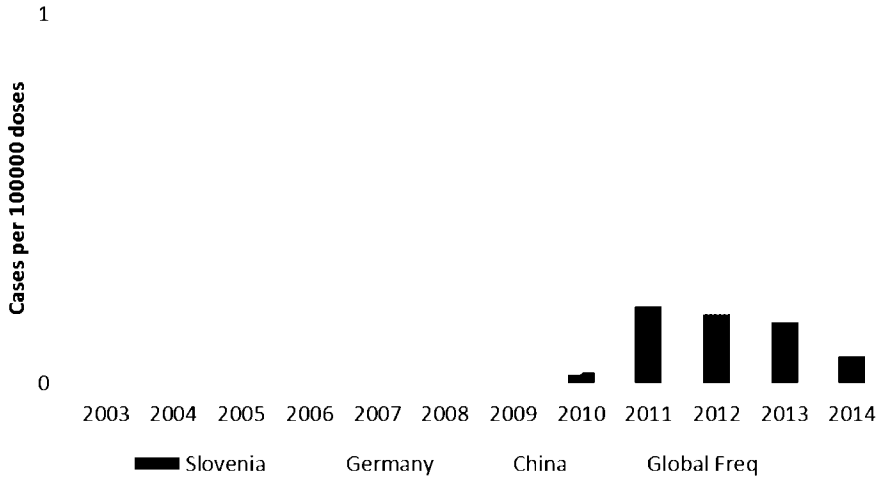
Figure 40 Proportion of ELS cases versus non-ELS cases reported for Infanrix hexa over time in the Netherlands



5.5.5. Boostrix

Changes in the global ELS reporting frequency over time for Boostrix were mainly triggered by Slovenia, Germany and China (Figure 41).

Figure 41 Countries that triggered changes in the global ELS reporting frequency for Boostrix



5.5.5.1. Boostrix in Slovenia

The current Slovenian immunization programme recommends three doses of acellular pertussis vaccine in the first year (at 3, 4–5 and 6 months of age) followed by a booster in the second year of life [Grgič-Vitek, 2008].

Since 2009, a dTPa booster is recommended at 8 years of age. This is reflected by the sales data in Figure 42, as well as by spontaneous case reporting in Figure 43. The age reported in ELS cases was children 8-13 years (data not shown), as expected in view of the Slovenian immunization schedule (adolescent booster). All cases were received from Slovenian regulatory authorities.

The highest yearly local reporting frequency was 277 ELS case per 100000 doses distributed in Slovenia (i.e. rare), which is the incidence currently mentioned in the Boostrix product information (see Section 1.2.3). No new information was received with these ELS cases.

Figure 42 Boostrix sales in Slovenia

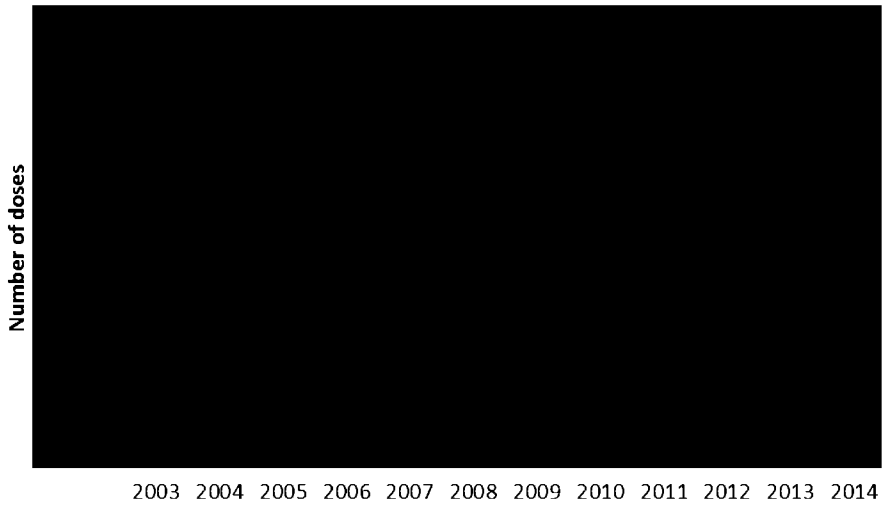
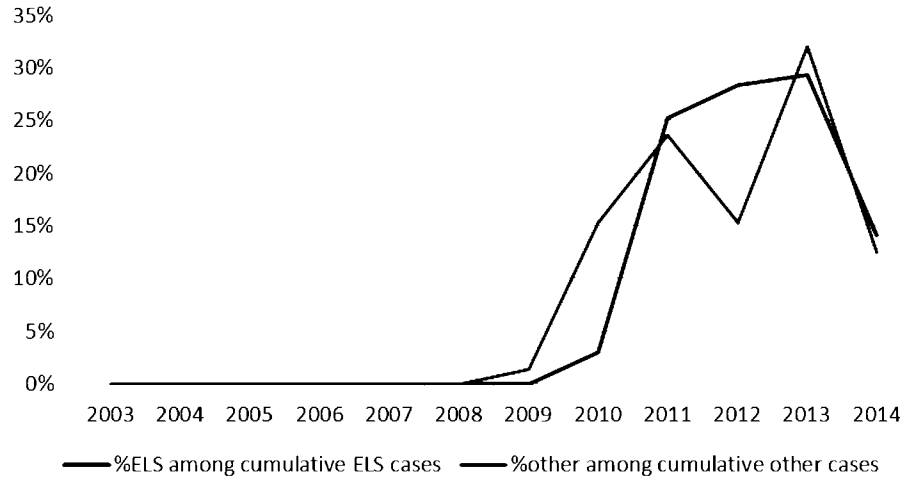


Figure 43 Proportion of ELS cases versus non-ELS cases reported for Boostrix over time in Slovenia



5.5.5.2. Boostrix in Germany

In Germany, acellular pertussis (aP) vaccines were introduced in 1995. German vaccine guidelines for infants recommend pertussis immunization at 2, 3, and 4 months with a toddler booster dose between 11 and 14 months (Infanrix hexa). Pre-school and adolescent boosters (Boostrix) are also recommended, between 5-6 year and 9-17 years, respectively [RKI, 2014].

Figure 44 shows that Boostrix sales in Germany constantly increased since 2003. Figure 45 shows that German spontaneous reporting for Boostrix was already ongoing in 2003, however ELS reporting only started in 2011 (more than 8 years later). The age reported in

ELS cases was mainly 5-7 year old children and, to a lower extend, subjects above 16 years (Figure 46).

Delayed ELS reporting compared to spontaneous reporting of other events was observed for Infanrix-IPV in the Netherlands (see Section 5.5.2.1), for Infanrix-IPV in Italy (see Section 5.5.2.4), for Infanrix-IPV/Hib in Poland (see Section 5.5.3.2), for Infanrix hexa in Poland (see Section 5.5.4.2) and for Infanrix hexa in France (see Section 5.5.4.3). The fact that spontaneous reporting of a listed event starts years after introduction of a vaccine, instead of starting at the same time, can result from the fact that a certain threshold of subjects need to be vaccinated to detect the event in a spontaneous reporting setting. Also, most health care providers might not report the first ELS case(s) they observe and only start ELS reporting after having observed several ELS cases over time.

Most (91%) ELS cases were reported by health care providers. Increased attention of health care providers to report ELS as of a certain point in time, potentially encouraged by local health authorities, might also have triggered ELS reporting.

The highest yearly local reporting frequency was 1 ELS case per 100000 doses distributed in Germany (i.e. very rare), which is 100 times lower than the incidence currently mentioned in the Boostrix product information (see Section 1.2.3). No new information was received with these ELS cases.

Figure 44 Boostrix sales in Germany

Figure 45 Proportion of ELS cases versus non-ELS cases reported for Boostrix over time in Germany

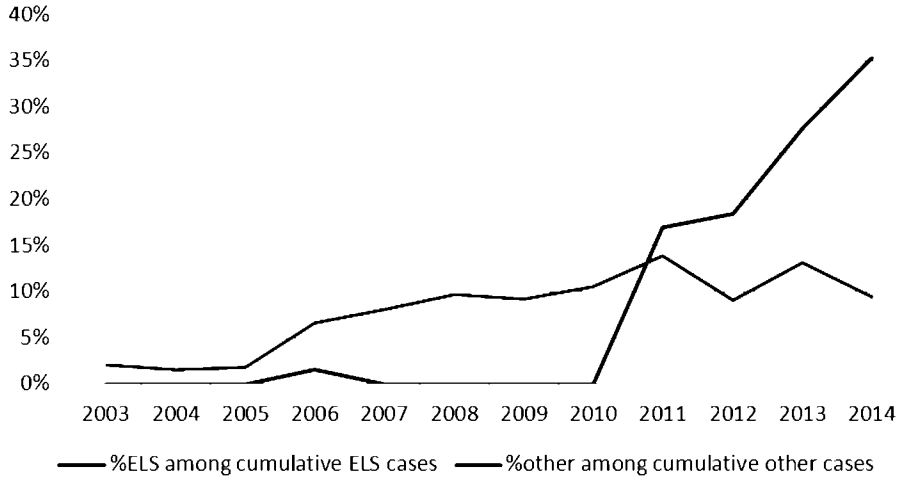
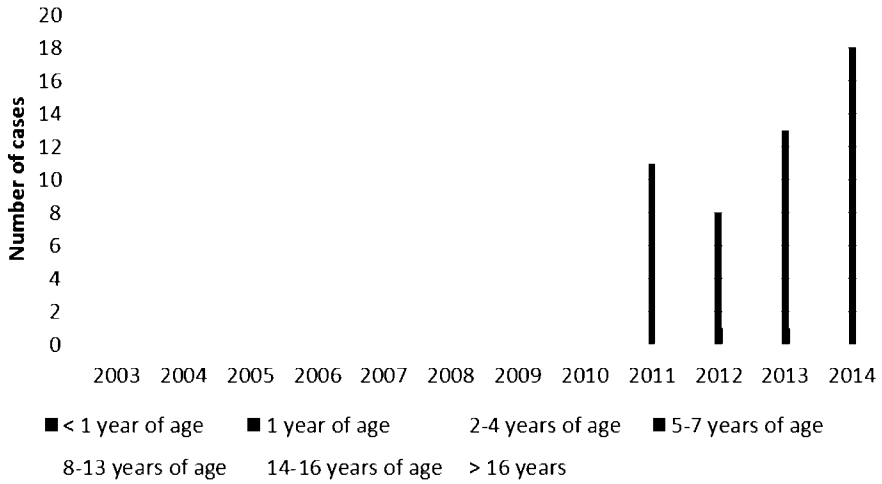


Figure 46 Age reported for Boostrix ELS cases from Germany



5.5.5.3. Boostrix in China

In the People's Republic of China, vaccination against pertussis was started in the early 1960s, when 3 doses of Pw vaccine combined with diphtheria and tetanus toxoids were given at 3, 4, and 5 months of age. In 1982, a booster dose at 18 months of age was added. Pw vaccines are free of charge in China. Acellular pertussis (Pa) vaccines have been introduced in 1995. However, because Pa vaccines are offered at the patient's expense, use of these vaccines has been minimal, especially in some resource-limited areas. Although since 2007 Pa vaccines have been included in the national expanded program on immunization, Pa and Pw vaccines are still used in most provinces because of limited availability and cost of Pa vaccines [Zhang, 2010].

Regarding Boostrix, there was a temporary sales peak in China in 2010 and 2011 (Figure 47), with the highest monthly sales occurring in November and December 2010. As expected, spontaneous reporting, including ELS, occurred in 2011 and 2012. The age reported in ELS cases was 5-7 year old children (Figure 49). All cases were received from Chinese regulatory authorities.

The highest yearly local reporting frequency was 12 ELS case per 100000 doses distributed in China (i.e. very rare), which is 10 times lower than the incidence currently mentioned in the Boostrix product information (see Section 1.2.3). No new information was received with these ELS cases.

Figure 47 Boostrix sales in China

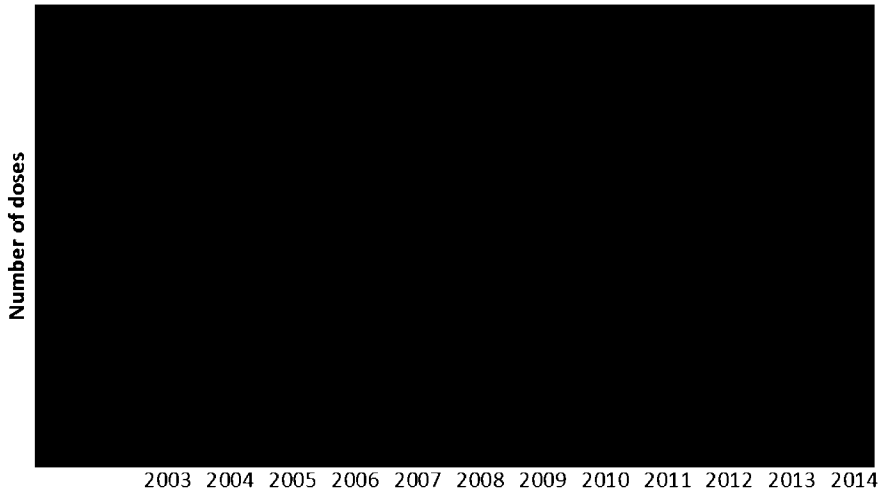


Figure 48 Proportion of ELS cases versus non-ELS cases reported for Boostrix over time in China

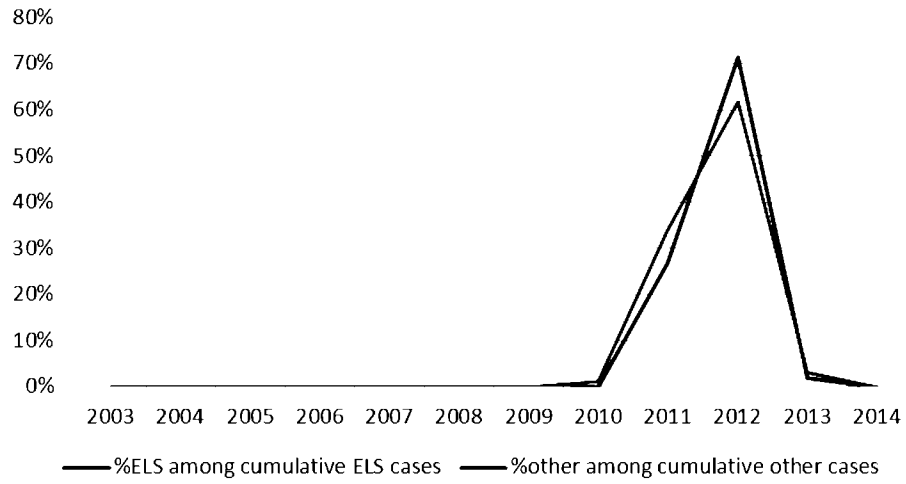
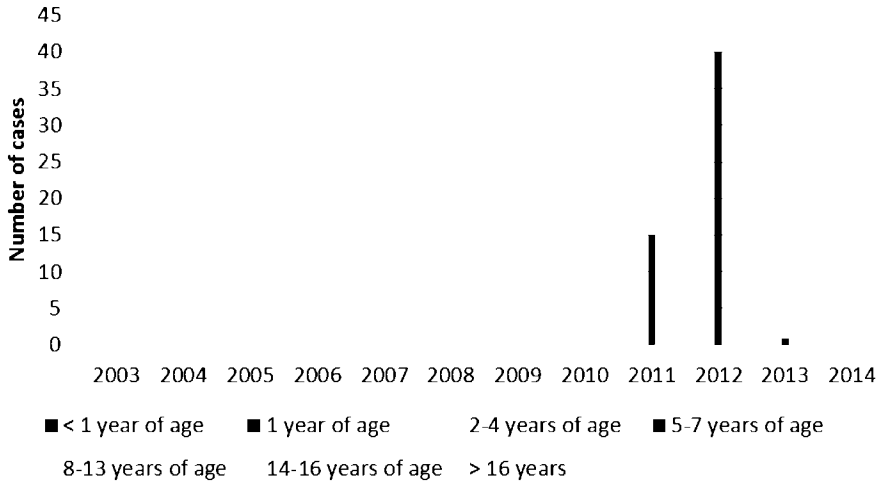


Figure 49 Age reported for Boostrix ELS cases from China



6. INTEGRATED EVALUATION OF POTENTIAL ROOT CAUSES

Limitations to quantitative analysis of spontaneous reports

Post-marketing surveillance for suspected adverse reactions is required to characterise the full safety profile of vaccines. Individual case safety reports are the primary source of information to detect potential risks in regular clinical practice. However such reports are anecdotal in nature and do not represent a random sample; they are not suitable as a basis for statistical inference, but statistical methods can provide real value in identifying outstanding reporting patterns for further investigation (signals) and in flagging reporting artefacts that may otherwise be misleading. Indeed invalid information may be generated because of several factors including: biased reporting, under-reporting, secular trends, media effects, missing or limited information, absence of case validation, absence of adequate comparator group.

Potential root causes of extensive limb swelling case reports associated with GSK DTPa vaccines

ELS is a known class effect of DTPa vaccines and is listed in the RSI of DTPa-containing vaccines (Section 1.2). It is also known that children primed with acellular pertussis vaccines are more likely to experience swelling reactions after booster administration in comparison with children primed with whole cell vaccines. The frequency of these local reaction increases with successive DTPa doses, but remains below the level seen after a fourth or fifth dose of a whole-cell pertussis vaccine (Halperin, 1995; Halperin, 1999; Pichichero, 1997).

Regarding new clinical trial data (Section 3.2), the observed frequency of ELS was in line with the GPIs of DTPa vaccines (no new clinical trial data is available for Tdap vaccines, i.e. Boostrix and Boostrix-IPV.

Increased ELS spontaneous reporting frequencies were observed for Infanrix, Infanrix-IPV, Infanrix-IPV/Hib, Infanrix hexa and Boostrix. Thirteen different countries were involved: Poland, Czech Republic, Sweden, the Netherlands, Belgium, Ireland, Italy, Slovakia, Slovenia, Poland, France, Germany and China. It must be noted that current country-specific reporting is such that an increased event reporting trend might not be detected in all countries.

In the spontaneous reporting setting, actual triggers of increased ELS reporting are difficult to identify. The following were the most likely root causes for increased ELS reporting rates observed in the above countries:

- Increased attention, specifically to ELS, by Polish authorities, also possibly triggered by pertussis outbreaks, and regardless of (increasing or decreasing) sales.
  - Infanrix in Poland (Section 5.5.1.1)
  - Infanrix-IPV/Hib in Poland (Section 5.5.3.2)
  - Infanrix hexa in Poland (Section 5.5.4.2)
- Increased vaccine use due to introduction of GSK vaccines in local national immunization programmes leading to an overall increase in local spontaneous reporting including, but not limited to, ELS
  - Infanrix-IPV in the Netherlands (Section 5.5.2.1)
  - Infanrix-IPV in Belgium (Section 5.5.2.2)
  - Infanrix-IPV in Ireland (Section 5.5.2.3)
  - Infanrix-IPV in Italy (Section 5.5.2.4)
  - Infanrix-IPV/Hib in Slovenia (Section 5.5.3.1)
  - Infanrix hexa in France (Section 5.5.4.3)
  - Infanrix hexa in the Netherlands (Section 5.5.4.4)
  - Boostrix in Slovenia (Section 5.5.5.1)
  - Boostrix in Germany (Section 5.5.5.2)
  - Boostrix in China (Section 5.5.5.3)
- National/regulatory initiatives to increase local spontaneous reporting, specifically of ELS or not
  - Infanrix in Czech Republic (see Section 5.5.1.2)
  - Infanrix-IPV in Ireland (Section 5.5.2.3)
  - Infanrix-IPV in Italy (Section 5.5.2.4)
  - Infanrix-IPV/Hib in Slovenia (Section 5.5.3.1)
  - Infanrix hexa in Italy (Section 5.5.4.1)
- Pre-school boosting following switch from DTPw priming to DTPa priming
  - Infanrix-IPV in Belgium (Section 5.5.2.2)
  - Infanrix-IPV in Slovakia (Section 5.5.2.5)

- Pertussis vaccination catch-up programmes
  - Infanrix in Sweden (Section 5.5.1.3)
- Local studies and communications related to ELS
  - Infanrix-IPV in the Netherlands (Section 5.5.2.1)
  - Infanrix-IPV in Belgium (Section 5.5.2.2)

Different aspects of cellular and humoral immune response have been explored (T helper type response [Th1 vs Th2 reaction], vaccine formulation) to explain the increased onset of ELS observed at the preschool booster dose, seen less frequent at the age of adoscelent booster (Rowe, 2005; Langley, 2007; Rieber, 2008; Scheifele, 2009; Kataoka, 2009; Rieber, 2011; Sharma, 2012). Although the etiology of local reactions following immunization is not fully understood, evidence suggests that both antigen content and pre-vaccination immunity may play a role (Rennels, 2000; Rennels, 2003). Several DTPa vaccine components (i.e. diphtheria toxoid, tetanus toxoid, aluminium adjuvant, acellular pertussis) have already been shown to be associated with increased reactogenicity (Greco, 1996; Gold, 2003; CDC, 2000; Scheifele, 2001; Blennow, 1994; Scheifele, 2005; Rennels, 2002). The number of consecutive doses of the same aP combination vaccines may also influence the occurrence of local reactions after immunization, which suggests an immunologic mechanism or dose-dependent cumulative toxicity (Halperin, 1999; Rennels, 2003; Scheifele, 2001; Halperin, 2003; Halperin, 1995). It has been proposed to apply the booster injection in the thigh instead of the arm to reduce the likelihood of ELS reactions (Jackson, 2008; Jackson, 2011). Prophylaxis with anti-inflammatory or antihistaminic treatment before vaccination has not led to observed decrease in the onset of ELS (Jackson, 2006). It can be concluded that the aetiology of local reactions after booster vaccinations is complex, controversial and probably multifactorial.

7. CONCLUSION

In view of the above, including the limitations of this evaluation which was essentially based on spontaneous post-marketing data (see Section 5.2), GSK considers that the identified ELS safety signal does not indicate a safety concern and hereby closes this signal. However the Company will continue to monitor cases of ELS.

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APPENDIX 7B.5 : Infanrix hexa Observed to Expected analysis of Sudden Death

In order to fulfill the requirements for the 1-year international PBRER and the 3-year EU PBRER, period-specific data in the present evaluation is provided for 2 different periods: from 23 October 2013 to 22 October 2014 (1 year period), and from 23 October 2011 to 22 October 2014 (3 year period).

1. CASES WITH A FATAL OUTCOME

During the period between 23 October 2011 and 22 October 2014, 61 cases with a fatal outcome (spontaneous and PMS case types) were received. 54% of these cases were male and age ranged between 29 days and 22 months. In line with overall spontaneous reporting, most were reported from Italy (31.1%), Germany (19.7%), France (9.8%) and the Netherlands (6.6%).

Thirty one (31) of these cases were suggestive of sudden deaths (SDs), of which 12 were reported without information on whether an autopsy was performed, or reported that no autopsy was performed ([redacted]). These cases were categorized as sudden unexpected death (SUD) in infancy. Sudden infant death syndrome (SIDS) was assessed in the 19 other cases where autopsy confirmed the absence of an underlying cause [redacted].

Death occurred in a context of underlying condition(s) in the 30 other fatal cases as detailed in Table 1.

Table 1 Fatal cases with known causes of death

Case ID	Cause of death	Case ID	Cause of death
[redacted]	Sepsis, meningococcal bacteraemia	[redacted]	Cardiomyopathy, cardiopulmonary failure, pneumonia
[redacted]	Congenital cardiovascular tumor	[redacted]	Congestive cardiomyopathy, cardiac failure
[redacted]	Meningococcal sepsis	[redacted]	Subdural hematoma, child maltreatment syndrome
[redacted]	Fibroelastosis	[redacted]	Encephalitis
[redacted]	Thrombocytopenia	[redacted]	Hemorrhagic enterocolitis
[redacted]	Encephalitis	[redacted]	Kawasaki's disease complicated with giant coronary aneurysm with cardiac ischemia and infarction
[redacted]	Pneumonia	[redacted]	Epstein-Barr virus infection, haematophagic histiocytosis
[redacted]	Choking, syndromal disorder congenital	[redacted]	Pertussis in a subject with an incomplete vaccination schedule
[redacted]	Diarrhea, congenital cardiovascular abnormality	[redacted]	Necrotising enterocolitis neonatal
[redacted]	Pneumonia, H1N1	[redacted]	Shaken baby syndrome
[redacted]	Cerebral edema, pneumococcal sepsis	[redacted]	Congenital heart disease
[redacted]	Early motor progressive encephalopathy	[redacted]	Encephalopathy, sepsis, respiratory insufficiency
[redacted]	Fatal intracranial syndrome, coagulation	[redacted]	Fulminant hepatic failure, adenovirus

	syndrome		
[redacted]	Congenital spinal muscular atrophy	[redacted]	Hereditary cardiomyopathy
[redacted]	Acute lymphocytic leukemia		Intussusception, dehydration

From the review of all fatal cases received between 23 October 2011 and 22 October 2014 there is no indication of any consistent clinical pattern or specific risk associated with *Infanrix hexa* immunisation. In half of the cases an underlying condition or concurrent disease was the most plausible cause of death. The company continues close monitoring of cases with a fatal outcome.

As shown in Table 2, 118 cases suggestive of SD (51 SUD and 67 SIDS) have been received since launch, corresponding to a cumulative reporting frequency of 0.10 (95% CI: 0.08-0.12) per 100 000 doses distributed. This cumulative reporting frequency is not significantly different from the one presented in PSUR 16 (period between 23 October 2010 and 22 October 2011).

During the period between 23 October 2013 and 22 October 2014, the SD reporting frequency was 0.11 (95% CI: 0.07-0.18) per 100 000 doses distributed, which is approximately the double compared to the two previous one year periods: 0.05 (95% CI 0.02-0.09) between 23 October 2012 and 22 October 2013 and 0.04 (95% CI 0.01-0.09) between 23 October 2011 and 22 October 2012. This increase was due to the receipt of 12 SIDS in one literature article [Matturri, 2014].

Table 2 Reporting rate of SUD and SIDS since launch per PSUR period

PSUR #	Period	Time period	Number of doses sold*	Number of SUD**	Number of SIDS**	Number of SDs** (SUD+SIDS)	Reporting frequency of SD per 100000 doses distributed	Poisson Exact 95% CIs	
19***	23oct13-22oct14	1Y	16068297	5	13	18	0.11	0.07	0.18
18***	23oct12-22oct13	1Y	17207841	4	4	8	0.05	0.02	0.09
17***	23oct11-22oct12	1Y	13617681	3	2	5	0.04	0.01	0.09
16	23oct10-22oct11	1Y	13389471	5	5	10	0.07	0.04	0.14
15	23oct09-22oct10	1Y	11929763	7	5	12	0.10	0.05	0.18
14	23oct08-22oct09	1Y	11508809	7	6	13	0.11	0.06	0.19
13	23oct07-22oct08	1Y	10000673	6	5	11	0.11	0.05	0.20
12	23oct06-22oct07	1Y	7825396	3	5	8	0.10	0.04	0.20
11	23oct05-22oct06	1Y	6820528	6	4	10	0.15	0.07	0.27
10	23apr05-22oct05	6M	2027744	1	2	3	0.15	0.03	0.43
9	23oct00-22apr05	4.5Y	9193457	4	16	20	0.22	0.13	0.34
8	23apr04-22oct04	6M	1454777	0	1	1	0.07	0.00	0.38
7	23oct03-22apr04	6M	1202341	1	4	5	0.42	0.13	0.97
6	23apr03-22oct03	6M	1241571	1	3	4	0.32	0.09	0.82
5	23oct02-22apr03	6M	1041975	0	1	1	0.10	0.00	0.53
4	23apr02-22oct02	6M	973380	0	0	0	0.00	0.00	0.31
3	23oct01-22apr02	6M	833168	0	2	2	0.24	0.03	0.87
2	23apr01-22oct01	6M	578375	0	1	1	0.17	0.01	0.96
1	23oct00-22apr01	6M	429965	0	0	0	0.00	0.00	0.70

* Assuming that the time lag between actual distribution to a country and recording in the database is one month on average, and since the data lock point of *Infanrix hexa* PSURs/PBRERs is on 22 October, it was decided as of PSUR 17 to provide the number of doses distributed between, and including, October and September (12 month periods). This allows the sales data to be less subject of change at the time it is extracted from the sales database, i.e. in November for *Infanrix hexa* PSURs/PBRERs.
** This cumulative number of SUD/SIDS includes cases excluded from the observed-to-expected analysis (see exclusion criteria of the observed-to-expected analysis in Section 2.2 Methods).
***PBRER period 23oct11-22oct2014

2. OBSERVED TO EXPECTED EVALUATION FOR CASES OF SUDDEN DEATH

2.1. Introduction

In the assessment report (dated 3 March 2010) of PSUR 14, EMA request that "*The MAH should try to collect relevant and recent data of background incidence rates of sudden death in other European countries. An observed/expected analysis of sudden death should be performed in the next PSUR as well.*"

A cumulative review of Sudden Death (SD) since launch has been performed. Follow-up information received for older cases was taken into account. Design of the below observed to expected analysis was revisited in view of comments EMA expressed in the assessment report of PSUR 15-16 (dated 26 April 2012).

This is an update of the observed to expected analysis of SD presented in the previous PSUR (No 18); new data on Infanrix hexa dose distribution, SD cases and available SD incidence rates were taken into account. The method for estimating the distribution of the age at vaccination was based on age at onset of the first event in a case. The proportion of SDs in the second year of life among SDs between the second and fifth year of life was estimated using a published proportion assessed in a European study [McGarvey, 2012].

2.2. Methods

Literature search
In order to collect relevant and recent data, a literature review of sudden infant death was performed. The German [GBE, 2014], French [INSERM, 2014] and Dutch national statistics websites [CBS, 2014] were also consulted on line in November 2014.

Observed to Expected Analysis
Two types of SD were considered: Sudden Infant Death Syndrome (SIDS) defined as deaths occurring in the first year of life which remain unexplained after autopsy, and Sudden Unexpected Death (SUD) defined as death occurring in the two first years of life which remain unexplained after clinical and final event history but without autopsy (Jorch, 2007). Cumulatively, 118 fatal cases received following *Infanrix hexa* vaccination were considered to be SD. Among these, 12 were excluded for the following reasons:

- age at vaccination not reported [redacted])
- time-to-death not reported ([redacted], [redacted], [redacted], [redacted], [redacted])
- time-to-death greater than 19 days ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted]).

The risk period considered was 20 days, thus the maximum time-to-death considered for inclusion was 19 days: Day 0 to Day 19. This threshold was defined based on the actual time-to-death in SD cases. In the 6 cases excluded from the analysis because of this threshold, the time-to-death varied between 27 days and 7 months. Including these cases would increase the risk period considered for the observed cases as well as for the

expected cases. As will be shown later, with a risk period of 20 days, the expected number of cases within the 20-day risk period is already more than 169-fold greater in the first year of life than the cumulatively observed number of cases. Thus increasing the risk period beyond 20 days would only further increase this expected number of cases, while increasing the number of observed cases by only 6 cases.

Because of the decreasing trend over calendar time in the incidence rate of SIDS, mainly due to the "back to sleep" campaign, the incidence rates were selected from sources providing incidence rates by year for European countries (74.1% of doses were distributed to European countries). A weighted average by calendar time of the German, French and Dutch (representing 47.2% of European doses) incidence rates of SDs (ICD-10 codes R95-99, i.e. SIDS *and* SUD) in the first year of life was calculated to estimate the global expected incidence. The weights were based on the geographical and yearly distribution of doses in these three countries (Table 3). A similar weighted average of the incidences of SDs (ICD-10 codes R96-99, i.e. SUD) in the second year of life was calculated to estimate the global expected incidence (Table 4).

Table 3 Background incidence rates (per 1000 live births) of SDs (SIDS & SUD) in the first year of life by calendar year for Germany, Netherlands, France and weighted average for these three countries

	Germany		The Netherlands		France		
Year	Yearly proportion of doses	Yearly incidence rate [GBE, 2014]	Yearly proportion of doses	Yearly incidence rate [CBS, 2014]	Yearly proportion of doses	Yearly incidence rate [INSERM, 2014]	
2014*	4.8%	0.308**	16.1%	0.120**	14.5%	0.508**	
2013	7.2%	0.308**	21.3%	0.120**	19.9%	0.508**	
2012	8.8%	0.308	21.3%	0.120	17.4%	0.508**	
2011	8.6%	0.359	17.1%	0.133	15.4%	0.508	
2010	9.8%	0.374	6.2%	0.136	15.3%	0.565	
2009	8.5%	0.414	4.7%	0.119	9.1%	0.522	
2008	9.2%	0.453	5.3%	0.135	6.7%	0.477	
2007	9.2%	0.446	5.2%	0.116	0.6%	0.431	
2006	9.2%	0.464	2.8%	0.113	0.5%	0.500	
2005	6.1%	0.582	0.0%	0.181	0.3%	0.473	
2004	4.8%	0.597	0.0%	0.180	0.1%	0.519	
2003	5.0%	0.644	0.0%	0.260	0.1%	0.556	
2002	4.7%	0.577	0.0%	0.257	0.0%	0.540	
2001	3.6%	0.719	0.0%	0.306	0.0%	0.639	
2000	0.9%	0.771	0.0%	0.266	0.0%	0.622	
Country average weighted by yearly proportion of doses		**0.447**		**0.124**		**0.516**	**0.441**
Proportion of doses by country		**61.8%**		**8.1%**		**30.1%**	

Average weighted by country and by yearly proportion of doses

* For 2014 sales data up to and including September 2014 were taken into account

** For 2012, 2013 and 2014, when no yearly incidence rate was available, the last background incidence rate was used

Table 4 Background incidence rates (per 1000 live births) of SDs (SUD only) in the second year of life by calendar year for Germany, Netherlands, France and weighted average for these three countries

Year	Germany		The Netherlands		France		
	Yearly proportion of doses	Yearly incidence rate [GBE, 2014]	Yearly proportion of doses	Yearly incidence rate [CBS, 2014]	Yearly proportion of doses	Yearly incidence rate [INSERM, 2014]	
2014*	4.8%	0.0066**	16.1%	0.0067**	14.5%	0.0131**	Average weighted by country and by yearly proportion of doses
2013	7.2%	0.0066**	21.3%	0.0067**	19.9%	0.0131**	
2012	8.8%	0.0066	21.3%	0.0067	17.4%	0.0131**	
2011	8.6%	0.0074	17.1%	0.0112	15.4%	0.0131	
2010	9.8%	0.0115	6.2%	0.0145	15.3%	0.0123	
2009	8.5%	0.0098	4.7%	0.0144	9.1%	0.0123	
2008	9.2%	0.0123	5.3%	0.0121	6.7%	0.0115	
2007	9.2%	0.0115	5.2%	0.0128	0.6%	0.0123	
2006	9.2%	0.0123	2.8%	0.0178	0.5%	0.0115	
2005	6.1%	0.0139	0.0%	0.0144	0.3%	0.0156	
2004	4.8%	0.0131	0.0%	0.0131	0.1%	0.0139	
2003	5.0%	0.0098	0.0%	0.0121	0.1%	0.0172	
2002	4.7%	0.0115	0.0%	0.0264	0.0%	0.0205	
2001	3.6%	0.0148	0.0%	0.0246	0.0%	0.0123	
2000	0.9%	0.0172	0.0%	0.0231	0.0%	0.0156	
Country average weighted by yearly proportion of doses		**0.0101**		**0.0081**		**0.0109**	**0.0102**
Proportion of doses by country		**61.8%**		**8.1%**		**30.1%**	

* For 2014 sales data up to and including September 2014 were taken into account

** For 2012, 2013 and 2014, when no yearly incidence rate was available, the last background incidence rate was used

Given that the actual number of doses administered is not directly available to the Company, the number of vaccine doses distributed worldwide was used for the purpose of this analysis. The total number of vaccine doses distributed worldwide since launch until September 2014 was 119 595 685. In the main analysis, the unit used is the number of *doses*, not the number of *subjects* since each dose/vaccination contributes to a fixed time at risk. Indeed, since the risk period for SD of 20 days is smaller than the lag between two consecutive doses (i.e. at least one month), each dose can be considered as contributing independently to the total risk period for a given individual. It was assumed that the risk is identical at each dose and does not increase with each additional dose. As sensitivity analysis, an observed to expected analysis of SDs after vaccination with a 1st dose of *Infanrix hexa* was performed.

Since the distribution of the age at which subjects are vaccinated is not directly available, it was assumed that the frequency distribution of the age at onset of the first event in spontaneous cases reported to the MAH is representative of the actual age distribution at vaccination. The age distribution from all (i.e. SD and non-fatal) spontaneous cases in the safety database with known age at event onset for *Infanrix hexa* by 22 October 2014 was used to approximate the age distribution: 73.2% of *Infanrix hexa* doses were administered

in the first year of life, while 20.2% of doses were administered in the second year of life (6.6% of doses were not taken into account because the age at vaccination was equal or greater than 2 years). According to the distribution of the age at event onset, the number of doses distributed to subjects in their first and second years of life was estimated to be 87 592 164 and 24 123 257, respectively.

Germany, France and the Netherlands represent 35% of *Infanrix hexa* doses distributed, while the other doses where distributed in countries where no yearly SD incidence rates are available. Also, 67% of SDs were reported from Germany, France and the Netherlands. Therefore it was assumed that the weighted average of the incidences of SD observed in those countries is representative for the entire population of *Infanrix hexa* recipients. The incidence rate in the 1st year of life was estimated at 0.441/1,000 live births (Table 3); and the one in the second year of life at 0.0102/1,000 live births (Table 4).

The rate for the first year of life is in line with the rates in Table 5 which displays the background incidence rate of SD (SIDS and/or SUD depending on the publication) in Europe from available publications. Incidence rates of SUD in the second year of life were not available as such and were therefore estimated based on SUD incidences available for subjects 1 to 4 years old multiplied by 0.82. Indeed McGarvey [2012] reported that, in Ireland, among SUDs occurring in subjects aged 1-4 years, 82% occur in the second year of life (1 year old children).

To estimate the expected numbers, the incidence rate of SD was considered homogenous within the 1st and within the 2nd years of life; therefore the expected number over any day was linearly extrapolated (i.e. 1/365.2425) from the prevalence per birth cohort. The number of cases expected to occur within a predetermined risk period following vaccination (Ne) for children under 1 year of age and those between 1 and 2 years of age is derived from the following formula:

$Ne = Inc \times Nbc \times Risk\ Period \times \alpha$
where
Inc = the incidence of the disease in the first (< 1 year old) or second year of life ($1 \leq$ age <2)
Nbc = the number of doses of vaccine sold since launch (assumption: proportion of adverse events by age is representative for the actual age distribution at vaccination).
Risk Period = adjustment from a predetermined risk period (Days/365.2425)

α = healthy vaccinee correction factor (taken here to be 0.8 based on various case-control studies of SIDS or SUID [Fine, 1992]).

Table 5 Incidence rate of SD (<1 year of age) per 1,000 live births

Country/Population	Proportion of doses distributed	Time period	Incidence Rate (/1 000 live birth)	Source
Data from the European Concerted Action on SIDS. Case-control studies of SIDS done in 20 regions in Europe.	74.1%	1992-1996	European range: 0.17 – 1.3 (median: 0.6)	Carpenter, 2004
Ireland. SIDS rate (National Sudden Infant Death Register)	1.2%	1993-1997	0.80	Mehanni, 2000
Austria. SIDS rate (Autopsy records in the Tyrol)	2.0%	1994-1998	0.4	Kiechl-Kohlendorfer, 2001
Italy. (Mortality registry of the 15 health districts in the Lombardy region) SIDS rate 'Possible SIDS' rate	14.9%	1990-2000	 0.13 0.54*	Montomoli, 2004
Sweden. SIDS rate (Medical Birth Registry of Sweden)	1.0%	1999	0.30	Alm, 2001
Sweden. SIDS rate (Literature review of Scandinavian studies)		2004	0.2-0.3	Wennergren, 2004
Sweden. SIDS rate (Medical Birth Register of Sweden)		1997-2005	0.23	Möllborg, 2010
France. National statistics from CepiDc-Inserm SIDS (ICD-10 code R95) SUD + SIDS (ICD-10 code R95-R99)	10.5%	 2010 2010	 0.28 0.58	INSERM, 2014
Germany. Data extracted from the Federal Health Monitoring of Germany SIDS (ICD-10 code R95) SUD + SIDS (ICD-10 code R95-R99)	21.6%	 2011 2011	 0.22 0.36	GBE, 2014
Netherlands. (Dutch Central Bureau of Statistics) SIDS (ICD-10 code R95) SUD + SIDS (ICD-10 code R95-R99).	2.8%	 2012 2012	 0.07 0.12	CBS, 2014
Ireland. SIDS rate (Irish National Sudden Infant Death Register)	1.2%	2005	0.38	Hauck, 2008
Ireland. (Irish National Sudden Infant Death Register) SIDS rate SUD rate (without SIDS)		1994-2008	0.59 0.14	McGarvey, 2012
Denmark. SIDS rate (Danish Cause of Death registry)	0.1%	2000-2006	0.22	Winkel, 2011

* deaths classified with ICD-9 codes that might reasonably include SIDS: ventricular fibrillation and flutter (427.4), cardiac arrest (427.5), heart failure unspecified (428.9), unspecified circulatory system disorder (459.9), pneumonia due to inhalation of food or vomit (507.0), pneumonia due to solids and liquids– other (507.8), other pulmonary insufficiency (518.8), respiratory arrest (770.8), intraventricular haemorrhage (772.1), other and ill-defined conditions originating in the perinatal period–other specified (779.8), other and ill-defined conditions originating in the perinatal period-unspecified (779.9), vomiting (787.0), respiratory failure (799.1), other unknown and unspecified causes (799.9)

2.3. Results

- **Observed/Expected Analysis of SDs in the <u>first year of life</u>**

The results of this analysis are presented in Table 6 which shows the number of SDs that could be expected to occur by chance within a range of days post vaccination.

Table 6 Cumulative number of observed and expected cases of SD (SIDS & SUD) following *Infanrix hexa* for children in their first year of life

Time since vaccination	Observed	Cumulative Observed (Poisson 95% CI)		Background incidence rate	Doses	Cumulative expected SIDS + SUD
0 day	16	16	(9.15, 25.98)	0.441	87592164	84.66
1 day	18	34	(23.55, 47.51)	0.441	87592164	169.33
2 days	19	53	(39.70, 69.33)	0.441	87592164	253.99
3 days	13	66	(51.04, 83.97)	0.441	87592164	338.66
4 days	8	74	(58.11, 92.90)	0.441	87592164	423.32
5 days	8	82	(65.22, 101.78)	0.441	87592164	507.99
6 days	1	83	(66.11, 102.89)	0.441	87592164	592.65
7 days	4	87	(69.68, 107.31)	0.441	87592164	677.32
8 days	2	89	(71.47, 109.52)	0.441	87592164	761.98
9 days	2	91	(73.27, 111.73)	0.441	87592164	846.65
10 days	0	91	(73.27, 111.73)	0.441	87592164	931.31
11 days	3	94	(75.96, 115.03)	0.441	87592164	1015.97
12 days	0	94	(75.96, 115.03)	0.441	87592164	1100.64
13 days	2	96	(77.76, 117.23)	0.441	87592164	1185.30
14 days	0	96	(77.76, 117.23)	0.441	87592164	1269.97
15 days	2	98	(79.56, 119.43)	0.441	87592164	1354.63
16 days	1	99	(80.46, 120.53)	0.441	87592164	1439.30
17 days	0	99	(80.46, 120.53)	0.441	87592164	1523.96
18 days	1	100	(81.36, 121.63)	0.441	87592164	1608.63
19 days	1	101	(82.27, 122.72)	0.441	87592164	1693.29

This analysis shows that the number of SD cases reported after vaccination with *Infanrix hexa* is significantly below the number of cases expected in children when vaccinated in their 1st year of life for any risk period between 0 and 19 days post vaccination.

Traversa [2011] showed an increased risk following vaccination with hexavalent vaccines after the first dose. As the observed number of SD is higher after the first dose than after any other consecutive dose (44.3% of the observed cases were reported after dose 1, 22.6% after dose 2, 13.2% after dose 3, 2.8% after dose 4; dose number was not reported for the remaining 17.0% of cases), the observed and expected number of SD after Dose 1 was provided in Table 7. As the actual proportion of patients administered 1, 2, 3 and 4 doses is unknown, two exposure assumptions were assessed: between one quarter and one half of doses distributed were assumed as being Dose 1.

Table 7 Cumulative number of observed and expected cases of SD following Dose 1 of *Infanrix hexa*

Time since vacci-nation	Observed	Cumulative Observed Poisson 95% CI			Cumulative expected SIDS + SUD assuming 50% of the total doses distributed are Dose 1	Cumulative expected SIDS + SUD assuming 25% of the total doses distributed are Dose 1
0 day	9	9	(4.12,	17.08)	57.80	28.90
1 day	8	17	(9.90,	27.22)	115.60	57.80
2 days	8	25	(16.18,	36.90)	173.40	86.70
3 days	7	32	(21.89,	45.17)	231.20	115.60
4 days	4	36	(25.21,	49.84)	289.00	144.50
5 days	6	42	(30.27,	56.77)	346.80	173.40
6 days	1	43	(31.12,	57.92)	404.59	202.30
7 days	2	45	(32.82,	60.21)	462.39	231.20
8 days	1	46	(33.68,	61.36)	520.19	260.10
9 days	0	46	(33.68,	61.36)	577.99	289.00
10 days	0	46	(33.68,	61.36)	635.79	317.90
11 days	0	46	(33.68,	61.36)	693.59	346.80
12 days	0	46	(33.68,	61.36)	751.39	375.69
13 days	0	46	(33.68,	61.36)	809.19	404.59
14 days	0	46	(33.68,	61.36)	866.99	433.49
15 days	0	46	(33.68,	61.36)	924.79	462.39
16 days	0	46	(33.68,	61.36)	982.59	491.29
17 days	0	46	(33.68,	61.36)	1040.39	520.19
18 days	1	47	(34.53,	62.50)	1098.19	549.09
19 days	0	47	(34.53,	62.50)	1155.98	577.99

This analysis shows that the number of SD cases reported after vaccination with a first dose of *Infanrix hexa* was significantly below the number of cases expected in children when vaccinated in their 1st year of life for any risk period between 0 and 19 days post vaccination. And that, as long as the number of first doses is between half and one fourth of the total number of doses distributed which is a realistic and sensitive range.

An observed to expected analysis of SDs by dose is likely to highlight some violation in the assumption of uniform incidence rate of SD over the entire first year of life. The actual shape of the incidence rate of SD being unknown makes the observed to expected analysis by dose very hard to interpret. Indeed, the different doses are characterized by different time periods in the life of the vaccinated subjects and these time periods may have different incidence rates of SD than the averaged one computed over the first year of life.

- **Observed/Expected Analysis of SDs in the second year of life**

Given the attention that has been given to the occurrence of SDs in children in the second year of life within 14 days of the administration of hexavalent vaccines [von Kries, 2005], the Company evaluated whether the number of SDs reported in this age group exceeded the number one could expect to occur by coincidence, i.e. from the background incidence of SDs.

The results of this analysis are presented in Table 8 which shows the number of SDs that could be expected to occur by chance within a range of 19 days post vaccination.

Table 8 Cumulative number of observed and expected cases of SD (SUD only) following *Infanrix hexa* for children in their second year of life

Time since vaccination	Observed	Cumulative Observed Poisson 95% CI			Background incidence rate	Doses	Cumulative expected SUD
0 day	0	0	0.00	3.00	0.0102	24123257	0.54
1 day	2	2	0.24	7.22	0.0102	24123257	1.08
2 days	1	3	0.62	8.77	0.0102	24123257	1.62
3 days	0	3	0.62	8.77	0.0102	24123257	2.16
4 days	0	3	0.62	8.77	0.0102	24123257	2.70
5 days	0	3	0.62	8.77	0.0102	24123257	3.24
6 days	0	3	0.62	8.77	0.0102	24123257	3.77
7 days	0	3	0.62	8.77	0.0102	24123257	4.31
8 days	1	4	1.09	10.24	0.0102	24123257	4.85
9 days	0	4	1.09	10.24	0.0102	24123257	5.39
10 days	0	4	1.09	10.24	0.0102	24123257	5.93
11 days	0	4	1.09	10.24	0.0102	24123257	6.47
12 days	0	4	1.09	10.24	0.0102	24123257	7.01
13 days	1	5	1.62	11.67	0.0102	24123257	7.55
14 days	0	5	1.62	11.67	0.0102	24123257	8.09
15 days	0	5	1.62	11.67	0.0102	24123257	8.63
16 days	0	5	1.62	11.67	0.0102	24123257	9.17
17 days	0	5	1.62	11.67	0.0102	24123257	9.71
18 days	0	5	1.62	11.67	0.0102	24123257	10.24
19 days	0	5	1.62	11.67	0.0102	24123257	10.78

For the second year of life, the observed number of SDs (point estimate) was higher than expected within a risk period of 1 to 4 days post vaccination, though not significantly.

2.4. Discussion and conclusion

The yearly reporting frequencies of SDs during the period between 23 Ocober 2011 and 22 October 2014 were not significantly different (Table 2).

Cumulatively, in the first year of life, the number of SD cases reported after vaccination with Infanrix hexa was significantly below the number of cases expected in children for any risk period between 0 and 19 days post vaccination. This was true when the analysis was done regardless of dose number (Table 6), as well as when specifically performed for Dose 1 (Table 7).

For the second year of life, the observed number of SDs was higher than expected within a risk period of 1 to 4 days post vaccination, though not significantly (Table 8). A cumulative total of 5 SDs were reported for the second year of life during the past 14 years, covering more than 24 million doses. Given that only one dose of Infanrix hexa is usually recommended per subject in the second year of life, it can be assumed that these 5 SDs covers more than 24 million subjects. The reporting frequency for the second year of life is 2 SDs per 10.000.000 doses and per 10.000.000 subjects. These SDs are likely to result from random occurrences and are therefore not considered a safety signal.

In the analyses of both the first and second years of life, most SDs were reported temporally related to vaccination. This is the result of a well-known spontaneous

reporting bias (not restricted to SDs) according to which reporting of cases does not occur independently of the time from vaccination to event. On the contrary, available data show that potential reporters are much more likely to think about a potential causal association, and thus report an event, when the event occurs shortly after vaccination than when it occurs weeks later [GVP, 2013].

Assumptions

- Country repartition of doses between Germany, Netherlands and France was assumed constant over calendar time.
- The incidence rate of SDs is assumed to be constant over the time period considered (first and second year of life).

Limitations

There are several limitations for observed to expected analyses, and several levels of uncertainty. The major factors affecting observed to expected analyses are related to:

- Underreporting, reporting biases, and incomplete case details.
- Uncertainty on the number of subjects actually vaccinated.
- Uncertainty on the distribution of the age at which subjects are vaccinated.
- Lack of background incidence rate for other countries. Italy and Spain represent a large proportion of the sales (14.9% of global Infanrix hexa doses where distributed in Italy and 5.9% in Spain) but no recent age and year stratified data about background incidence rates of SDs were available.
- No age stratification within the two age groups.

In view of these assumptions and limitations, the company considers that the cumulative data received so far did not suggest that there is an increased risk of sudden death following administration of Infanrix hexa.

A reasonable number of studies have shown that immunization does not increase the risk of SD [Hoffman, 1987; Griffin, 1988; Mitchell, 1995; Fleming, 2001; Jonville-Bera, 2001]. It is known that SIDS is the most common cause of death in infants between two weeks and one year of age [Merck Manual]. More recently, a study assessed the risk of SIDS following hexavalent vaccination in Italy on the basis of in-depth examination of the autonomic nervous system; according to the author these results to not suggest a causal relationship between hexavalent vaccination and SIDS [Matturri, 2014]. According to Heininger [2004], pertussis vaccination might actually prevent SIDS as epidemiologic evidence from the United Kingdom, Sweden, and Norway indicated that SIDS is associated with *Bordetella pertussis* infection.

The Company monitors fatal cases and their reporting frequencies on an ongoing basis.

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APPENDIX 7B.6 : Kawasaki's disease

Vaccines' Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Infanrix hexa: Kawasaki's disease

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Date of review	July / August 2014
Vaccine terms included	Infanrix™ hexa
Adverse events (MedDRA*preferred terms) included	Kawasaki's disease

BACKGROUND OF THE REQUEST

The [redacted] Department of Pharmacovigilance has recently received a vaccination report about a case of Kawasaki syndrome in a 4 months old male baby, reported with a temporal connection to the administration of GSK vaccines Rotarix and Infanrix hexa. The case had an unfavourable outcome, the patient died on [redacted] after severe complications (major coronary artery aneurisms, occlusion of the ramus interventricularis anterior, cardiac underperfusion, and cardiac arrest) despite intensive hospital treatment. The last vaccination cycle (Rotarix, Prevenar, and Infanrix hexa) was performed on [redacted]

Following this case the Company received questions related to Kawasaki disease after vaccination with Rotarix and Infanrix hexa. In order to answer these questions two evaluations were performed by GSK, i.e. one for each GSK vaccine administered. This evaluation will cover Infanrix hexa. Note that for both evaluations the same case definition and methodology was used.

KAWASAKI DISEASE

Kawasaki disease was first described in 1967 by Tomisaku Kawasaki and has replaced acute rheumatic fever as the leading cause of acquired heart disease among children in developed countries [Taubert ,1999]. Kawasaki disease is an acute vasculitis of childhood that predominantly affects the coronary arteries. The etiology of Kawasaki disease remains unknown, although an infectious agent is strongly suspected based on clinical and epidemiologic features. A genetic predisposition is also likely, based on varying incidences among ethnic groups, with higher rates in Asians. Symptoms include fever, conjunctival injection, erythema of the lips and oral mucosa, rash, and cervical lymphadenopathy. Some children with Kawasaki disease develop coronary artery aneurysms or ectasia, ischemic heart disease, and sudden death. Children <5 years of age are primarily affected, and the disease is more common in males. Approximately 20% of untreated patients and 4% of treated patients develop coronary artery dilatation and aneurysm.

In the United States, the KD incidence in children aged <18 years was estimated to be 6.4 per 100,000 person-years in 1997 and 5.9 per 100,000 person-years in 2000. In children <5 years of age, the incidence was approximately 9 to 19 per 100,000 person-years during 1993–1996. The annual incidence of Kawasaki disease (KD) in children of Japanese descent is about 150 per 100,000 children younger than five years.

A review of the background incidence rate of KD was made. The background incidence rates of KD in the first 5 years of life are presented in ANNEX 1. This review shows that the incidence rate range varies between 1.6 to 218.6/100 000 person years worldwide. For Europe, the range varies from 1.6 to 15.2/100 000 person years.

The case definition for KD developed by the American Heart Association includes the presence of fever for at least 5 days (or until date of intravenous immunoglobulin administration if given before the 5th day) and four of the five criteria below, and the lack of another known disease process to explain the illness [Newburger, 2004]:

- Polymorphous rash
- Bilateral conjunctival injection
- Changes of the mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue
- Changes of the extremities: peripheral oedema, peripheral erythema, periungual desquamation
- Cervical adenopathy

Clinical features may not be present simultaneously, and taking a careful history is necessary in children who lack a clear explanation for fever. If the typical clinical findings are present in a child with fever for less than five days, the diagnosis still can be made by experienced physicians and treatment can be initiated. In addition, classic Kawasaki disease can be diagnosed with three clinical features if coronary artery abnormalities are observed on echocardiography. [Freeman, 2006]

The concept of 'incomplete' (atypical) KD should be used for patients with fever for at least five days, at least two of the clinical criteria for KD, no other reasonable explanation for the illness, and laboratory findings consistent with severe systemic inflammation [Newburger, 2004]. Incomplete Kawasaki disease is more common in children younger than one year, in whom the rate of coronary artery aneurysms is paradoxically higher if not treated; therefore, establishing the diagnosis and initiating treatment are essential.

KD can occur in a temporal relationship with vaccination, but a causal association has not been established [Hua,2009]. Seasonal variation in KD incidence has been reported. Outbreaks of KD have been linked to weather patterns, with clusters of KD cases occurring in association with precipitation. The cause of KD remains unknown, although a common infectious agent is suspected. Recently cytoplasmic inclusion antibodies were identified in the ciliated bronchial epithelium of children with fatal acute KD, leading the authors of that study to suggest viral infection as the cause of KD. However the hunt for any single infectious agent has so far not proved fruitful, a fact most recently highlighted by the negative results that emerged from studies examining the potential link between coronavirus infection and KD in Taiwan. The peak incidence in the toddler group with only rare cases in infants and adults suggests a role for transplacental antibodies conferring protection and development of protective immunity as a result of asymptomatic infection in most individuals. However not one single causative agent has been detected up to now. The hypothesis that bacterial toxins acting as superantigens

could trigger the cascade of events that lead to KD has been widely debated [Newburger, 2004]. Recent studies suggest a respiratory portal of entry of the suspected pathogen, although no infectious agent has been etiologically associated with the disease [Rowley, 2007].

RESPONSE TO QUESTIONS

1. QUESTION 1

What information (including publication) does your company have in respect to this adverse drug reaction (KD), namely data from preclinical, clinical and epidemiological studies as well as spontaneous reports?

Company response

1.1. Preclinical Data of Infanrix hexa

Kawasaki disease (KD) was not specifically studied in the nonclinical pharmacology/immunology testing programs of Infanrix hexa.

No symptoms resembling Kawasaki disease were observed in the mice injected with Infanrix hexa.

1.2. Epidemiological Studies data of Infanrix hexa:

No cases of Kawasaki disease from postmarketing surveillance studies or epidemiological studies were retrieved with Infanrix hexa.

1.3. Clinical data of Infanrix hexa – Kawasaki disease cases:

1.3.1. Case Definition and identification

To identify potential KD cases in clinical trials, the GSK global safety database was searched for the MedDRA Preferred Term "Kawasaki disease". The KD case definition of the American Heart Association [Newburger, 2004] was used for the review of the cases and included three categories: classic, incomplete and not confirmed. The database was searched since launch until July 2014.

Classic KD diagnosis include the presence of 5 or more days of fever, and 4 of the 5 principal clinical features: bilateral non-exudative conjunctivitis, changes of the lips and oral cavity, rash, changes of extremities, and cervical lymphadenopathy.

The concept of 'incomplete' (atypical) KD was used for patients with fever for at least five days, at least two of the clinical criteria for KD, no other reasonable explanation for

the illness, and laboratory findings consistent with severe systemic inflammation [Burns, 2004].

Not confirmed KD is used for cases that were reported as KD but lack clinical data to meet the case definition for classic or incomplete KD.

1.3.2. Analysis

Classic, incomplete and not confirmed cases were included in the analyses. Descriptive analysis was used to characterise age, gender, time from vaccination to adverse event onset, concomitant vaccine administration and possible confounding factors. A line listing including all reported KD cases in clinical trials is reported in ANNEX 2. Individual case descriptions including the case narrative and GSK company comments are in ANNEX 3.

Table 1 describes the clinical trials that reported Kawasaki disease after Infanrix hexa administration. Most of the cases are reported in clinical studies where Infanrix hexa and Synflorix (GSK's 10-valent pneumococcal conjugate vaccine) were coadministered (i.e. studies labelled as 10PN-PD-DIT).

Table 1 Clinical studies with Kawasaki Disease cases

Clinical Trials	Number of KD cases
10PN-PD-DIT-028	9
10PN-PD-Dit-048	2
10PN-PD-DIT-001	1
10PN-PD-DIT-011	1
10PN-PD-Dit-031	1
10PN-PD-DIT-066	1
DTPA-HBV-IPV-074	1
MenACWY-TT-083	1
UNDECA-PN-010	1
Grand Total	**18**

The majority of cases are reported in study 10PN-PD-DIT-028 although none of these cases occurred in close temporal relationship to study vaccination (TTO ranged from 35 days to 20 months).

1.3.3. Results

Since launch until July 2014, 18 clinical cases were reported as KD in clinical studies after Infanrix hexa administration. Upon medical review12 cases were categorized by GSK as classic cases, 6 as incomplete and 0 as not confirmed. None of these cases were found causally related by the investigator to the study vaccines including Infanrix hexa.

Three cases did have a temporal association (within the 30 days risk period) with the study vaccines. Details of these cases are described below.

1.3.3.1. Demographic Characteristics

Table 2 summarises the demographic characteristics of the 18 clinical KD cases received since launch until July 2014. Most of the Classic KD cases were reported in infants between 3 to 6 months of age and in infants more than 12 months of age. Five cases were reported from Europe, 4 from Asia, and 9 cases from Latin America (i.e. study 10PN-PD-DIT-028). Most of the cases were reported after receiving the 3rd Dose of the Infanrix hexa vaccine.

Table 2 KD Cases by Case Category and Demographic Characteristics, N = 18

Demographic Characteristics	KD Case Category		
	Classic N= 12	Incomplete N= 6	Not confirmed N= 0
Age group			
3 months	0	0	0
3 - 6 months	4	2	0
7 - 12 months	3	1	0
> 12 months	5	3	0
Unknown	0	0	0
Gender			
Male	8	4	0
Female	4	2	0
Unknown	0	0	0
Country			
Europe	3	2	0
Latin America	7	2	0
Asia	2	2	0

1.3.3.2. Concomitant vaccines and other confounding factors (ie. Concomitant infections)

Out of the 12 classic KD cases, 6 are reported with a concomitant infection (respiratory infection, sinusitis, candidiasis, urinary infection). Out of the 6 incomplete KD cases two are reported with concomitant infections (respiratory infection, urinary infection).

Out of the 18 cases, nine cases are reported with coadministration of Synflorix and Infanrix hexa, one case reports concomitant vaccination with Synflorix, Neisvac C and Infanrix hexa. There is also one case with concomitant vaccination of Synflorix, Infanrix hexa and Rotarix: [redacted] but the time to onset, being the same day, seems too

acute for a KD to be triggered by study vaccination although it has to be noted the event occurred after the second dose. This subject was however not reportedly treated with ASA or IVIG although these are the pillars of KD treatment.

1.3.3.3. Time to onset

During review of the cases the time to onset was defined as the onset of fever, as first symptom of KD, after vaccination. Of the 18 clinical KD cases, 3 cases had onset reported within 30 days of vaccination:

1. Case number [redacted] had a time to onset of 15 days, but even though there is temporal association to study vaccines there were signs of a concurrent respiratory infection which should be considered a plausible trigger for KD to develop. This case was classified as a Classic KD.
2. Case number [redacted] (described in the above section) had a time to onset the same day which is rather short time to onset to develop KD, although it was the second dose for the three study vaccines. This case was classified as Incomplete KD.
3. Case number [redacted] had a temporal association with vaccination as the time to onset is seven days. There was coadministration of Synflorix and Infanrix Hexa, and it was classified as a Classic KD.

None of the cases where reported by the investigator as causally related to Infanrix Hexa or the study vaccines.

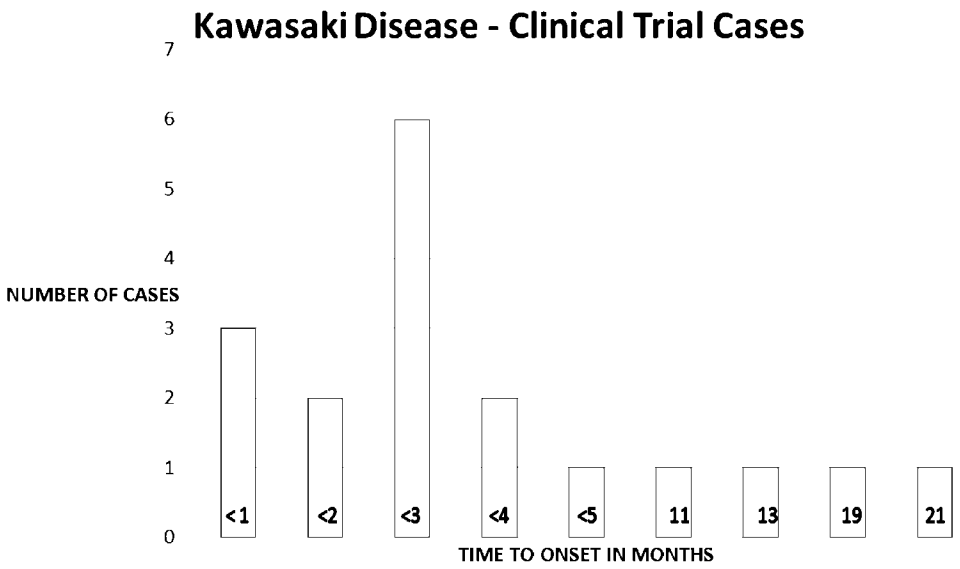
*More information on these cases is in ANNEX 3.

There are two cases where the time to onset was borderline:

1. Case [redacted] with time to onset 35 days after vaccination of Synflorix and Infanrix hexa, with a concomitant pneumonia reported and classified as a classic KD
2. Case [redacted] with time to onset of 32 days after coadministration of Synflorix and Infanrix hexa, classified as incomplete KD with only 2 clinical features of diagnosis of KD plus fever. None of these cases were assessed as causally related to the Infanrix hexa or the study vaccines.

The rest of the cases (13) did not have a temporal association to the study vaccines with a time to onset well beyond the 30 days risk period.

Figure 1 Time to onset of KD cases in clinical trials (n=18)



1.3.4. Cases from the Clinical Development Programme of Infanrix hexa

Only two cases were reported from clinical development program of Infanrix hexa coming from study number DTPA-HBV-IPV-074, one case among the Infanrix hexa arm, and one case among the control group arm. The case from the control group received Infanrix/IPV/HiB and Engerix B ([redacted]). The other case received Infanrix hexa ([redacted]). None of these two cases were reported by the investigator as causally related to the study vaccines. The first case did have a diagnosis as well of scarlet fever. The second case did not have enough symptoms suggesting Kawasaki disease, it was an Incomplete KD, and the time to onset was of 71 days after vaccination. Both cases have their symptoms resolved.

1.3.5. Overall Evaluation

Since launch until 1st of July 2014, 18 cases of KD were reported after administration of *Infanrix hexa*: 12 were categorized as classic cases, 6 as incomplete and 0 as not confirmed. In 15 of the 18 confirmed cases (classic and incomplete KD), confounding factors, including concomitant vaccines and/or concurrent infections were present. Among all the cases, only three cases had time to onset in the risk period (thirty days) and two cases had borderline time to onset (32 and 35 days). Among the three cases within the risk period of thirty days, one case had concomitant respiratory infection, two cases had coadministration with Synflorix and one case had coadministration with Synflorix and Rotarix. The descriptive narrative and Company comment of the cases in clinical

trials are in ANNEX 3. None of the cases were reported as causally related to study vaccines or Infanrix hexa.

1.3.6. Conclusion of cases in Clinical Trials

The cumulative review of clinical KD cases does not currently indicate a specific safety concern.

1.4. Spontaneous reports of Infanrix hexa – Kawasaki disease cases

1.4.1. Case Definition and identification

To identify potential KD cases in spontaneous reporting, the GSK global safety database was searched for the MedDRA Preferred Term "Kawasaki disease". The KD case definition of the American Heart Association [Newburger, 2004] was used for the review of the cases and included three categories: classic, incomplete and not confirmed. The database was searched since launch until July 2014.

Classic KD diagnosis include the presence of 5 or more days of fever, and 4 of the 5 principal clinical features: bilateral non-exudative conjunctivitis, changes of the lips and oral cavity, rash, changes of extremities, and cervical lymphadenopathy. (ANNEX 4)

The concept of 'incomplete' (atypical) KD was used for patients with fever for at least five days, at least two of the clinical criteria for KD, no other reasonable explanation for the illness, and laboratory findings consistent with severe systemic inflammation [Newburger, 2004].

Not confirmed KD is used for cases that were reported as KD but lack clinical data to meet the case definition for classic or incomplete KD.

1.4.2. Analysis

Classic, incomplete and not confirmed were included in the analyses. Descriptive analysis was used to characterise age, gender, time from vaccination to adverse event onset, concomitant vaccine administration and possible confounding factors. Individual summary of the cases are described in ANNEX 5. Individual analysis with the case narrative and GSK company comment of Kawasaki cases in spontaneous reporting is described in ANNEX 6.

1.4.3. Results

Since launch until 15 July 2014, 37 spontaneous cases were reported as KD: 10 were categorized as classic cases, 12 as incomplete or atypical cases and 15 as not confirmed. Details of these cases are described in ANNEX 5 that summarizes all the cases found.

1.4.3.1. Demographic Characteristics

Table 3 summarises the demographic characteristics of the 37 clinical KD cases received since launch until July 2014. Most of the Classic KD cases were reported in infants between 3 to 6 months of age. Among the classic cases five were female, 4 cases were male and one case gender unknown. Eight cases were reported from Europe and 2 from Asia. The European countries with most of the cases reported are: Italy and Germany. Out of the ten cases of Classic Kawasaki disease there are three coming from Italy, four coming from Germany, two from Singapore and one from Belgium.

Among the 12 Incomplete Kawasaki cases, 9 cases are reported in children less than six months. Eight cases are in male children and four in female children. All cases except one, come from Europe, mainly from Germany (6 cases) and Italy (4 cases).

Among the Not Confirmed cases most of the cases are also among children less than six months (11 cases), mainly males (nine cases). Most of these cases come from Germany (six cases) and Italy (four cases).

Table 3 KD Spontaneous Cases by Case Category and Demographic Characteristics, N = 37

Demographic Characteristics	KD Case Category		
	Classic N= 10	Incomplete N=12	Not confirmed N= 15
Age group			
< 3 months	4	4	4
3 - 6 months	2	5	7
7 - 12 months	3	1	2
> 12 months	1	2	1
Unknown	0	0	1
Gender			
Male	4	8	9
Female	5	4	4
Unknown	1	0	2
Country			
Europe	8	11	15
Latin America	0	0	0
Asia	2	1	0

1.4.3.2. Concomitant vaccines and other confounding factors (ie. Concomitant infections)

Out of the 10 classic KD cases, one is reported with a concurrent throat infection. In the 9 other cases, although they report the symptoms of classic Kawasaki disease, there is not

enough information regarding diagnostic tests to exclude other diseases causing the KD, such as bacterial or viral diseases.

Out of the 37 cases, 30 cases are reported with coadministration of Synflorix and Infanrix hexa, Infanrix hexa and Prevenar, Infanrix hexa and Meningococcal Vaccine, or Rotavirus vaccine. Seven cases are reported after vaccination of Infanrix hexa alone.

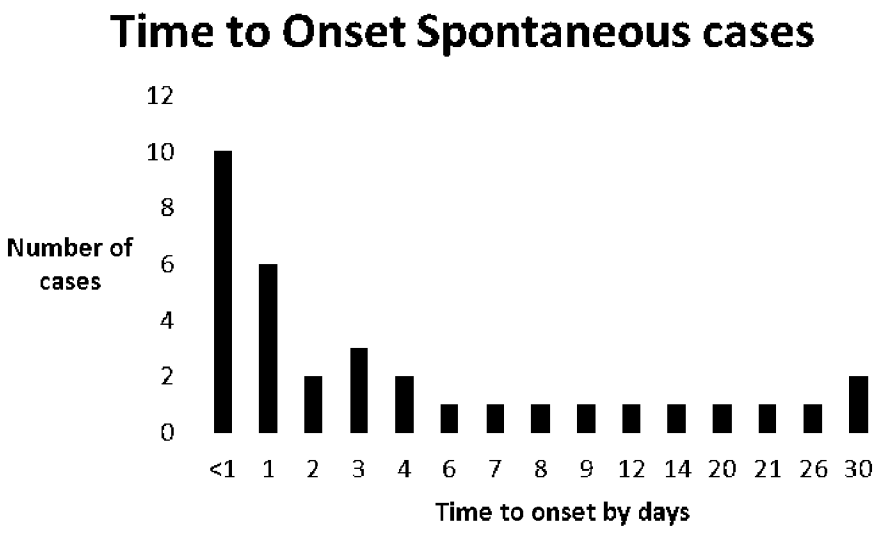
All incomplete cases except one have coadministration of vaccines, such as Infanrix hexa with Synflorix, or other Pneumococcal vaccine, as well Rotavirus vaccines. Six cases out of the twelve cases were reported with concomitant infections such as Bronchitis, Pyelonephritis, Respiratory infections, etc. A detailed summary of the cases is presented in ANNEX 5. Complete case narratives and GSK company comments are present in ANNEX 6.

1.4.3.3. Time to Onset

The analysis is again driven by the time period at risk given after vaccination that is 30 days, according to VAERS and other publications [Hua, 2009]. There are 34 cases within the risk period of 30 days. Three cases are reported after the risk period (48, 49, 80 days). Figure 2 describes the amount of cases within the risk period of 30 days. Most of the cases (ten in total), are less than one day after vaccination, reported immediately after vaccination or within some minutes- hours. These cases have a time to onset too short to imply a relationship with vaccination with Infanrix hexa. These cases may have another cause that triggered the KD syndrome, as the cases do not describe diagnostic tests to exclude viral and/or bacteriological diseases. There are as well six cases that develop symptoms of KD one day after vaccination.

Among the 10 classic cases of KD, nine cases had a time to onset between 0 and 30 days. Among the 12 incomplete cases, ten cases have a time to onset between 0 and 30 days. Among the 15 not confirmed cases, 14 cases are among our time risk period.

Figure 2 **Distribution of Spontaneous cases among the risk period of 30 days N=34**



2. QUESTION 2

Company response

Size and Relevant characteristics of the exposed collective, eg. With the aid of international sales figures of recent years, broken down according to country (especially for US, Japan, EU) including Switzerland, estimate of incidence rates (reporting rates).

2.1. Reporting Rates

Vaccine Adverse Event Reporting System (VAERS) was used to describe and analyse all Kawasaki cases from all US licensed vaccines from 1990 to 2007. [Hua, 2009]. In this analyse we use the same methodology as used in VAERS publication, to calculate the reporting rates with the following formula:

The number of KD cases within 30 days after vaccination was divided by the estimated person time of observation (ie. number of doses distributed multiplied by 30 days of observation divided by 365.25).

GSK does not have the total number of the doses administered, to estimate the amount of doses given, we use the amount of doses distributed. A search in the sales database of GSK was performed for that purpose until the 30th of April of 2014, as this database can be updated every month, in order to obtain the real number of doses distributed, the search must be performed two months back in time. As the cases of KD were search in

GSK safety database in July 2014, the search for the doses distributed was done since launch until end of April 2014.

In order to calculate Reporting Rates for this Kawasaki Analysis the 'worst case scenario' was taken into account, meaning, all cases whether they are classic, atypical or not confirmed were counted, that is a total of 34 KD cases found since launch until July 2014 reported with Infanrix hexa within the risk period of 30 days. Worldwide sales data was search and a total of 112'944705 million doses were distributed of Infanrix hexa since launch until April 2014. In Europe there were a total of 86' 484 145 million doses distributed since launch until April 2014. In Switzerland there are a total of 1'379 289 million doses distributed since launch until April 2014. Infanrix hexa is not licensed in the United States or in Japan.

Table 4 Observed to Expected Analysis: Reporting Rates per Region

Region	Observed Number of cases within the 30 days risk period [IC*]	Sales data	Reporting Rates (VAERS methodology) per 100 000 persons years	"Expected Range" Background Incidence Rates/ 100 000	"Observed Range" Intervals of Confidence IC 95%– Poisson Distribution
Worldwide	34 [23.55-47.51]	112944705	0.37	1.6 - 113	0.25-0.51
Europe	31[21.06-44.0]	86484145	0.44	1.6 - 9	0.29-0.61
Asia	3[0.62-8.77]	5548386	0.66	2.59 -113	0.13-1.92
Switzerland	1 [0.03-5.57]	[redacted]	0.88	1.6 - 9	0.02 - 4.91

*[95% Poisson Exact Confidence Interval]

As observed in Table 4, the calculated worldwide reporting rates, as well the ones for Europe, Asia and Switzerland are among the "expected range" covered by the background incidence rates per region and worldwide. There were 34 out of 37 cases, worldwide within the risk period, 31 coming from Europe, 3 from Asia and one is from Switzerland. In order to obtain the observed range the 95% Intervals of Confidence of the Poisson distribution were used.

There are several limitations in Observed to Expected analyses, and several levels of uncertainty. The major factors affecting this Observed to Expected analysis are presented below. They relate to:

- The estimation of the background rate and its heterogeneity
- The uncertainty on the use of the distributed vaccines and the completeness of the reporting
- Absence of dose stratification.
- Small number of observed cases

2.2. Conclusion of cases in Spontaneous data:

The reporting rates and the observed range (95% IC) of Kawasaki disease cases are below or within the expected range for Worldwide, European and Asian background incidence rates.

In a worst-case scenario considering classic, incomplete and not confirmed cases of Kawasaki disease, the numbers of observed cases are below or within the expected range.

This analysis reflects that there is not a safety concern with Kawasaki disease for Infanrix hexa vaccine.

3. QUESTION 3

What is your assessment of the Risk?

Company response

Within clinical cases, none of the reported Kawasaki cases were considered by the investigator as causally related to Infanrix hexa. There were 18 cases of KD, only 3 temporally associated to vaccination with Infanrix hexa, in which one case did have a concomitant infection that is a confounding factor.The three cases had concomitant vaccination (two with Synflorix and one with Synflorix and Rotarix). The cumulative review of clinical KD cases does not indicate a specific safety signal. The individual case assessment is in ANNEX 2 (summary) and individual case narratives with respective GSK company comments are in ANNEX 3.

The cumulative review of spontaneous KD cases does not indicate a signal either, as the reporting rate calculated according VAERS methodology [Hua, 2009], is either below or among the expected range (background incidence rates worldwide, European incidence rates and Asian incidence rates). Although this kind of observed to expected analysis have limitations, a worst case scenario was considered to calculate our reporting rates taken into account classic cases, incomplete KD, and Not Confirmed KD cases within the time risk period of thirty days after vaccination with Infanrix hexa.

In conclusion after both reviews (clinical and spontaneous) there is no safety concern of Kawasaki disease after vaccination with Infanrix hexa.

4. QUESTION 4

What is your assessment of the Risk-Benefit Ratio?

Company response

GSK has extensive clinical and post-marketing experience with *Infanrix hexa*. Since launch over 100 million doses have been distributed worldwide. *Infanrix hexa* is currently licensed in 100 countries and has not been withdrawn from any country due to

regulatory action or safety concern. *Infanrix hexa* has a long-established safety and efficacy profile which has not altered after many years on the market. Vaccination has greatly reduced the burden of infectious diseases. Diphtheria, tetanus, pertussis, hepatitis B, polio and diseases caused by *Haemophilus influenza* type b are a common cause of disease in children worldwide, with significant morbidity and mortality. A dramatic decline in the incidence of diphtheria, tetanus, pertussis, hepatitis B, polio and diseases caused by *Haemophilus influenza* type b have been evidenced in countries in which infants are routinely immunised against these diseases.

The current *Infanrix hexa* product and patient information appropriately reflects the product's safety profile. No new safety concerns that would impact the benefit-risk ratio have been identified.

Although the under-reporting inherent to any spontaneous reporting setting is a limitation of this integrated assessment, it is concluded, at population level, that (potentially) severe Infectious diseases are prevented by the use of *Infanrix hexa* compared to the relatively low risk of side effects. Overall, the benefit-risk profile of *Infanrix hexa* for immunization against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and Hib in infants continues to be favourable.

5. QUESTION 5

What actions do you plan, particularly in respect of adapting product and patient information? Please substantiate your position

Company response

Based upon this review, the individual analysis, and the ongoing monitoring of Infanrix hexa, there are no plans to adapt product or patient information regarding risk of Kawasaki disease associated to vaccination with Infanrix hexa at this stage.

6. QUESTION 6

Please also let us know about any measures planned by other authorities

Company response

GSK is not aware of planned measures by other authorities regarding this question for Infanrix hexa.

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ANNEX 1 KAWASAKI DISEASE INCIDENCE RATES, FIRST FIVE YEARS OF LIFE

Country for IR calculation	Period and population for IR calculation	KD incidence rate (IR) per 100 000 py (< 5 years-old)	Number of KD cases	Reference
Czech Republic	1997-1999 Prospective study	1.6	19	Dolezalova et al. 2004
Malta	1992-1997 Computerised ward admission St Luke Hospital.	3.2	5	Grech V. 1999
British Isles	1990 Cases reported to the British Paeditric Surveillance Unit.	3.4	-	Dhillon R. et al. 1993
Thailand	1998-2002 Retrospective study in national registry	3.43-2.59	710	*Durongpisitkul et al. 2006*
Finland	1982-1992 Hospitals record	3.1-7.2	162	Salo E. 1993
Denmark	1981-2004 hospital discharge data	3.58	261	Fischer et al. 2007
Australia	1993-1995 National surveillance of KD	3.7	94	Royle et al. 1998
England (West Midlands)	1996-1999 Prospective study.	5.5	58	Gardner-Medwin J. et al. 2002
Sweden	1990-1992 Prospective study	6.2	79	Schiller et al. 1995
Chile	2001-2007 Retrospective review of hospital discharge data	6.8		Borzutzky et al. 2012
New Zealand	2001-2002 Prospective study	8	42	Heaton et al. 2006
England	1999-2000 Database NHS hospitals.	8.1	-	Harnden A. et al. 2002
Portugal	1996-2003	8.2		Gouveia C. Rev Port Cardio. 2005
England	1998-2003 Hospitals admission data	8.39	1228	Harnden et al. 2009
France	2005-2006 Prospective multicenter cohort study	9	25	Heuclin et al. 2009
United States	1993-1996 Data from Vaccine Safety DataLink	9-19.1	195	Belay et al. 2000
Finland Norway Sweden	1999-2009 Hospital discharge data	11.4 5.4 7.4	Globally 1390	Salo et al. 2012
US	1997-1999 Hospital discharge.	10.2	5677	Belay E. et al. 2003
Spain	1999-2002 Hospitals discharge.	15.1	37	Martinez Ruiz M. et al. 2003

Country for IR calculation	Period and population for IR calculation	KD incidence rate (IR) per 100 000 py (< 5 years-old)	Number of KD cases	Reference
Ireland	1996-2000 Hospitals discharge data	15.2*	194	Lynch et al. 2003
US	1997-2000 Hospital discharge.	17.6	3277	Holman et al. 2003
US	1992-1999 Hospital database of Michigan.	18.7	168	Abuhammour et al. 2005
US (San Diego)	1998-2003 Hospital discharge data	21.7	258	Kao et al. 2008
Canada	1995-2006 Hospitals discharge data	2004-06 26.24 2001-03 24.13 1998-2000 20.41 1995-97 14.39	528 486 411 317	Lin et al. 2010
Shanghai	1998-2002 Hospitals discharge.	27	654	Huang et al. 2006
Hawaii	1994-1997 Retrospective study. Discharge records.	47.7	175	Holman et al. 2000
Taiwan	1996-2002 Prospective study, NIH database.	66	6988	Chang et al. 2004
Korea	2003-2005 Hospitals discharge.	105	±9600	Park et al. 2007
Korea	2006-2008 Retrospective hospital survey	113.1	7864	Park et al. 2011
Japan	2005-2002 Retrospective survey. Hospitals database.	184.6	±20000	Nakamura et al. 2008
Japan	2007-2008 Retrospective survey in hospitals database	216.9	23337	Nakamura et al. 2010
Lit. review Japan Taiwan China India United States Italy	 2008 2003-2006 2007 2009 1981-1982	 218.6 69 26-49.4 4.5 19 14.7		Uehara et al. 2012

*Hospitalization rate

ANNEX 2 SUMMARY OF KD CASES FROM CLINICAL TRIALS

CASE ID	Protocol ID	COUNTRY	AGE	GENDER	SUSPECTED DRUGS – NUMBER OF DOSE	Time to Onset	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Com-ments
[redacted]	10PN-PD-DIT-028	[redacted]	6 Months	Male	Synflorix, Infanrix hexa(coadministration) – 2nd Dose	72 Days	5	No	Classic KD	Resolved	Concomitant Respiratory Infection
[redacted]	10PN-PD-DIT-028		7 Months	Male	Synflorix, Infanrix hexa(coadministration) – 3rd Dose	35 Days	5	No	Classic KD	Resolved	Concomitant Pneumonia
[redacted]	10PN-PD-DIT-028		9 Months	Female	Synflorix, Infanrix hexa(coadministration)- 3rd Dose	85 Days	5	No	Classic KD	Resolved	Multiple drugs
[redacted]	10PN-PD-DIT-028		8 Months	Female	Synflorix, Infanrix hexa(coadministration)- 3rd Dose	77 Days	5	No	Classic KD	Resolved	Urinary Infection
[redacted]	10PN-PD-DIT-028		20 Months	Male	Synflorix, Infanrix hexa (coadministration)- 3rd dose	69 Days	4	No	Incomplete KD	Resolved	Concomitant Respiratory Infection

CASE ID	Protocol ID	COUNTRY	AGE	GENDER	SUSPECTED DRUGS – NUMBER OF DOSE	Time to Onset	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Com-ments
[redacted]	10PN-PD-DIT-028	[redacted]	27 Months	Female	Infanrix hexa - 3rd Dose, Synflorix, Infanrix-polio-HIB.	TTO to Infanrix Hexa was 21 months to the other vaccines was 10 months	5	No	Classic KD	Resolved	Multiple vaccines
[redacted]	10PN-PD-DIT-028		20 Months	Male	Infanrix hexa - 3rd Dose, Synflorix, Infanrix-polio-HIB	TTo to Infanrix Hexa was 13 months, to the other vaccines was 4 months	4	No	Incomplete KD	Resolved	Multiple vaccines .
[redacted]	10PN-PD-DIT-028		24 Months	Male	Infanrix hexa-3rd Dose, Synflorix, Infanrix-polio-HIB	TTO for Infanrix Hexa was 19 months, for the other vaccines was 7 months.	5	No	Classic KD	Resolved	Urinary Infection possible.

CASE ID	Protocol ID	COUNTRY	AGE	GENDER	SUSPECTED DRUGS – NUMBER OF DOSE	Time to Onset	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Com-ments
[redacted]	10PN-PD-DIT-028	[redacted]	16 Months	Male	Synflorix, Infanrix hexa(coadministration) – 3rd Dose	11 Months	5	No	Classic KD	Resolved	Concurrent Acute Sinusitis
[redacted]	DTPA-HBV-IPV-074		15 Months	Male	Infanrix hexa - 4rd Dose	71 Days	2	No	Incomplete KD	Resolved	
[redacted]	UNDECA-PN-010		20 Months	Male	Pneumonia 11-valent protein D conjugate vaccine, Infanrix hexa – 4rd Dose	TTO : 88 days after Infanrix Hexa, 8 months to Pneumonia 11 valent protein D conjugate vaccine.	5	No	Classic KD	Resolved	

CASE ID	Protocol ID	COUNTRY	AGE	GENDER	SUSPECTED DRUGS – NUMBER OF DOSE	Time to Onset	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Com-ments
[redacted]	10PN-PD-DIT-001	[redacted]	3 Months	Male	Synflorix, Infanrix hexa(coadministration)- 1st Dose	15 Days	5	Yes	Classic KD	Resolved with Sequelae	Concomitant Vaccination, and Respiratory Infection
[redacted]	10PN-PD-DIT-011	[redacted]	12 Months	Female	Synflorix, Infanrix hexa 3rd Dose, Meningococcal polysaccharide vaccine group C (Non-GSK)	TTO to Infanrix Hexa and Synflorix was 5 months, TTO to Meningococal vaccine was 7 months	5	No	Classic KD	Resolved	Concomitant vaccines.

CASE ID	Protocol ID	COUNTRY	AGE	GENDER	SUSPECTED DRUGS – NUMBER OF DOSE	Time to Onset	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Com-ments
[redacted]	10PN-PD-Dit-031	[redacted]	3 Months	Female	Synflorix, Infanrix hexa, Rotavirus vaccine(coad ministration) – 2nd Dose	Same day	4	No	Incomplete KD	Resolved	Concomi tant vaccines .
[redacted]	10PN-PD-Dit-048	[redacted]	5 Months	Male	Synflorix, Infanrix hexa 1st Dose, Rotavirus vaccine, Infanrix-polio-HIB	TTO: 107 Days after Infanrix Hexa , the other vaccines were given the same day and TTO is 72 days.	5	No	Classic KD	Resolved	

CASE ID	Protocol ID	COUNTRY	AGE	GENDER	SUSPECTED DRUGS – NUMBER OF DOSE	Time to Onset	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Com-ments
[redacted]	10PN-PD-Dit-048	[redacted]	5 Months	Male	Synflorix, Infanrix hexa, Rotavirus vaccine, Infanrix-polio-HIB- 2nd Dose	TTO with Synflorix and Infanrix Hexa was 7 days, for the other coadministration Rotavirus and Infanrix Polio Hib was 86 days.	5	No	Classic KD	Resolved	Concomitant vaccines.
[redacted]	10PN-PD-DIT-066	[redacted]	3 Months	Male	Synflorix, Infanrix hexa(coadministration) – 1st Dose	32 Days	3	No	Incomplete KD	Resolved	Concomitant vaccines

CASE ID	Protocol ID	COUNTRY	AGE	GENDER	SUSPECTED DRUGS – NUMBER OF DOSE	Time to Onset	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Com-ments
[redacted]	MenACWY-TT-083	[redacted]	15 Months	Female	MMR vaccine (Non-GSK), N. Meningitidis Group C polysaccharide, Infanrix hexa, Synflorix (coadministration) 4th Dose	TTO : 94 days after Synflorix, Neisvac C and Infanrix Hexa vaccine TTO to a MMR vaccine (Non-GSK) was 4 days.	4	No	Incomplete KD	Resolved	Genital candidiasis concomitant.

ANNEX 3 INDIVIDUAL CASES CLINICAL TRIALS (NARRATIVE AND COMPANY COMMENT)

Cases of KD occurring outside the 30-day risk window (n=15)

1. **Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) - case [redacted] ([redacted]) - Kawasaki's disease**

On [redacted] **72 days** after the second dose of Synflorix, this six-month-old male developed KD. The subject was treated with paracetamol, decongestant, diclofenac, Theraflu, hydration therapy, ceftriaxone, normal immunoglobulin, ranitidine hydrochloride and aspirin. The subject started to cough and had rhinorrhoea since [redacted] and received treatment. On [redacted] the subject developed fever (38 °C), maculopapular exanthema (rash), vomiting and diarrhoea. On that day, received attention at a private clinic that indicated treatment. On [redacted], the rash got worse and was evaluated by a paediatrician, who referred the subject to a hospital. At the hospital, the subject presented with cough, lethargy, irritability, with heart rate of 124 per minute, respiratory rate 60 per minute, thoracic retractions, no wheezing and no rales. Chest x-ray performed on [redacted] showed no pulmonary infiltrates. The subject was admitted with diagnoses of gastroenteritis, moderate dehydration, and exanthema. The surveillance coordinator considered this subject could have suspected sepsis and before x-ray was taken community acquired pneumonia was suspected but ruled out. Treatment was initiated in the hospital after a blood culture was taken. After evaluation done at hospital, the diagnosis was changed to Kawasaki Disease (more than 5 days of fever, maculopapular rash, bilateral conjunctivitis, cervical adenopathy, hand and feet oedema) and medication was administered. The subject was discharged on [redacted] with medications and was asymptomatic (event resolved) since [redacted]. The investigator considered that there was no reasonable possibility that the KD may have been caused by investigational product and that the event was possibly an incidental illness.

Company comment: *Based on available clinical data, this case fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 72 days. More than 5 days of fever, maculopapular rash, bilateral conjunctivitis, cervical adenopathy and hand and feet oedema. Treatment with paracetamol, decongestant, diclofenac, Theraflu, hydration therapy, ceftriaxone, normal immunoglobulin, ranitidine hydrochloride and aspirin. In this case, the events are not temporally related with study vaccinations . Subject presented with respiratory and gastrointestinal symptoms (concurrent infection).*

2. **Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) case [redacted] ([redacted]) - Kawasaki's disease**

On [redacted] **35 days** after the third dose of Synflorix, a seven-month-old male developed pneumonia and KD. The subject developed fever and liquid stools since [redacted] and was hospitalised on [redacted]. He presented

with temperature of 38.5 °C, respiratory rate of 55 per minute, heart rate of 120 per minute, and physical examination without focus. Diagnosis of pneumonia was made according to white blood count and chest x-ray. Medication (ampicillin trihydrate, normal immunoglobulin and aspirin) was started on [redacted]. The subject continued to have fever and his medication was changed. The subject had rash, conjunctiva eyes, lips with erythema, genital rash and perineal rash, hands oedema since [redacted] and a dermatologist suspected Kawasaki disease. The subject had fever for more than 5 days and had discoloration periungual in hands and feet. Kawasaki disease start date was [redacted] The subject received treatment. In the hospital, the subject had a kidney echography showing pyelectasia bilateral on [redacted] No urinary symptoms. The pneumonia was resolved on [redacted] and the KD resolved on [redacted]. Echocardiogram on [redacted] was normal, platelets 305000 /mm3 and C-reactive protein 17 mg/L on [redacted] The mother reported that the subject required oral 800 mg acetylsalicylic per day from [redacted] to [redacted] and then 5 mg per day from [redacted] to [redacted]. The subject recovered completely. The acetylsalicylic was prescribed preventively because of risk of coronary aneurysm. The investigator considered that there was no reasonable possibility that the pneumonia and KD may have been caused by investigational product and that the events were possibly an incidental illness.

Company comment: *Based on available clinical data, this case fulfilled the case definition of Kawasaki syndrome (Newburger, 2004).TTO 35 days. Treatment with ampicillin trihydrate, normal immunoglobulin and aspirin. In this case, the events are not closely temporally related with study vaccinations . Subject presented with pneumonia (Chest X-ray confirmed) and gastrointestinal symptoms. Infection is a plausible trigger of KD. Echocardiogram normal.*

3. Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) case [redacted] - Kawasaki's disease

On [redacted], **85 days** after the third dose of Synflorix, this nine-month-old female developed KD. The subject was hospitalised and treated with ceftriaxone, dipyrone, diphenhydramine, metoclopramide, midazolam, aspirin, normal immunoglobulin and ranitidine hydrochloride. On [redacted], the subject experienced fever (38 to 39 °C). On [redacted] the subject continued to have fever and she presented exanthema all over her body. She was treated. On [redacted], the subject presented left sub maxillary ganglion. On [redacted] the subject consulted on emergency room and she was admitted with diagnosis of exanthema febrile. On [redacted] the subject was transferred to a different hospital and was admitted with the same diagnosis. The subject was treated while hospitalized. On [redacted], the subject was evaluated by an infectologist for generalized micropapular exanthema, left maxillar adenomegaly, conjunctival infection, foot and hand oedema, increased C-reactive protein, leukocytes increased, and decreased sodium. Kawasaki disease was diagnosed. The subject was discharged from the hospital on [redacted] with the diagnosis of KD. The KD was resolved on [redacted]. The investigator considered that there was no

reasonable possibility that the KD may have been caused by investigational product and that the event was possibly an incidental illness.

Company comment: *Based on available clinical data, this case fulfilled the case definition of Kawasaki syndrome (Newburger, 2004) TTO 85 days. Treatment with ceftriaxone, dipyrone, diphenhydramine, metoclopramide, midazolam, aspirin, normal immunoglobulin and ranitidine hydrochloride. In this case, the events are not temporally related with study vaccinations.*

4. **Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) case [redacted] - Kawasaki's disease**

On [redacted] **77 days** after the third dose of Synflorix, this eight-month-old female developed KD. The subject was hospitalised. The subject was treated with ceftriaxone, aspirin, ranitidine hydrochloride, cefotaxime, paracetamol, dipyrone, amikacin, cefepime, chloral hydrate and normal immunoglobulin. The subject experienced fever associated with vomiting and liquid stools since [redacted] She was evaluated on [redacted] and discharged with recommendations and labs were solicited. She continued to have fever, was evaluated on [redacted] and was admitted. She presented with a pulse of 156 per minute, respiratory rate of 56 times per minute, temperature of 38.5 °C and canker sore in the mouth. According to the initial labs, urinary tract infection was considered and the subject received treatment as of [redacted] The subject was recovering. According to the medical record, urinary tract infection was ruled out after lab results. The paediatrician considered that the subject presented KD after analysing the clinical course and results of the para-clinical. The subject presented with: prolonged fever without focus, initially with conjunctival injection and oedema in hands and feet, erythema in thorax and abdomen and desquamation of hands. She was discharged asymptomatic with prescriptions for medications until further medical recommendations. During hospitalization she received treatment. The event resolved on [redacted] The investigator considered that there was no reasonable possibility that the KD may have been caused by investigational product and that the event was possibly an incidental illness.

Company comment: *Based on available clinical data, this case fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 77 days. Treatment with ceftriaxone, aspirin, ranitidine hydrochloride, cefotaxime, paracetamol, dipyrone, amikacin, cefepime, chloral hydrate and normal immunoglobulin. In this case, the events are not temporally related with study vaccinations. Subject presented with gastrointestinal symptoms.*

5. **Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) case [redacted] ([redacted]-Kawasaki's disease**

On [redacted], **69 days** after the 3rd dose of Synflorix, this 20-month-old male developed KD. The subject was treated with normal immunoglobulin, aspirin, paracetamol, oxacillin sodium, salbutamol sulphate, potassium chloride + dextrose + normal saline, clarithromycin and amoxycillin/clavulanic acid. The subject started on

[redacted] with rhinorrhoea and cough. On [redacted], the subject started with non-quantified fever and on [redacted] developed an erythematous rash on the face, trunk, and extremities with desquamation of the lips and hands and also mild dyspnoea. On [redacted], the subject started vomiting and diarrhoea and her mother took the subject to the emergency room. She was then admitted on [redacted] On [redacted] the subject was evaluated and KD was confirmed and treatment started. The subject had fever on [redacted] and then remained afebrile. The subject was evaluated by a cardiologist and had a normal echocardiogram. The event resolved on [redacted] and the subject was discharged asymptomatic on [redacted] and will continue check-ups as an outpatient with both infectologist and cardiologist. The investigator considered that there was no reasonable possibility that the KD may have been caused by investigational product and that the event was possibly due to incidental illness.

Company comment: *Based on available clinical data, this case incompletely fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 69 days. Treatment with normal immunoglobulin, aspirin, paracetamol, oxacillin sodium, salbutamol sulphate, potassium chloride + dextrose + normal saline, clarithromycin and amoxycillin/clavulanic acid. In this case, the events are not temporally related with study vaccinations. Subject presented with concurrent respiratory and gastrointestinal symptoms (concurrent infection). Normal echocardiogram.*

6. Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) - case [redacted] ([redacted] - Kawasaki's disease

On [redacted], **11 months** after the fourth dose of Synflorix, this 27-month-old female developed KD. The subject was treated with hydration therapy, normal immunoglobulin, diphenhydramine, dipyrone, aspirin and ranitidine hydrochloride. The subject presented on [redacted] with maculopapular exanthema with pruritus, fever of 38 °C, ampullar lesion in mouth, adenopathy, and conjunctival infection. She was taken to the emergency room at a private centre and was hospitalized by immunology specialist on [redacted] with KD diagnosis. Physical examination showed cardiac rate 133 beats per minute, respiratory rate 32 breaths per minute, temperature 36.6 °C, arterial tension: 90/50 mmHg, bilateral sub maxillary and inguinal adenopathy, polymorphic exanthema, toe with desquamation, ampulla in jugal mucosa, oral mucosa, erythematous, abdomen/bowel sounds: increased and hepatomegaly. Treatment was provided during hospitalization from [redacted] to [redacted] The subject was discharged on [redacted] with KD diagnosis. Ambulatory treatment was prescribed from [redacted] to [redacted] The KD episode finished on [redacted] The subject was going to be followed-up with her paediatrician once a week and meet with a cardiology specialist in 30 days. The subject fulfilled one elimination criteria of the study, having received human gamma globulin as hospital treatment. Per decision of the principal investigator, the subject continued in the study. The investigator considered that there was no reasonable possibility that the KD may have been caused by investigational product and that the event was possibly due to incidental illness.

Company comment: *Based on available clinical data, this case incompletely fulfilled the case definition of Kawasaki syndrome (Newburger, 2004).TTO 11 months. Treatment with hydration therapy, normal immunoglobulin, diphenhydramine, dipyrone, aspirin and ranitidine hydrochloride. In this case, the events are not temporally related with study vaccinations.*

7. **Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) - case [redacted] - Kawasaki's disease**

On [redacted], **four months** after the 4th dose of Synflorix, this 20-month-old male developed KD. The subject was treated with normal immunoglobulin, aspirin and ranitidine hydrochloride. The subject presented on [redacted] with fever of 39 °C, skin lesion all over the body, red eyes, hand and feet erythema and oedema on the extremities. The subject was evaluated at a hospital where it was decided to admit the subject in the night of [redacted] (arrival at the hospital ward on [redacted] with the diagnosis of KD. The subject received treatment. During the hospitalization, the subject had a good evolution. He was without fever, had decrease of extremities oedema, and general condition improvement. By [redacted], the subject had no fever and was discharged with prescription treatment for six weeks. The date of event resolution was considered to be the discharge date ([redacted]. The investigator considered that there was no reasonable possibility that the KD may have been caused by investigational product and that the event was possibly due to incidental illness.

Company comment: *Based on available clinical data, this case incompletely fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 4 month to Synflorix. TTO for Infanrix Hexa 13 months. Treatment with normal immunoglobulin, aspirin and ranitidine hydrochloride. In this case, the events are not temporally related with study vaccinations.*

8. **Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) - case [redacted] - Kawasaki's disease**

On [redacted], **eight months** after the fourth dose of Synflorix, this 24-month-old male developed KD. The subject was treated with hydration therapy, azithromycin, metoclopramide, cefixime, ceftriaxone, dipyrone, ranitidine hydrochloride, aspirin, normal immunoglobulin and diphenhydramine. On [redacted], the subject presented with fever of 37 °C and retro-adenopathy left maxillary angle. On [redacted] he continued to experience fever and presented with mouth lesions (cheilitis). He consulted and treatment was indicated. On [redacted] the subject continued with fever, papule erythematous macular rash appeared on trunk and neck, red eyes, vomiting and diarrhoea. He consulted again and the physician indicated laboratory tests and treatment. On [redacted], the subject presented with fever and antibiotic treatment was indicated by probable urinary tract infection. On [redacted], the subject continued with fever, added hyporexia and decay. The subject consulted the emergency room of a hospital and was admitted on [redacted] with the

diagnosis of KD. Physical examination showed regular malaise, mild dehydration, fever, polymorphous rash on the trunk and lower limbs, conjunctival injection, cheilitis, mucositis, enanthem and cleft lip. Hospital treatment was given. The subject was discharged on [redacted] with diagnosis of KD and received ambulatory treatment until [redacted]. The subject had a good evolution. The event resolved on [redacted]. The investigator considered that there was no reasonable possibility that the KD may have been caused by investigational product and that the event was possibly an incidental illness.

Company comment: *Based on available clinical data, this case fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 8 months. Treatment with hydration therapy, azithromycin, metoclopramide, cefixime, ceftriaxone, dipyrone, ranitidine hydrochloride, aspirin, normal immunoglobulin and diphenhydramine. In this case, the events are not temporally related with study vaccinations. Subject presented with gastrointestinal symptoms.*

9. Subject [redacted] in study 109563 (10PN-PD-DIT-028 in Argentina, Colombia, Panama) - case [redacted] - Kawasaki's disease

On [redacted], **11 months** after the third dose of Synflorix, this 16-month-old male developed sinusitis and KD. The subject was hospitalised. The subject was treated with amoxicillin trihydrate, aspirin, normal immunoglobulin and cefuroxime axetil. The subject experienced ocular secretions in both eyes and irritability on 10 [redacted]. On [redacted] he experienced with high level fever of 40 °C and was evaluated several times with persistent fever. On [redacted], it was considered an acute sinusitis (according to sinus x-ray) and he received treatment. On [redacted], he was evaluated again and found with conjunctivitis, generalized rash, and swelling of the hands and feet. On [redacted], he presented with conjunctival infection and erythema of the lips. According to these events, KD was diagnosed clinically. He received treatment, presented with good evolution and was discharged on [redacted] with medication. Ambulatory treatment was prescribed from [redacted] to [redacted]. The subject was recovering and the sinusitis resolved on [redacted]. The subject was evaluated by a cardiologist and treatment was suspended on [redacted]. The Kawasaki disease was resolved on [redacted]. The investigator considered that there was no reasonable possibility that the KD and sinusitis may have been caused by investigational product and that the events were possibly due to incidental illness.

Company comment: *Based on available clinical data, this case fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 11 months. Treatment with amoxicillin trihydrate, aspirin, normal immunoglobulin and cefuroxime axetil. In this case, the events are not temporally related with study vaccinations . Subject presented with acute sinusitis.*

10. Subject [redacted] in study 107005 (10PN-PD-DIT-011 in [redacted] - Case [redacted] –Kawasaki's disease

On [redacted], **five months** after the third doses of Synflorix and Infanrix hexa, seven months after the second dose of Meningitec, this 11-month-old subject developed suspected Kawasaki syndrome. The subject was hospitalised for 6 days. This female infant showed fever during 3 days, face and limbs exanthema and pharynx hyperaemia. Physical exam revealed fever, macular rash/pharyngeal redness, conjunctival injection, micropolyadenia. She was treated with intravenous gamma globulins as of the first admission day. Fever subsided on [redacted]. The hemogram, biochemistry, chest X-rays, serology and echocardiogram were all within normal ranges, except for a raised erythrocyte sedimentation rate. She did not suffer from any recent or concurrent infections. No additional echocardiogram was performed. The rest of symptoms had disappeared when subject was discharged on [redacted]. The investigator considered that there was no reasonable possibility that the suspected Kawasaki syndrome may have been caused by Synflorix, Infanrix hexa and Meningitec.

Company comment: *Based on available clinical data, this case incompletely fulfils the case definition of Kawasaki syndrome (Newburger, 2004). TTO 5 months. No temporal association with study vaccination; concurrent pharynx hyperaemia (possible pharyngitis?).*

11. Subject [redacted] in study 111654 (10PN-PD-DIT-048 PRI in Singapore and Malaysia)- case [redacted] ([redacted]- Kawasaki's disease

On [redacted], the subject received the first dose of either a commercial lot or a phase III clinical lot of Synflorix, Rotarix and Infanrix hexa. On [redacted], he received the second dose of Synflorix and Rotarix and a dose of Infanrix-IPV/Hib. On [redacted], he received a third dose Synflorix and a second dose of Infanrix hexa. On [redacted] this five-month-old subject developed KD. Subject presented with fever for six days (maximum 38.5 °C) associated with runny nose, decreased feeding for 3 days (from 150 ml 3 hourly to 120 ml 3 hourly) and decreased urine output. The subject also presented truncal rash for 4 days including upper and lower limb, rash erythematous, and blanchable. The subject also experienced conjunctivitis for 1 day, increased irritability and crying for 6 days. Subject was admitted in clinic on [redacted] for intravenous hydration while subject appears lethargic, irritable and mildly dehydrated but stable. Lips were red and cracked, small red papules were noted on knee area and hands. Clinical examination and reflexes were normal as well as urine and blood culture done on [redacted]. Nasopharyngeal aspirate results were normal. Heart function sonography done on [redacted] shows normal coronaries. Subject was diagnosed with KD, and was treated as follows; paracetamol, Dextrose + potassium chloride + sodium chloride, aspirin, ranitidine hydrochloride, white soft paraffin, oxymetazoline hydrochloride,ampicillin trihydrate, gentamicin sulphate and immunoglobulin. Subject was discharged in good condition on [redacted] with the following medications: Aspirin 70 mg 6 hourly for 3 days, then aspirin 35 mg daily for 2 weeks, Ranitidine 30 mg 2 times a day for 3 weeks, iliadin 1 nose drop 2 times a day for 3 days and paracetamol suspension 96 mg 6 hourly on an ad hoc base for 5 days. The event resolved on [redacted]. The physician that examined the subject on [redacted] stated that he has fully recovered from KD. The investigator considered that there was no reasonable possibility that the KD may

have been caused by vaccinations and that the event was possibly due to an incidental illness.

Company comment: *Based on available clinical data, this case incompletely fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 72 days. Heart function sonography showed normal coronaries. Treatment with immunoglobulins, aspirin, paracetamol, antihistamines and antibiotics was started up very early after clinical admission. In this case, the events are not temporally related with study vaccinations . Subject presented a runny nose at the time the events occurred (possible concurrent upper airway infection?).*

12. Subject [redacted] in study 113151 (10PN-PD-DIT-066 in [redacted] - Case [redacted] - Kawasaki's disease

This male subject was enrolled in the prophylactic open study 113151 (10PN-PD-DIT-066). On [redacted], he received the first dose of Synflorix and Infanrix hexa. On [redacted], (**32 days** later) the subject was hospitalised. The subject had continuous high fever, bulging fontanel, no vomiting. Blood test showed an increase in WBC (30.88 k/uL), and CRP (88 mg/L). Lumbar puncture was normal. Blood culture: Staphylo-coagula negative (-).The initial diagnosis was infectious fever. On [redacted] the subject still had fever, with lymph node inflammation at neck, without rash. Non-typical KD was suspected. Cardiac ultrasonography performed on [redacted] showed normal results (without coronary artery dilation). On [redacted], Globulin IV 300 ml/1 time was used. The fever stopped. The SAE was confirmed as non-typical Kawasaki on [redacted], not infectious fever. Aspirin was indicated for the prevention of inflammation and coagulation. The event resolved on [redacted] and the subject was discharged. The investigator considered that there was no reasonable possibility that the KD may have been caused by Synflorix and Infanrix hexa. The subject was withdrawn from the study due to the SAE.

Company comment: *Based on available clinical data, this case incompletely fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 32 days. The subject experienced continuous fever and cervical lymph nodes. Cardiac ultrasound found no abnormalities. Skin or mucous reactions associated to Kawasaki's disease were not mentioned. The blood image showed systemic inflammation (elevated CRP and WBC count) but blood cultures were negative. Although borderline, there is no close temporal association with study vaccination.*

13. Subject [redacted] in study 113369 (MenACWY-TT-083 in Estonia, Germany, Spain) - case [redacted] - Kawasaki's disease

On [redacted], four days after a dose of MMRVaxPro, **94 days** after the third dose of Neisvac-C, 94 days after the fourth dose of Infanrix hexa and 94 days after the fourth dose of Synflorix, this 15-month-old female developed KD. On [redacted], she developed genital candidiasis. The subject was treated with normal immunoglobulin, aspirin, esomeprazole and clotrimazole.

A 15-month-old girl was admitted after five days of high degree fever of 39.5 °C, rash, rhinitis, conjunctivitis, loss of appetite and irritability. She had been vaccinated

with MMR vaccine four days before starting the clinical picture. Physical examination showed an irritable toddler with purpuric rash, conjunctivitis with ocular secretion and cervical lymphadenopathy of 1 cm of diameter. Laboratory results showed a CBC with mild anaemia and normal WBC and platelet count. The ESR was 83 mm/h. The CRP result was 150 mg/L. An echocardiogram during the admission and before discharge was normal. The girl was treated with one dose of gamma globulin (2 gr/kg) and oral aspirin (80 mg/kg during 7 days and 5 mg/Kg during 8 weeks). The fever disappeared 24 hours after gamma globulin administration. She has was seen at the cardiology office 41 days after the discharge and a new echocardiogram showed no anomalies. A genital candidiasis was diagnosed during her admission. The events resolved on [redacted]. The investigator considered that there was no reasonable possibility that the KD and genital candidiasis may have been caused by Neisvac-C, Infanrix hexa and Synflorix and that the events were possibly due to the concomitant medication, MMRVaxPro (non-GSK) and incidental illness.

Company comment: *Based on available clinical data, this case incompletely fulfilled the case definition of Kawasaki syndrome (Newburger, 2004). TTO 94 days. Treatment with normal immunoglobulin, aspirin, esomeprazole and clotrimazole. In this case, the events are not temporally related with study vaccinations. Concurrent rhinitis. Normal echocardiogram.*

14. Subject[redacted] in study 217744074 (DTPA-HBV-IPV-074) Case [redacted]

On [redacted], a booster of Infanrix Hexa (lot 21833A9/Hib407A47, IM L thigh) was given. On [redacted], 71 days after vaccination, this 15 month old boy developed persistent fever (up to 40 C) and deterioration of general condition. The following treatment was given : From [redacted] till [redacted] : Suprax (5 ml 1/d). From [redacted] till [redacted] : Zovirax (Acyclovir susp.). Since [redacted] : Paracetamol (prn). On [redacted], he was hospitalised. A diagnosis of Kawasaki was made. The following treatment was given : On [redacted] : Polyglobin (18 mg IV). From [redacted] till [redacted] : Aspisol (Lysine aspirin 250 g 3/d IV). From [redacted] till [redacted] : Electrolyte/Glucose (IV) and Sobelin (Clindamycin hydrochloride 150 mg 3/d IV). From [redacted] till [redacted] : Otriven (Xylometazoline hydrochloride - nose drops prn). On [redacted] : Polyglobin (18 mg IV). On [redacted], the fever had resolved. The following treatment was given : From [redacted] till [redacted] : Nystatin (300000 IE 3/d po). On [redacted] : Aspilol (45 mg IV). From [redacted] till [redacted] : Omniflora (1 cap 2/d po). From [redacted] till [redacted] : Aspirin (50 mg po). On [redacted], the child was discharged. On [redacted], he had recovered. In the investigator's opinion, the study vaccine did not contribute to the SAE.

Company comment: *There is insufficient evidence to relate this event to study vaccines Infanrix hexa. The patient developed high fever but there is not enough evidence of other symptoms of Kawasaki disease. The investigator considers this SAE was not related to Infanrix Hexa. TTO is 71 days.*

15. Subject [redacted], in study 347414010 Case [redacted]

On [redacted], 88 days after the booster dose of Infanrix Hexa and 8 months after booster dose of 11Pn-PD or Havrix, at 20 months of age, the subject developed fever of unclear etiology (which had lasted for 3 weeks) exanthema, edema of upper and lower extremities, lymphadenitis colli, conjunctivitis and pharyngitis. The maximum of child's body temperature was 40 C. On [redacted], the subject was hospitalised. A diagnosis of Kawasaki's disease was made. The subject was treated with amoxycillin + clavulanic acid, erythromycin (IV and IM) and immunoglobulin human normal. On [redacted], the subject was discharged from hospital. On [redacted], he had recovered. The investigator considered there was no reasonable possibility that the events may have been caused by the vaccine.

***Company comment** : According to the narrative the patient develop Classic Kawasaki disease according to Newburger,2004 KD classification. Time to onset was 88 days after Infanrix hexa. There is no causal relationship of these events and Infanrix Hexa vaccination and there is no temporal association either.*

Cases of KD occurring within the 30-day risk window (n=3)

1. Subject [redacted] in study 105553 (10PN-PD-DIT-001 in [redacted]) – Case [redacted] - Kawasaki's disease

On [redacted], **15 days** after the first dose of 10-Pn-PD-DiT and 15 days after the first dose of Infanrix hexa this 3-month-old male with an unremarkable medical history had mild rhinitis, was 'chesty' and developed high fever and light red macular rash over face and body. On [redacted] the subject was hospitalized. Physical examination showed: rash on face and body, red lips, strawberry tongue and bilateral conjunctivitis. Fever at admission was 39.7 °C. WBC count was elevated (14.9 $x10^9$/L) and CRP (C-reactive protein) was raised (81); hemoglobin 105 g/L on admission and 96 g/L on [redacted] Pneumonia was suspected but not confirmed. KD was diagnosed and the subject was treated with IVIG unknown dose), acetylsalicylic acid (150 mg 3 times daily) and cefuroxime (for 2 days unknown dose; stopped as pneumonia not confirmed). On [redacted] he was discharged in good medical condition with acetylsalicylic acid (25 mg once per day) until further notice. First echocardiography was performed on [redacted]: right coronary diameter was 3 mm and further downwards at the bend 2 mm; this was considered ectasia according to the reporter; normal heart function and measures; no pericardial effusion; no thrombi noticed. ECG and CSF were within normal limits. Physical exam revealed peeling of skin of fingers and toes. A second echocardiography performed in [redacted]: left coronary artery between 0.28 and 0.3 cm; right coronary artery 0.21 cm; no aneusysmata noticed. The subject continues on salicylate medication. According to the reporter there is no reasonable possibility that the SAE is caused by 10-Pn-PD-DiT and Infanrix hexa vaccine. The subject was withdrawn from the study.

Company comment: *Based on available clinical data, this case fulfils the case definition of Kawasaki syndrome (Newburger, 2004). TTO 15 days. The echocardiographic results are borderline ectatic. This male subject is 3 months old; patients with KD younger than 6 months are encountered infrequently but might be at increased risk for coronary-artery aneurysms. Treatment with IVIG and aspirin was started up early. The events are temporally related with study vaccination with Synflorix and Infanrix hexa. Subject suffered from a concurrent upper respiratory tract infection (rhinitis) which is a possible trigger of KD.*

2. **Subject [redacted] in study 109861 (10PN-PD-DIT-031 in [redacted]- Case [redacted] – Kawasaki's disease**

On [redacted], **same day** after the second dose of Synflorix, same day after the second dose of Infanrix hexa, same day after the second dose of Rotarix, this three-month-old female developed KD. Fever developed the same day after vaccination and persisted for 5 days. Bilateral conjunctivitis, neck lymphadenopathy and erythematous papule over BCG-site were found. There was no recent infection. The subject was admitted on [redacted] and discharged on [redacted]. During admission, leukocytosis, high CRP and pyuria were noted. Ampicillin and gentamicin were prescribed for suspected urinary tract infection. On follow up, desquamation over finger tips was noted. Initial echocardiogram on [redacted] was normal. Diagnosis was atypical KD. The subject was treated with ibuprofen, paracetamol, gentamicin sulphate, ampicillin trihydrate, Dextrose+saline and cephalexin. The event resolved on [redacted]. The investigator considered that there was no reasonable possibility that the KD may have been caused by Synflorix, Infanrix hexa and Rotarix and that the event was possibly due to incidental illness.

Company comment: *Based on available clinical data, this case incompletely fulfils the case definition of Kawasaki syndrome (Newburger, 2004). TTO same day. Three-month-old female; patients with KD younger than 6 months are encountered infrequently but might be at increased risk for coronary-artery aneurysms. Acute (i.e. same day fever started) onset time after study vaccination makes a causal link with any of the study vaccines administered (Synflorix, Infanrix hexa and Rotarix) unlikely; a concurrent urinary tract infection was a plausible trigger of KD; no mention of ASA or IVIG as treatment for KD.*

3. **Subject [redacted] in study 111654 (10PN-PD-DIT-048 PRI in Singapore and Malaysia)- case [redacted] - Kawasaki's disease**

This male subject was enrolled in the prophylactic double blind study 111654 (10PN-PD-DIT-048). On [redacted] he received the first dose of either a commercial lot or a phase III clinical lot of Synflorix, Rotarix and Infanrix hexa. On [redacted] he received the second dose of Synflorix and Rotarix and a dose of Infanrix-IPV/Hib. On [redacted], he received a third dose Synflorix and a second dose of Infanrix hexa. Subject had been travelling between Kuala Lumpur and Singapore by end of May. On [redacted], seven days after last study vaccinations this five-month-old subject was diagnosed with KD. He presented fever for 4 days (maximum 40 °C), rashes for 3 days, decreased feeding

for 2 days and conjuctival redness for 1 day. The subject was admitted in emergency ward on [redacted] *and, on examination, presented inflamed lips and oral cavity as well as bilateral hands and foot redness. On examination subject presented with maculopapular rash especially over the trunk and limbs and small cervical lymph nodes less than 0.5 cm diameter noted. Diagnosis of KD fulfilled the criteria of bilateral non-suppurative conjunctivitis, red lips, puffy feet and maculopapular rash. The subject was hospitalised. A nasopharyngeal swab done on* [redacted] *was negative. Blood culture (aerobic/anaerobic) done on* [redacted] *showed no finding. Urine culture and stool culture done on* [redacted] *were negative. On the evening of* [redacted]*, the subject's mother noted that subject's fontanel was bulging, while examination of subject reflexes was normal. To rule out meningitis, a lumbar puncture was performed. Results of CSF showed the following: (red blood cell):2, clarity clear and globulin negative. CSF culture shows negative, appearance clear, polymorphs 1+ and no organism. Enterovirus PCR was negative. Subject's bulging fontanel became normotensive 1 day later. The subject was treated with ceftriaxone sodium, paracetamol, aspirin, normal immunoglobulin as of* [redacted]*. Dextrose + potassium chloride + sodium chloride and Magnesium trisilicate mixture. Fever was resolved on* [redacted]*. The subject presented stable parameters, good oral intake, was active and alert and was discharged in good condition on* [redacted] *with medications. The event resolved on* [redacted] *The investigator considered that there was no reasonable possibility that KD may have been caused by study vaccinations and that the event was possibly due to an incidental illness.*
The following follow-up information was received on [redacted]*. The subject received aspirin as maintenance treatment. Platelet count done on* [redacted] *showed the following result: 583x109/L. Coronary arteries ultrasound performed on* [redacted] *was normal.*

***Company comment**: Based on available clinical data, this case incompletely fulfils the case definition of Kawasaki syndrome (Newburger, 2004). TTO 7 days. Fever was noted as having lasted only for 4 days. Events temporally associated with study vaccinations Synflorix and Infanrix hexa in a 5-month-old male subject. Treatment with immunoglobulins, aspirin, paracetamol, and antibiotics was started up early. No infectious aetiology for KD found as result of the medical investigations performed. Coronary arteries echocardiography was normal.*

ANNEX 4 DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE: PRINCIPAL CLINICAL FINDINGS (TAUBERT, 1999)

Fever persisting at least five days: the fever is generally high and spiking (often to 40°C [104°F] or higher) and persists in untreated patients for one to two weeks or longer.

Presence of at least four of the following five principal features:

1. Changes in extremities: these changes are distinctive and acutely include redness, swelling and, sometimes, induration of the hands and feet. One to three weeks after the onset of fever, desquamation of the fingers and toes occurs. Approximately one to two months after the onset of fever, Beau's lines (white lines across the fingernails) may appear.

2. Polymorphic exanthem: the skin eruption involves the trunk and extremities and may have several forms, including urticarial exanthem, a morbilliform maculopapular eruption (occasionally with target lesions) or a diffuse scarlatiniform rash. Bullae and vesicles are not seen. The rash usually appears within five days after the onset of fever.

3. Bilateral conjunctival injection: the bulbar conjunctivae, rather than the palpebral or tarsal conjunctivae, are involved. Typically, the limbic region is spared. The conjunctival injection is not associated with an exudate and is usually painless.

4. Changes in the lips and oral cavity: these changes include strawberry tongue, redness and cracking of the lips, and erythema of the oropharyngeal mucosa. Ulcerative lesions are not seen.

5. Cervical lymphadenopathy (at least one lymph node with a diameter of 1.5 cm or greater): the lymphadenopathy is usually unilateral, with firm and slightly tender nodes.

Exclusion of other diseases with similar findings.

Adapted from Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M, et al. Diagnosis and therapy of Kawasaki disease in children. Circulation 1993;87:1776–80.

ANNEX 5 SUMMARY OF KD CASES FROM SPONTANEOUS REPORTS

CASE ID	COUNTRY	AGE	GENDER	Time to Onset	SUSPECTED DRUGS – NUMBER OF DOSE	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Comments
[redacted]	[redacted]	5 Months	Female	1 Days	Infanrix hexa	5	No	Classic KD	Resolved	Patient recovered with sequelae
[redacted]		2 Months	Male	6 Days	Infanrix hexa	2	Yes	Incomplete KD	Unresolved	Concurrent medication (Ceftazidime), Concomitant Pneumonia
[redacted]		2 Months	Male	0 Days	Infanrix hexa	1	Yes	Incomplete KD	Improved	Concomitant RSV infection and pneumonia
[redacted]		1 Years	Male	2 Weeks	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	Unknown	No	Incomplete KD	Unknown	No further information was available
[redacted]		5 Months	Female	4 Days	Infanrix hexa	2	No	Incomplete KD	Resolved	

CASE ID	COUNTRY	AGE	GENDER	Time to Onset	SUSPECTED DRUGS – NUMBER OF DOSE	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Comments
[redacted]	[redacted]	12 Months	Male	1 Hours	Infanrix hexa, Meningococcal polysaccharide vaccine group C (Non-GSK), Pneumococcal vaccines (Non-GSK)	Unknown	Yes	Incomplete KD	Improved	Concominant Upper respiratory tract infection
[redacted]	[redacted]	19 Weeks	Male	48 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	Unknown	No	incomplete KD	Resolved	TTO : 18 days for Rotateq
[redacted]	[redacted]	3 Months	Female	1 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	No	Incomplete KD	Resolved	Coadministrations of vaccines
[redacted]	[redacted]	11 Months	Male	1 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4	No	Incomplete KD	Resolved	Coadministrations of vaccines

CASE ID	COUNTRY	AGE	GENDER	Time to Onset	SUSPECTED DRUGS – NUMBER OF DOSE	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Comments
[redacted]	[redacted]	2 Months	Male	2 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4	Yes	Incomplete KD	Unknown	Concurrent medical conditions: G6PD deficiency, conjunctivitis, upper respiratory tract infection
[redacted]		4 Months	Male	0 Days	Synflorix, Infanrix hexa	3	No	Incomplete KD	Resolved	Concomitant acute viral bronquitis and pyuria, coadministration of vaccines
[redacted]		8 Weeks	Female	0 Days	Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	5	Yes	Classic KD	Unknown	Coadministration of vaccines
[redacted]		12 Months	Female	0 Weeks	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	5	Yes	Classic KD	Resolved	Coadministration of vaccines
[redacted]		7 Months	Male	0 Days	Infanrix hexa	4	No	Incomplete KD	Resolved	Concurrent vaccinations: BCG non GSK vaccine, and pneumococcal vaccine

CASE ID	COUNTRY	AGE	GENDER	Time to Onset	SUSPECTED DRUGS – NUMBER OF DOSE	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Comments
[redacted]	[redacted]	8 Months	Female	80 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4	No	Incomplete KD	Resolved	Coadministration vaccinations : Prevenar
[redacted]		7 Months	Male	26 Days	Infanrix hexa, Rotavirus vaccine	5	No	Classic KD	Resolved	Concurrent Throat infection, coadministration of vaccines
[redacted]		15 Months	Female	30 Days	Infanrix hexa, Meningococcal polysaccharide vaccine group C (Non-GSK)	5	No	Classic KD	Resolved	Coadministration of vaccines
[redacted]		6 Months	Male	21 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	5	Yes	Classic KD	Resolved	Coadministration of vaccines
[redacted]		4 Months	Male	12 Days	Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Yes	Incomplete KD	Fatal	Concomitant Upper Respiratory Tract Infection

CASE ID	COUNTRY	AGE	GENDER	Time to Onset	SUSPECTED DRUGS – NUMBER OF DOSE	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Comments
[redacted]	[redacted]	Infant	Female	1 Months	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	Unknown	No	Incomplete KD	Unknown	Coadministration of vaccines
[redacted]		10 Weeks	Male	1 Weeks	Infanrix hexa, Prevenar	2	No	Incomplete KD	Improved	Coadministration of vaccines
[redacted]		14 Months	Female	1 Days	Infanrix hexa/ Prevenar	Unknown	No	Incomplete KD	Improved	Coadministration of vaccines
[redacted]		3 Months	Female	9 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	3	Yes	Incomplete KD	Resolved	Coadministration of vaccines

CASE ID	COUNTRY	AGE	GENDER	Time to Onset	SUSPECTED DRUGS – NUMBER OF DOSE	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Comments
[redacted]		4 Months	Male	< Week	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	2	Yes	Incomplete KD	Fatal	Coadministration of vaccines, concurrent medical conditions persistent foramen ovale. Intermitent exantema. Infections focus of intermitent exantema was suspected. Positive EBV IgM highly positive in autopsy report.
		5 Months	Male	1 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Yes	Incomplete KD	Unresolved	Coadministration of vaccines, concurrent coughing.
		4 Months	Unknown	3 Days	Infanrix hexa	Unknown	No	Incomplete KD	Unknown	
		3 Months	Male	2 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4	No	Incomplete KD	Improved	Coadministration of vaccines, concurrent anemia due to infection?

CASE ID	COUNTRY	AGE	GENDER	Time to Onset	SUSPECTED DRUGS – NUMBER OF DOSE	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Comments
[redacted]		4 Months	Female	3 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	No	Incomplete KD	Resolved	Coadministration of vaccines
		2 Months	Female	3 Days	Infanrix hexa	5	No	Classic KD	Resolved	
		12 Months	Male	3 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	5	Yes	Classic KD	Unresolved	In the narrative it says Atypical KD but there are five clinical features, Coadministration of vaccines
		12 Weeks	Female	0 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	2	Yes	Incomplete KD	Unresolved	Concurrent Norovirus infection
		11 Weeks	Male	8 Days	Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	5	No	Classic KD	Resolved	Concomitant vaccines

CASE ID	COUNTRY	AGE	GENDER	Time to Onset	SUSPECTED DRUGS – NUMBER OF DOSE	Main Clinical Features + Fever	Coronary Artery Abnor-malities	KD Diagnosis	Case outcome	Comments
[redacted]		3 Months	Male	49 Days	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	4	Yes	incomplete KD	Unknown	Concomitant Bronquitis
		19 Weeks	Male	28 days	Infanrix hexa, Rotavirus vaccine, Pneumococcal vaccines (Non-GSK)	3	Yes	Incomplete KD	Unknown	Suspected Pyelonefritis, Urine culture positive for Candida and Enterococos faecalis
		4 Months	Male	1 Days	Infanrix hexa, Synflorix	Unknown	No	incomplete KD	Unresolved	Medical History: Premature baby
		3 Months		Less than a month	Infanrix hexa, Prevenar	5	No	Classic KD	Resolved	Concomitant vaccines
		4 months	Unknown	4 Days	Infanrix hexa, Prevenar 13	Unknown	No	incomplete KD	Recurrent KD	Concomitant vaccines

ANNEX 6 INDIVIDUAL CASES SPONTANEOUS REPORTS (NARRATIVE AND COMPANY COMMENT)

[redacted]

This case received from the [redacted] Authorities describes the occurrence of kawasaki's syndrome in a 5-month-old girl receiving diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio and haemophilus influenza B vaccine (Infanrix Hexa) for prophylaxis. On [redacted], a dose of Infanrix Hexa (lot # 21m0122) was given. On [redacted], 1 day after vaccination, the girl developed fever (39-40 C). On [redacted], she was hospitalised. On [redacted], 3 days after vaccination, she developed a conjunctival hypervascularization, generalised maculopapular exanthema with swelling and hyperaemia of pharynx. A diagnosis of Kawasaki's syndrome was made. Lab tests were performed and showed: increase WBC, platelets count, ESR alpha 2 and hepatic indices. As of [redacted], at the time of this report, she had recovered with sequelae. The reporting physician considered the events to be possibly related to the vaccine. Further information has been requested.

Company comment:

Classic Kawasaki disease case in patient who recovered with sequelae. TTO one day, there is a temporal association with vaccination with Infanrix Hexa. In the narrative no tests to rule out infectious diseases are shown that can also trigger KD. Insufficient clinical and lab evidence to relate this event to Infanrix Hexa.

[redacted]

This case was reported by a regulatory authority and described the occurrence of Kawasaki disease in a 2 month-old-male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Concurrent medications included Ceftazidime sodium (Ceftazidime) 300 mg per day given from [redacted] until [redacted] for an unspecified indication. On [redacted] the subject received first dose of Infanrix hexa (intramuscular, unknown), lot number not provided. On [redacted] 6 days after vaccination with Infanrix hexa, the subject experienced skin inflammation. The subject was treated topically with hydrocortisone. A diagnostic ultrasound of gluteus was performed (no result provided). At the time of reporting, the event was improved. The regulatory authority reported that the events were possibly related to vaccination with Infanrix hexa. In follow up received on [redacted], the case has been upgraded to serious by the reporting physician who considered that the events were life threatening. It has also been reported that on [redacted], a cardiac echodoppler showed a moderate diffuse arterial coronary ectasia in the first tract of the 3 main arms and an inflammation of coronary arteries post Kawasaki disease had been then diagnosed. Aspirin and dipyridamole had also been prescribed for 3 months. Additional information has been requested. In the follow up received on [redacted] it was reported that the child had no relevant family and/or personal medical history. On [redacted], one day

after vaccination with Infanrix hexa, he suffered from right upper lobar pneumonia (reported as concomitant illness) for which he hospitalised on [redacted]. At this time, he also had conjunctivitis. Then skin inflammation occurred. At dismission, an increased of the erythrocyte sedimentation rate and low platelet count were observed. On [redacted], echo cardio doppler was performed, showing left arterial coronary ectasia and of anterior descending coronary. At the time of reporting, general conditions had improved but the inflammation of hypodermis (gluteus) was persisting.

Company comment: *Not Confirmed case of Kawasaki disease, with coronary artery abnormalities (Newburger,2004). Temporal association to Infanrix Hexa as the TTO is six days. There was a concomitant pneumonia, that may have trigger KD (infectious pneumonia).*

[redacted]

This case initially reported by a physician is now reported by the regulatory authority and described the occurrence of coronaritis in a 2-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine. (Infanrix hexa, GlaxoSmithKline) for prophylaxis. On [redacted], the subject received unspecified dose of Infanrix hexa (unknown route and injection site), lot number not provided. On [redacted], 7 days after vaccination with Infanrix hexa, the subject experienced Kawasaki's disease with high persistent fever. The subject was hospitalised for 1 month and the physician considered the events were clinically significant (or requiring intervention). At the time of reporting the outcome of the events was unspecified. The physician considered the events were possibly related to vaccination with Infanrix hexa. On [redacted]: Follow-up: On [redacted], the subject received unspecified dose of Infanrix hexa (unknown route and injection site). On [redacted], less than one day after vaccination with Infanrix hexa, the subject experienced high and persistent fever. On [redacted], 2 days after vaccination with Infanrix hexa, the subject experienced a right basal bronchopneumonia. On [redacted], he was hospitalised for 1 month. On [redacted], the subject developed coronaritis with coronary artery dilation. The laboratory test for respiratory syncytial virus was positive. The diagnosis of Kawasaki's disease was made. The regulatory authority considered the events were clinically significant (or requiring intervention). The subject was treated with aspirin, bath oil (unspecified), enoxaparin, methylprednisolone, normal immunoglobulin, ranitidine hydrochloride (Zantac), topical skin preparation (Skin cream) and thrombolytic agent (Thrombolytic agent). At the time of reporting the events were improved. The regulatory authority considered the events were possibly related to vaccination with Infanrix hexa. Additional information has been requested but could not be obtained. This case has therefore been closed.

Company comment: *Patient with Not confirmed Kawasaki disease case, as only fever is described. The time to onset is too short, less than one day. The patient had concomitant RSV infection and pneumonia that may have triggered the Kawasaki- like syndrome.*

[redacted]

This case was reported by a healthcare professional and described the occurrence of kawasaki disease in a 1-year-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline), pneumococcal vaccine unspecified (Prevenar) for prophylaxis. On [redacted] the subject received 4th dose of Infanrix hexa (unknown route and injection site), 4th dose of Prevenar (unknown route and injection site). In [redacted], 2 to 3 weeks after vaccination with Infanrix hexa and Prevenar, the subject was hospitalised with kawasaki disease. At the time of reporting the outcome of the event was unspecified. The healthcare professional considered the event was unlikely to be related to vaccination with Infanrix hexa and Prevenar. At the time of this report, no further information was available. This case was also reported by the regulatory authority ([redacted]) on [redacted], no new information was provided. Additional information has been requested but could not be obtained. This case has therefore been closed.

Company comment: *This is a not confirmed Kawasaki disease case with temporal association to the administered vaccines as the TTO is 2 weeks. There is not enough clinical evidence to assess causality.*

[redacted]

This case was reported by a regulatory authority ([redacted]Regulatory Agency #[redacted] and described the occurrence of Kawasaki's syndrome in a 5-month-old female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. The subject had no relevant medical history. Previous and/or concurrent vaccination included combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine. (GlaxoSmithKline;unknown) unknown given on [redacted]. This dose was unventful. On [redacted] the subject received 2nd dose of Infanrix hexa (unknown). On [redacted], 4 days after vaccination with Infanrix hexa, the subject developed pyrexia (above 38 deg. C), diarrhea, vomiting, decreased appetite and skin exfoliation on hands, fingers and feet. The subject was hospitalised. An echocardiogram was performed and found to be normal. A diagnosis of incomplete Kawaski disease was made. At the time of reporting the events were resolved. After the next vaccination with Infanrix hexa the events did not recur. The regulatory authority reported that the events were possibly related to vaccination with Infanrix hexa.

Company comment: *This is a case of not confirmed Kawasaki disease case, with TTO 4 days after vaccination with Infanrix Hexa, (temporally related). There is not enough evidence to assess causality (no lab test to exclude other aetiologies triggering KD)*

[redacted]

This case was reported by a regulatory authority [redacted] and described the occurrence of possible Kawasaki disease in a 12-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline), meningococcal polysaccharide vaccine group C (non-GSK) (Meningitec) for prophylaxis. On [redacted], the subject received 3rd dose of Infanrix hexa (intramuscular, unknown injection site), unspecified dose of Meningitec (intramuscular, unknown injection site). On [redacted], 1 hour after vaccination with Infanrix hexa and Meningitec, the subject experienced a mild skin eruption and fever (38,5 deg. C). Amoxicillin trihydrate (Amoxycillin) was prescribed for one week. On [redacted], the subject experienced fever (39,5 deg. C), rash at trunk lasting two days, bronchitis; Amoxicillin trihydrate + potassium clavulanate (Augmentin) was given until [redacted]. On [redacted], blood tests revealed erythrocyte sedimentation rate increased and platelet count increased. On [redacted], echocardiography showed a mild increased of left coronary diameter. On [redacted] he underwent a rheumatologic visit: diagnosis of suspected incomplete Kawasaki disease was made. Acetylsalicylic acid was prescribed. On [redacted], body temperature was normal. The regulatory authority reported that the events were clinically significant (or requiring intervention). At the time of reporting the events were improved. The vaccination course was discontinued for the next six months. The regulatory authority reported that the events were possibly related to vaccination with Infanrix hexa and Meningitec. Follow up information received on [redacted]: Subject's medical history: The subject was born after uncomplicated pregnancy at 36 weeks + 3 days of gestation from caesarean section due to foetal arrhythmia and car accident occurred to his mother. At time of birth his weight was 3030gr, EEG was normal, blood tests showed the following results: Red cells: 14160/mm3, Hemoglobin: 15,2 g/dlL, C-Reactive Protein: less than1. At 1 month of age, the subject experienced mild bronchiolitis. After that he had some infections at upper respiratory tract. He experienced fever (38 deg. C) after administration of the first dose ([redacted]) and after second dose ([redacted]) of hexavalent and anti pneumoccocal vaccines. The reporter clarified that no further information was available. Follow up information received on [redacted] Acetylsalicylic acid (30 mg) therapy was continuing. Next clinical examination in [redacted] Follow up information received on [redacted]: Despite request to follow-up, no additional information could be obtained. This case has therefore been closed.

Company comment: *Patient who develop immediately after vaccination Kawasaki like syndrome. It is unknown if other clinical manifestations where present besides rash in trunk. Concomitant Bronquitis that may have trigger KD. TTO too short (one hour after vaccination) to develop KD.*

[redacted]

This case was reported by a regulatory authority [redacted] and described the occurrence of kawasaki's disease in a male subject 19 week-old who was vaccinated with combined diphtheria,

tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine. (Infanrix hexa, GlaxoSmithKline), pneumococcal vaccines (non-gsk) (Prevenar) and rotavirus vaccine (non-gsk) (RotaTeq) for prophylaxis. Previous and/or concurrent vaccination included rotavirus vaccine (non-gsk) ;Sanofi Pasteur MSD;oral given on [redacted]. On [redacted] the subject received unspecified dose of Infanrix hexa (unknown), unspecified dose of Prevenar, On [redacted] and [redacted] the subject received 3rd dose and 2nd dose of RotaTeq (oral). On [redacted], 48 days after vaccination with Infanrix hexa, Prevenar and 2nd dose of RotaTeq; 18 days after vaccination with 3rd dose of RotaTeqthe subject experienced kawasaki's disease. The subject was hospitalised. At the time of reporting the event was resolved. In the follow up received on [redacted] it was mentioned that the subject was 19 week-old. None subject's medical history. Unfortunately no further information could be obtained about: signs and symptoms of kawasaki, lab test results or treatment.

Company comment: *This is a case of not confirmed Kawasaki disease, is not temporally associated to vaccination with Infanrix Hexa as it is more than the time risk period of thirty days, TTO is 48 days. This case is temporally associated to Rotavirus vaccination as TTO for Rotateq is 18 days.*

[redacted]

This case was reported by a regulatory authority [redacted] and described the occurrence of kawasaki disease in a 3-month-old female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline), pneumococcal vaccines (non-GSK) (Prevenar) for prophylaxis. On [redacted], the subject received unspecified dose of Infanrix hexa (intramuscular, unknown injection site), unspecified dose of Prevenar (intramuscular, unknown injection site). On [redacted], 1 day after vaccination with Infanrix hexa and Prevenar, the subject experienced kawasaki disease and macrophage activation. The subject was hospitalised. Laboratory tests were performed during hospitalisation periods, but no results were provided. On [redacted], the events were resolved. The regulatory authority reported that the events were possibly related to vaccination with Infanrix hexa and Prevenar. Follow up information received on [redacted]: On [redacted], the subject received 1st dose of Infanrix hexa (intramuscular, unknown injection site), unspecified dose of Prevenar (intramuscular, unknown injection site). On [redacted], 1 day after vaccination with Infanrix hexa and Prevenar, the subject experienced fever (39-40 deg. C) with irritability, erythematous rash on face and legs. The subject started a treatment with wide-spectrum antibiotics and was hospitalised in the care of the infectious disease care unit on [redacted]. There the subject also experienced tumefaction with pain at feet, bilateral. The subject experienced polymorphous rash, peripheral oedema and peripheral erythema Initial tests showed progressive increase of inflammation index, liver dysfunction, hypoalbuminemia, ferritin increase. An infective etiology of the adverse events was dismissed and the following tests were performed: cardiac ECHO, cranial CT scan, total body CT scan, cerebrospinal fluid analysis, dry tap (referred to bone marrow analysis) and normal concentration of vanilmandelic and

homovanilmandelic acids in urine. The suspect of Kawasaki's disease was substantiated by the following interventions, performed on [redacted]: immunoglobulin infusion, ASA administration, without any improvement of the symptoms. The subject received hemotransfusion due to marked signs of anemia. It was followed by a high-dose therapy with steroids that lead to a rapid improvement in symptoms and clinical data. Steroid therapy, then, was quickly reduced and withdrawn. After 48 hours from the suspension of the steroid therapy, the subject experienced new high fever and was hospitalised in the care of Hospital. There physicians defined the diagnosis of secondary macrophage activation syndrome in the context of an atypical form of Kawasaki's disease. The subject was treated with steroids (high dose) and cyclosporine (low dose). These therapies lead rapidly to a new improvement in symptoms and clinical data. On [redacted], the subject was discharged from hospital, in a good general condition. Then the subject was monitored periodically, always with good clinical results. Even if the subject was stable (at time of reporting), parents and physicians decided to stop any other vaccination on the subject.

Company comment: *This is a case of Incomplete Kawasaki disease. It is temporally associated to Infanrix Hexa as TTO is one day. There is also coadministration of vaccines. The narrative states that an infective etiology of KD was dismissed but the results of these test and which test were done are not available.*

[redacted]

This case was reported by a regulatory authority [redacted] and described the occurrence of maculo-papular exanthema in a 11-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) and pneumococcal vaccines (non-gsk) (Prevenar) for prophylaxis. On [redacted], the subject received an unspecified dose of Infanrix hexa (intramuscular, administration site unknown) and an unspecified dose of Prevenar. On [redacted], 1 day after vaccination with Infanrix hexa and Prevenar, the subject experienced maculo-papular exanthema at back and lower limbs, conjunctivitis, edema of hand, pedal edema, possible kawasaki disease and fever (>39 deg.C). The subject was hospitalised. The subject was treated with cephalosporins (Cephalosporin). On [redacted] the events were resolved. The regulatory authority reported that the events were possibly related to vaccination with Infanrix hexa and Prevenar. As no additional information could be obtained, the case has been closed.

Company comment: *This is a case of Incomplete Kawasaki disease, Temporally associated to Infanrix hexa and Pneumooccal vaccines as TTO is one day. There is not enough clinical evidence to relate this case to vaccination, the patient did received as treatment antibiotics, and improved. Therefore we can suspect that it may be that the patient did have in fact an infectious disease that may trigger KD.*

[redacted]

This case was reported by a regulatory authority [redacted] and described the occurrence of kawasaki disease in a 2-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine. (Infanrix hexa, GlaxoSmithKline), pneumococcal vaccines (non-gsk) (Prevnar) for prophylaxis. Concurrent medical conditions included G6PD deficiency, conjunctivitis and upper respiratory tract infection. On [redacted] the subject received unspecified dose of Infanrix hexa (intramuscular, unknown), unspecified dose of Prevnar (intramuscular, unknown). On [redacted], 2 days after vaccination with Infanrix hexa and Prevnar, the subject experienced maculo-papular exanthema on trunk, spreading to the whole body and face, diarrhea and high fever. On [redacted], the baby was hospitalised due to these symptoms. After 4 days of hospitalisation, the baby presented cheilitis, perianal desquamation, pedal edema and erythema of soles of feet with persisting fever. Kawasaki disease was suspected. Relevant test results included ECG (normal), chest X-ray on [redacted] and [redacted] (both negative), echocardiogram (mild pericardial effusion), ultrasound of the abdomen (mild fluids below liver and behind bladder as well as troponin (normal). The subject was treated with antibiotics, anti-inflammatory (Antiinflammatory), IgG (IV, 20 unt/kg) and dipyridamole (Dipiridamol). At the time of reporting the outcome of the events was unspecified. The regulatory authority reported that the events were possibly related to vaccination with Infanrix hexa and Prevnar. No additional information could be obtained and this case has been closed.

Company comment: *Patient with Incomplete case of Kawasaki Disease, that had concurrent medical conditions : G6PD deficiency and upper respiratory tract infection. Due to the concomitant infectious is unlikely that KD was trigger because of vaccination with Infanrix Hexa.*

[redacted]

This case was reported by a physician via regulatory authority [redacted] and described the occurrence of Kawasaki disease in a 4-month-old male subject who was vaccinated with synflorix (GlaxoSmithKline), combined diphtheria, tetanus-acellular pertussis, hepatitis B and inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa) for prophylaxis. The subject's medical history included acute viral bronchitis. Concurrent medications included Butamirate citrate (Sinecod), Vigantol and Clenbuterol hydrochloride (Spiropent). On [redacted] the subject received unspecified dose of Synflorix (intramuscular, unknown injection site), unspecified dose of Infanrix hexa (intramuscular, unknown injection site). On [redacted], less than one day after vaccination with Infanrix hexa and Synflorix, the subject developed fever (38.5 deg C) which lasted 2 days. On [redacted], the subject experienced itchy maculopapular rash and redness of face. On the left side of the neck, the subject experienced a painful erythematous infiltrate (5x3cm). The subject was hospitalised from [redacted] to [redacted] Relevant tests were performed during hospitalisation: ECG, echocardiography, abdominal ultrasound, neck ultrasound, x-ray thorax. The diagnosis was incomplete form

of Kawasaki disease. The subject was treated with normal immunoglobulin (Immunoglobulin), anopyrin and antibiotics. At the time of reporting the outcome of the events was unspecified. Follow up information received on [redacted]: The subject's medical history included acute viral bronchitis and catarrh. The subject was healthy at time of vaccination and had no other disease in anamnesis. According to reporter, the subject had not fully recovered from the reaction. The relation between vaccination and development of incomplete form of Kawasaki disease has been confirmed. The final diagnosis was incomplete form of Kawasaki disease initiated by vaccination with Infanrix hexa and Synflorix. At the time of reporting, the events were improved and the subject was treated in pediatric and cardiologic clinic. Next vaccinations will be performed after consultation with vaccination center. Follow up information received on [redacted]: Laboratory test results included: CRP increased: 217 mg/L; White blood cells: increased; Hepatic enzymes: increased; Pandy's test increased: 2g/L Follow up information received on [redacted]: Hospital report received. On [redacted], the subject was admitted due to fever, exanthema and cervical lymphadenopathy on the left side. At examination, he was grumpy; no alteration of the general health state; maculopapular rash on the neck and trunk; papules on the lower limbs; normal vascularization and hydration; warm peripheral parts; ENT without any discharge; round isoscoric pupils; reaction to light positive; clear oral cavity; suffused nasopharynx; tonsils without content; painful packet of lymph nodes along the left sternoclenomastoid muscle sized 3x4 cm; no other enlarged lymph nodes; clear vesicular breathing without side phenomena or attenuation. Regular heart action; two delimited heart sounds; no audible murmur; abdomen in the level of thorax; soft; well palpable; no peritoneal signs; liver and spleen are not enlarged; no meningeal signs; testes in correct position; great fontanel sized 2x1 cm in the level of the skull. Laboratory examinations presented elevation of the inflammatory markers, pyuria according to urine examination but control urine sample was negative. Cervical lymph nodes were without colliquation according to ultrasound. Intravenous antimicrobial therapy was initiated using the crystallic penicillin. Fever still persisted; control blood samples presented progression of the inflammatory parameters. Chest x-ray, ultrasound of the lymph nodes and abdomen and ENT consultation were performed in terms of the differential diagnosis to exclude infectious foci. All examinations were normal apart from the persistent stable lymphadenopathy. Viral serology was negative (Toxoplasma, Listeria, Parvovirus B19, EBV, CMV, VZV, Enterovirus, Adenovirus, HSV). Heart ultrasound was performed several times during hospitalization and showed no findings. Antibiotics were switched to intravenous administration of Zinacef. Control samples presented again rise of the inflammatory parameters, anemia and low albumin level. Lumbar centesis was performed with serous finding. Heart ultrasound was normal. Clinical and laboratory findings evidenced the incomplete form of the Kawasaki syndrome. Therefore immunoglobulins were administered on the 7th day at dose 2 g/kg and Anopyrin therapy was initiated at dose 100 mg/kg/day. Clinical condition improved after administration of IVIG. The subject did not have any fever. Febrile peak occurred again on the 9th day with occurrence of multiple watery diarrheas (unknown etiology). The antibiotics therapy was terminated on the 11th day. The subject remained febrile; control samples presented again elevation of the inflammatory parameters, liver tests and thrombocytosis. Peeling of the skin on fingers occurred on the 12th day on the upper limbs and later on the lower limbs. Clinical state evidence the recurrence of the Kawasaki syndrome and therefore the second dose of immunoglobulins intravenously was

administered on the 14th day at dose 2 g/kg. The subject remained without fever after that. General clinical condition improved gradually. The subject was active, happy and cardiopulmonary stable. He had a good appetite and gained some weight. Control laboratory tests prior discharge presented still thrombocytosis, elevation of liver tests. Inflammatory markers dropped. Abdominal ultrasound presented no signs of hepathopathy. Anopyrin was administered at reduced dose. Repeated control cardiology examination and heart ultrasound presented normal findings. After consultation with the vaccination centre it could not have been excluded that the vaccination (Inflanrix Hexa + Synflorix) could have been the trigger for the Kawasaki syndrome. Further vaccination was not recommended. The subject was discharged home in good general condition, without fever and cardiopulmonary compensated. The final diagnosis at discharge was mucocutaneous syndrome of the lymph nodes (Kawasaki syndrome). The subject was treated with normal immunoglobulin (Immunoglobulin), anopyrin, cefuroxime sodium (Zinacef), midazolam, lactic-acid-producing organisms (Lactobacillus), paracetamol (Paralen), methylprednisolone sodium succinate (Solumedrol), ibuprofen (Nurofen), normal immunoglobulin (Flebogamma) and plasma-lyte (Plasmalyte). Subsequently, the subject was examined in 18 June 2012. Worse visibility of the coronary arteries; dilated; descending dilations at times. Greater aneurysms were not detected within the visible segments of arteries. On [redacted], laboratory tests included: WBC: 11.00; RBC: 4.46; HB: 109.0; HCT: 0.331; MCV: 74.1; MCH: 24.5; MCHC: 331.00; Plt: 583, Neutrophils: 17.20%, Eosinophils: 3.40%, Basophils: 1.700%, Monocytes: 7.70%, Lymphocytes: 70.00%, Alb: 46.4; AST: 0.77; ALT: 0.41; Bil: 3.0, GMT: 0.49, No complaints since the last examination.

Company comment: *Patient that develop Incomplete Kawasaki disease. TTO is too short to establish causality with vaccination (Infanrix hexa and Synflorix). The patient did have history of viral bronquitis and pyuria. In lab test received, Lymphocytes are still high. Viral test for some virus were performed, but still lymphocytes are high. It is not possible to conclude that the KD was triggered by vaccination because of the short time to onset and lab test found.*

[redacted]

This case was reported by a physician via a sales representative and described the occurrence of kawasaki disease in a 8-week-old female subject who was vaccinated with live attenuated human rotavirus vaccine (Rotarix, GlaxoSmithKline), combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa) and pneumococcal vaccines (non-gsk) (Prevenar 13) for prophylaxis. On an unspecified date, the subject received unspecified dose of Rotarix (unknown). Within hours of vaccination with Rotarix, during the night, the subject experienced fever which lasted for 5 days. The subject was hospitalised because of his bad condition. The subject was diagnosed with kawasaki disease. At the time of reporting the subject was totally healed. Follow-up information received by a physician on [redacted]: On an unspecified date the subject received unspecified dose of Rotarix (unknown), unspecified dose of Infanrix hexa (unknown route and injection site), unspecified dose of Prevenar 13 (unknown route and injection site). Within 24 hours, less than one day after vaccination with Infanrix hexa, Prevenar 13 and Rotarix, the subject experienced fever (up to 39-40 Deg. C). Follow-up information

received by a physician on [redacted]: On [redacted], the subject received 1st dose of Rotarix (oral), 1st dose of Infanrix hexa (intramuscular, unknown injection site), 1st dose of Prevenar 13 (intramuscular, unknown injection site). In [redacted], within 24 hours of vaccination with Infanrix hexa, Prevenar 13 and Rotarix, the subject experienced fever which lasted for 5 days, no clear focus. On [redacted], Kawasaki disease was diagnosed. At an unspecified time after vaccination with Infanrix hexa, Prevenar 13 and Rotarix, the subject experienced rash on hand palms and food soles then generalized rash, conjunctivitis, cervical lymphadenitis and stomatitis. The subject was hospitalised and the physician considered the events were disabling and life threatening. A cardiac echography showed a slightly widened coronary. On [redacted], Kawasaki disease was improved. At the time of reporting the outcome of rash, generalized rash, conjunctivitis, cervical lymphadenitis and stomatitis was unspecified. The vaccination course with Infanrix hexa, Prevenar 13 and Rotarix was discontinued. The physician considered fever and Kawasaki disease were probably related to vaccination with Rotarix, Infanrix hexa and Prevenar 13.

Company comment: *The patient had a classic KD after vaccination with Rotavirus, Infanrix Hexa and pneumococcal vaccines. No lab tests to exclude viral/ bacterial infections were done. TTO too short after vaccination (the same day) to establish causality to the vaccines given.*

[redacted]

This case was reported by a physician via a regulatory authority [redacted] and described the occurrence of Kawasaki disease in a 12-month-old female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline), pneumococcal vaccines (non-gsk) (Prevenar 13) for prophylaxis. On [redacted], the subject received unspecified dose of Infanrix hexa (.5 ml, intramuscular, unknown site of injection), unspecified dose of Prevenar 13 (.5 ml, intramuscular, unknown site of injection and batch number). In [redacted], less than one week after vaccination with Infanrix hexa and Prevenar 13, the subject experienced fever and was treated with paracetamol (Tachipirina) on [redacted]. On [redacted] 14 days after vaccination with Infanrix hexa and Prevenar 13, the subject experienced kawasaki disease described as scarlatiniform rash, cervical lymphadenopathy, edema of hands and feet, oral mucositis and hyperemic conjunctiva. The subject was hospitalised. On [redacted], the C-reactive protein level of the subject was measured and gave a result of 14.5. On [redacted], the events were resolved. At the time of reporting, the fever outcome was unspecified. The regulatory authority reported that the Kawasaki disease was possibly related to vaccination with Infanrix hexa and Prevenar 13. Follow-up information received on [redacted]: On [redacted], the subject was treated with amoxicillin trihydrate + potassium clavulanate (Augmentin) and was hospitalized. During, her hospitalization an echocardiogram showed an expansion of 3 mm and a tickening of her left coronary artery. The subject

was treated with lysine aspirin (Cardirene). Rash and fever disappeared and clinical conditions improved. On [redacted], the physical examination was normal and the subject was discharged.

Company comment: *Patient with Classic KD, no lab tests to exclude viral/bacteriological infectious diseases. TTO was less than a week after vaccination with Infanrix hexa and Pneumococal vaccines. Not possible to exclude or conclude causality to vaccines given.*

[redacted]

This case was reported by a regulatory authority [redacted] and described the occurrence of Kawasaki disease in a 7-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. The subject's sister had fever, cough and running nose a week prior the subject's vaccination. Historic medical conditions included heart murmur. Concurrent medical conditions included abnormal single palmar crease, hearing problem and heart murmur. Concurrent vaccination included bacillus calmette-guerin vaccine (non-gsk, left deltoid) given on an unspecified date, combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) given on [redacted] pneumococcal vaccines (Prevenar 13,non-gsk) given on [redacted]. On [redacted], the subject received unspecified dose of Infanrix hexa (intramuscular, unknown site of injection and batch number). On [redacted], less than one day after vaccination with Infanrix hexa, the subject experienced fever (Maximal temperature 39.5 deg.C). On [redacted], two days after vaccination with Infanrix hexa, the subject experienced redness of eyes and lips. On [redacted] three days after vaccination with Infanrix hexa, the subject experienced irritability and poor oral feeding. The subject was hospitalized for prolonged fever. It was also noted that the subject experienced bacillus calmette-guerin erythema on left deltoid. In [redacted], within a week after vaccination with Infanrix hexa, the subject experienced generalized maculo-papular rash and rash on penile area. On [redacted], the subject was discharged stable with a diagnosis of Kawasaki disease. On [redacted], the subject was followed as outpatient for Kawasaki disease with residual transaminitis and thrombocytosis.

Company comment: *Patient who develop Incomplete KD less than one day after vaccination with Infanrix Hexa. Concurrent vaccinations were BCG non GSK vaccine and pneumococcal vaccine. No lab tests to exclude viral/bacterial infectious diseases.*

[redacted]

This case was reported by a physician via a regulatory authority [redacted] and described the occurrence of Kawasaki disease in a 8-month-old

female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline), pneumococcal vaccines (non-gsk) (Prevenar 13) for prophylaxis. On [redacted] the subject received 2nd dose of Infanrix hexa (intramuscular, unknown injection site), 2nd dose of Prevenar 13 (intramuscular, unknown injection site). On [redacted], 80 days after vaccination with Infanrix hexa and Prevenar 13, the subject experienced Kawasaki disease, fever, mucositis, upper respiratory tract inflammation, conjunctivitis and rash on trunk, lower limbs and palms. The subject was hospitalised. The subject was treated with paracetamol (Tachipirina), lysine aspirin (Cardirene) and normal immunoglobulin (Immunoglobulin). On [redacted], the events were resolved. Follow-up information was received on [redacted] Family and medical history included nothing relevant. Since [redacted] the subject had fever regardless of antibiotic therapy with amoxicillin. The subject was hospitalized from [redacted] for suspected Kawasaki disease. On arrival at ER, she was in good general conditions. Cardiovascular parameters: normal; abdomen: normal; Chest: coarse airborne noise, occasional gasps and large bubbles, body temperature: 40,6 degC. Additional test results have been added. During hospitalization, she was treated with Augmentin and Cardirene. The subject was discharged in good conditions on [redacted] with prescription of Cardirene 120 mg 4 times/day. No further information available. Case closed.

Company comment: *Incomplete KD case, coadministration of Infanrix Hexa and Prevenar, TTO 80 days. No temporal association to vaccination.*

[redacted]

This case was reported by a regulatory authority [redacted] and described the occurrence of kawasaki disease in a 7-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type B vaccine (Infanrix hexa, GlaxoSmithKline), live attenuated human rotavirus vaccine (Rotarix) for prophylaxis. The subject was a full term baby and his medical history included large pda with pulmonary hypertension S/P and ligation, left chylothorax S/P, chest tube insertion, and hypospadias. Historic vaccination included bacillus calmette-guerin vaccine (non-gsk) given on [redacted] with injection site erythema still present; pneumococcal vaccines (Prevenar 13, non-gsk) given on [redacted]. On [redacted], the subject received unspecified dose of Infanrix hexa (unknown route, injection site and batch number), unspecified dose of Rotarix (oral, unknown batch number). On [redacted], 26 days after vaccination with Infanrix hexa and Rotarix, the subject experienced fever (max 39 Deg. C, daily spikes but no rigors) and decreased appetite. On [redacted], 28 days after vaccination with Infanrix hexa and Rotarix, the subject was seen at the emergency department due to fever and throat infection. The subject was diagnosed with upper respiratory tract infection and discharged with paracetamol and Choline salicylate oral gel. On [redacted] 29 days after vaccination with Infanrix hexa and Rotarix, the subject experienced maculopapular rash (over face, bilateral upper limbs, lower limbs and feet), light lip redness without strawberry tongue and bilateral non-

exudative conjunctivitis. On [redacted], the subject was seen at the emergency department. On examination, liver Edge was palpable about 2cm below costal margin and the subject had slightly puffy hands. The subject was still active. The subject was hospitalised and the regulatory authority reported that the events were clinically significant (or requiring intervention). On [redacted], blood culture was negative, nasopharyngeal airways was negative, antistreptosilin titer was normal, white blood cell count of 10.6, haematocrit level of 33, 9% of monocytes, 6% of eosinophiles, erythrocyte sedimentation rate of 33, renal sodium of 137, a C-reactive protein level of 24 and 20 white blood cells in urine analysis The subject was treated with normal immunoglobulin (IVIG). The subject was discharged stable after being afebrile for more than 48 hours with a diagnosis of Kawasaki disease. On [redacted], the subject had fever (max 39.5 Deg. C) without cough, vomiting or nausea. The subject was readmitted on [redacted]. On [redacted], liver function test showed a level of 85 of proteins, alanine aminotransferase level of 41, negative nasopharyngeal airways, erythrocyte sedimentation rate of 33, white blood cell count of 20.53, platelet count of 529, 49% of neutophiles, 7% of monocytes, renal sodium of 133, and C - reactive protein level of 4.4. The subject was treated with omeprazole, aspirin and ampicillin trihydrate (Ampicillin). On [redacted], all the events were resolved. Post patent ductus arteriosus ligation was without leak. Proximal coronary arteries size was normal. The subject was discharged stable with diagnosis of fever And Kawasaki Disease.

Company comment: *Classic KD case, concurrent throat infection. Coadmnisitration of Infanrix Hexa and Rotarix vaccine. TTO in the risk period as it is less than 30 days (26 days). Throat infection may have trigger KD case.*

[redacted]

This case was reported by a regulatory authority ([redacted]) and described the occurrence of kawasaki disease in a 15-month-old female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type B vaccine (Infanrix hexa, GlaxoSmithKline), meningococcal polysaccharide vaccine group c (non-gsk) (Menjugate) for prophylaxis. On [redacted], the subject received 3rd dose of Infanrix hexa (intramuscular, unknown injection site), 1st dose of Menjugate (intramuscular, unknown injection site). On [redacted], 30 days after vaccination with Infanrix hexa and Menjugate, the subject experienced kawasaki disease, hyperpyrexia and erythema. The subject was hospitalised on [redacted]. The subject was treated with antipyretic, cortisone and normal immunoglobulin (Immunoglobulin). On [redacted], the events were resolved and the subject was discharged. Follow-up information received on [redacted]: Concurrent vaccination included 1st dose of combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type B vaccine (GlaxoSmithKline); 1st dose of meningococcal polysaccharide vaccine group c (non-gsk) both given on [redacted]. On [redacted], the subject received 2nd dose of Infanrix hexa (unknown route, injection site and batch number). 2nd dose of Menjugate (unknown route, injection site and batch number). At an unspecified time after vaccination with 2nd dose of Infanrix hexa and Menjugate, the subject

experienced fever for 24 hours. On [redacted], the subject received 3rd dose of Infanrix hexa (intramuscular, unknown injection site), 3rd dose of Menjugate (intramuscular, unknown injection site). On [redacted], 30 days after vaccination with Infanrix hexa and Menjugate, she experienced high fever unresponsive to paracetamol. Approximately 48 hours later she had skin erythemato-papular pruritic rash on hands and feet which then involved trunk, limbs and face. On [redacted], Bentelan was given and skin symptoms improved, but fever did not resolve. After that, 1 month after vaccination with Infanrix hexa and Menjugate, she experienced bilateral conjutivitis which resolved quickly, swelling of hands and feet, irritability, mild meningism. She was treated with paracetamol but fever persisted. Physical examination on admission on [redacted] showed a body weight of 9,85 kg, severe irritability, mild meningism, generalised erythemato-papular rash, edema on hands and feet and hyeperemia of pharynx. A blood test was also performed. Clinical picture was considered compatible with diagnosis of Kawasaki syndrome. Immunoglobulins IV were administered. Fever disappeared on [redacted]. Skin signs resolved too. The subject was discharged on [redacted] with a home therapy of acetylsalicylic acid tab 25 mg.

Company comment: *Classic case of KD, coadmnistration of Infanrix hexa and meningococcal vaccine. TTO is 30 days, temporally associated to vaccines given. No lab test results to exclude infectious diseases that can trigger KD.*

[redacted]

This case was reported by a regulatory authority ([redacted]) and described the occurrence of Kawasaki disease in a 6-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type B vaccine (Infanrix hexa, GlaxoSmithKline) and pneumococcal vaccine (Prevenar 13, non-GSK) for prophylaxis. The subject's father was allergic to aspirin. The subject had no travel history, but was in contact with a caregiver who had fever and runny nose. His feeding was reduced and there was no history of fits. Concurrent vaccination included a dose of combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and Haemophilus influenzae type B vaccine (Infanrix IPV/HiB, GlaxoSmithKline) and pneumococcal vaccine (manufacturer unspecified) given on 4 November 2013 and another dose of combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and Haemophilus influenzae type B vaccine (Infanrix IPV/HiB, GlaxoSmithKline) and live attenuated human rotavirus vaccine (Manufacturer unspecified) given on [redacted]. On [redacted], the subject received unspecified dose of Infanrix hexa (unknown injection site and batch number) and unspecified dose of Prevenar 13 (unknown injection site and batch number). On [redacted], 21 days after vaccination with Infanrix hexa and Prevenar 13, the subject was taken to the emergency department and experienced fever (40.3 Deg. C) for 3 days. No chills and rigors were observed. On [redacted], the subject observed papular rash over the limbs and runny nose for 2 days. There was no cough, sobbing, foul smelling urine, abdominal pain or neck stiffness. The subject was hospitalised and treated with ceftriaxone sodium (Rocephine). The subject still had fever despite the treatment

with the antibiotics. The subject underwent full blood count, urine and blood culture and polymerase chain reaction, but no significant findings were observed. On [redacted], rashes were note on trunk It was not confirmed weather they were heat rash or not. There was no puffiness of extremities, redness of eyes or throat ulcer. The subject underwent lumbar puncture and was given intravenous hydration every 6 hours. On [redacted], the subject experienced redness of eyes with no purulent discharge, redness of lips, strawberry tongue, polymorphous rashes over the body, peeling of fingers, left arm lymphadenopathy and right cervical lymphadenopathy. The subject was treated with Vaseline lip therapy, sodium chloride eye drop, paracetamol, Ibuprofen syrup and zinc oxide. On [redacted], the subject experienced bilateral non- purulent conjunctivitis and polymorphous rashes on trunk. There was no peeling of fingers or lymphadenopathy. The regulatory authority reported that the events were clinically significant (or requiring intervention). The subject was treated with immunoglobulin (IVIG) and high doses of asprin. Fever resolved after treatment with IVIG. The subject developed periorbital swelling after high doses of aspirin. There was no angioedema, shortness of breath or rashes. The subject was continued with low doses of aspirin. No further reactions were seen. On [redacted], the subject underwent echography which showed mildly dilated left coronary artery and left anterior descending artery. The subject was discharged with a diagnosis of Kawaski disease. At the time of reporting, the events were resolved.

Company comment: *Classic KD case temporally associated to vaccines given Infanrix Hexa, Pneumococal vaccines. We cannot exclude or confirm that vaccination did trigger KD.*

[redacted]

This case was reported by a pharmacist via a regulatory authority [redacted]) and described the occurrence of kawasaki disease in a 4-month-old male subject who was vaccinated with live attenuated human rotavirus vaccine (Rotarix liquid formulation, GlaxoSmithKline), combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type B vaccine (Infanrix hexa) and pneumococcal vaccine (Prevenar, non-GSK) for prophylaxis. Concurrent vaccination included 1st doses of live attenuated human rotavirus vaccine (Rotarix liquid formulation, GlaxoSmithKline), combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type B vaccine (Infanrix hexa) and pneumococcal vaccine (Prevenar, non-GSK), given on [redacted]. On [redacted], the subject received 2nd doses of Rotarix liquid formulation (oral), Infanrix hexa (unknown route, site of injection and batch number) and Prevenar (unknown route, site of injection and batch number). On [redacted], 12 days after vaccination with Infanrix hexa, Prevenar and Rotarix liquid formulation, the subject experienced upper respiratory tract infection, which had resolved. The subject was weaned from [redacted]. On [redacted] the subject experienced fever (39 Deg. C) occurred with conjunctivitis. On [redacted], the subject underwent cardiopulmonary reanimation. Under extracorporeal membrane oxygenation resolution was obtained. The subject was retrospectively diagnosed with Kawasaki syndrome, with

massive coronary aneurism with cardiac ischemia and infarction. The subject was hospitalised and the regulatory authority reported that the events were life threatening. At the time of reporting, the events were unresolved. The regulatory authority reported that the events were possibly related to vaccination with Rotarix liquid formulation, Infanrix hexa and Prevenar. Follow-up information received on [redacted] from the regulatory authority: The events upper respiratory tract infection, coronary artery aneurysm and cardiac ischemia were confirmed by the regulatory authority. On [redacted], the subject experienced coronary artery aneurysm with cardiac ischemia and infarction. At the time of reporting, outcome of coronary artery aneurysm, cardiac ischemia and cardiac infarction was unknown. Follow-up information received on [redacted] from the regulatory authority: The subject had giant coronary aneurysm and obliteration of Ramus interventricularis anterior in the context of a Kawasaki syndrome. On the day of admission, asystolia occurred, most likely in the context of a cardiac underperfusion, requiring a mechanical medicamentous reanimation and transfer to the extracorporeal membrane oxygenation. In the further course due to left ventricular functional impairment, the subject was switched to a left ventricular assist device. In addition the subject had right ventricular failure which caused hepatic and renal dysfunction. In the context of a gastrointestinal infection, deterioration of his general condition occurred with deterioration of the coagulation. On [redacted], the subject died after stopping medical measures due to extended cerebral infarction after complete obliteration of the Arteria carotis interna left by an embolus. It was unknown whether an autopsy was performed or not.

Company comment: *Patient developped 12 days after vaccination upper respiratory tract infection and not confirmed KD (Newburger, 2004). Patient had as complication a massive coronary aneurism with cardiac ischemia and infarction. Temporally associated to Rotavirus, Infanrix Hexa and Pneumococcal vaccines. No lab tests shown to exclude infectious etiology. This is a fatal case where it is unknown whether an autopsy was performed. Due to the lack of lab tests information, it is not possible to exclude other etiologies that may trigger KD, it is not possible either to exclude vaccination due to the time to onset. The concomitant respiratory infection may have trigger KD too.*

[redacted]

This case was reported by a physician, via a GSK sales representative, and described the occurrence of Kawasaki disease in a female subject of about 4 or 5 months old who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) and pneumococcal vaccine (Prevenar, non-gsk) for prophylaxis. Medical conditions and concurrent medications, if any, were unspecified. The subject was born in 2013. On [redacted], at the age of 4 months, ie after the age of 2 months (inappropriate age at vaccine administration according to the French recommended immunization schedule), the subject received a 1st dose of Infanrix hexa (batch, route and injection site unknown) and a 1st dose of Prevenar (batch, route and injection site unknown). In [redacted], about 1 month after vaccination with Infanrix hexa and Prevenar, the subject presented with Kawasaki disease. On [redacted] the subject was treated with immunoglobulin (Tegeline). This case was assessed as medically serious by GSK. At the time of reporting ([redacted], the outcome of Kawasaki

disease was unspecified. The reporter's assessment for Kawasaki disease was unspecified. Upon follow up received on [redacted] from the physician: The physician considered Kawasaki disease as unrelated to vaccination with Infanrix hexa and Prevenar. No more information expected. Case closed.

Company comment: *Patient with not confirmed KD, after vaccination with Infanrix Hexa and Pneumococcal vaccines. Time to onset about a month after vaccination. No lab tests to exclude other etiologies that may trigger KD case.*

[redacted]

This case was reported by a regulatory authority ([redacted] and described the occurrence of Kawasaki syndrome in a 10-week-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Concurrent vaccination included pneumococcal vaccines (non-GSK manufacturer) given on an unspecified date. In [redacted] the subject received unspecified dose of Infanrix hexa (unknown). On [redacted], 1 week after vaccination with Infanrix hexa, the subject experienced kawasaki syndrome, generalized maculopapular rash and fever. The subject was hospitalised. At the time of reporting the events were improved. Clarification has already been required for the reason why Prevenar 13 has been considered as concomitant and not co-suspect.

Company comment: *Patient with Not confirmed KD case. TTO one week after vaccination with Infanrix Hexa. Cosuspect vaccine was Prevenar 13. No lab tests to exclude other causes that may trigger KD.*

[redacted]

A physician reported the occurrence of Kawasaki syndrome in a 14-month-old female who was vaccinated with diphtheria-tetanus-pertussis(a)-poliomyelitis-hepatitis B/haemophilus influenzae b vaccine (Infanrix hexa) for prophylaxis. Co-suspect vaccination was pneumococcal vaccine (Prevenar, by Wyeth) This report was received from the regulatory authority ([redacted]). The subject's past medical history included three previous vaccinations with diphtheria-tetanus-pertussis(a)-poliomyelitis-hepatitis B/haemophilus influenzae b vaccine in early 2002, which were well tolerated. On [redacted] the subject received the fourth dose of diphtheria-tetanus-pertussis(a)-poliomyelitis-hepatitis B/haemophilus influenzae b vaccine, lot number 21H0099, and the first dose pneumococcal vaccine, lot number 62706, contralaterally. Both vaccinations were intramuscularly administered. One day post vaccination on [redacted] the subject developed Kawasaki syndrome. She was hospitalised and treated with acetylsalicylic acid. The symptoms were acute for one week and improved thereafter. Several examinations were made both in medical practice and in hospital. Other high-febrile exanthematous diseases were excluded. At the time of reporting the reporter considered the subject to be recovered but mentioned still outstanding final examinations.

Company comment: *Patient with not confirmed KD case. TTO one day after vaccination with Infanrix Hexa, cosuspect vaccine is Prevenar. No enough clinical evidence to assess this case to Infanrix Hexa vaccination.*

[redacted]

This case was reported by a regulatory authority [redacted] (vaccines, biologicals) [redacted] and described the occurrence of atypical Kawasaki disease in a 3-month-old female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Co-suspect vaccinations included pneumococcal vaccine (Prevenar, Wyeth) and rotavirus vaccine (non-GSK) (RotaTeq, Sanofi Pasteur MSD). The physician's report to the authority, as well as the hospital report only mentioned RotaTeq. Infanrix hexa and Prevenar were only mentioned by the authority with reference to a telephone note. Previous vaccinations with the first doses of combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline), pneumococcal vaccine (Prevenar, Wyeth) and rotavirus vaccine (RotaTeq, Sanofi Pasteur MSD) were given on [redacted]. Previous vaccinations have been well tolerated. On [redacted] the subject received the second dose of Infanrix hexa (0.5 ml, unknown) in combination with the second dose of Prevenar (0.5 ml, unknown) and the second dose of RotaTeq (0.5 ml, oral). Approximately nine days post vaccination with Infanrix hexa, Prevenar and RotaTeq, on [redacted], the subject experienced atypical Kawasaki disease. The event was confirmed by antibiotic resistant fever, inflammatory parameters, exanthema, thrombocytosis, skin scaling on the fingers and response to therapy. By differential diagnosis sepsis, meningitis and other bacterial infections have been excluded. On [redacted] the subject was hospitalised for atypical Kawasaki disease for nine days. Anamnesis: On [redacted] the subject experienced signs of disease with increased body temperature up to 39.1 degC, sleepiness, whimpering, reduced food intake and reduced general condition. On [redacted] the subject experienced exanthema with small spots on the knees and on the neck which generalised and increased in size during course of time. On [redacted] the subject experienced greenish stool. On admission to hospital, on [redacted], the subject was in reduced general condition, good nutritional condition and good nursing treatment. The subject showed refusal to eat food, dryness of mucous membranes, pallor of the moth-nose triangle with livid discoloration, confluent macular exanthema with an emphasis towards the trunk, immediate adduction and bending of the limbs towards the upper part of the body when bending the head, state of agitation with jumpiness, normal reactivity of the pupils, normal tympanic membranes, purulent conjunctivitis both eyes (left more than right) with conjunctival hemorrhage both sides, unsteady soft systolic murmur, auscultatory normal lungs, soft abdomen without signs of hepatosplenomegaly, of pathological resistances or of pain on pressure, and without abnormal bowel sounds. Laboratory examinations showed increased inflammatory parameters and thrombocytosis. The subject showed no infection in blood culture, CSF culture, urinalysis, pharyngeal swab, eye swab and stools examination except moderate amount of

Staphylococcus aureus in stool. Electrocardiogram (ECG) showed no conduction or repolarisation disorder. Abdominal and cranial sonography, as well as thoracic X-ray, was normal. Echocardiogram showed small pericardial effusion left, but no signs of coronary aneurism. The subject was initially treated for suspected sepsis with gentamicin sulphate (Gentamycin), ampicillin trihydrate (Ampicillin) and ceftriaxone (Ceftriaxon), but fever persisted and general condition improved only slightly. Additionally the subject received infusion therapy due to refusal to eat. Generalised exanthema improved and was finally resolved on [redacted]. Greenish stool was resolved on [redacted], associated with improved consistence of stools and improved feeding / drinking behaviour. The hospital physician(s) diagnosed atypical Kawasaki disease due to persistent fever and persistent increase of inflammatory parameters and considered that atypical Kawasaki disease might be related to previous vaccination with RotaTeq. On [redacted] the subject was treated once with normal immunoglobulin (Immunoglobulin G). Additionally, the subject received treatment with aspirin (ASS) at 3 x 50 mg daily, followed by 30 mg once daily for another six weeks. Purulent conjunctivitis improved quickly on treatment with ecolicin ophthalmic ointment. The subject was discharged from hospital on [redacted] in good general condition without fever for further treatment. On an unknown date in October, post discharge from hospital, the subject experienced scaling of skin of finger tips, observed by the subject's parents. Follow-up echocardiogram, performed on [redacted], still showed small pericardial effusion left and a course of vessels of the main trunk of the left coronary artery which was considered to look a little bit suspicious. After about 14 days, on an unknown date in [redacted], atypical Kawasaki disease was resolved. The events did not recur without timely relationship to vaccination with RotaTeq. The vaccination courses with Infanrix hexa, Prevenar and RotaTeq were discontinued. No further information will be available.

Company comment: *Patient with Incomplete KD case. TTO nine days after Infanrix Hexa, Pneumococcal vaccines and Rotavirus vaccine. Stool exam: Staphylococcus aureus moderate amount. No infection in blood culture. Staphylococcus aereus was found in stool, that can indicate a possible infectious aetiology that may have trigger KD, besides the patient had greenish stool and signs of dehydratation.*

[redacted]

This case was reported by a regulatory authority ([redacted] (vaccines, biologicals)[redacted] and described the occurrence of Kawasaki's disease in a 4-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline), for prophylaxis. Co-suspect vaccination included pneumococcal vaccine (Prevenar, Wyeth) and rotavirus vaccine (non-gsk) (RotaTeq, Sanofi Pasteur MSD). The physician's report to the authority, as well as the hospital report only mentioned RotaTeq. Infanrix hexa and Prevenar were only mentioned by the authority with reference to a telephone note. Concurrent medical conditions included persistent foramen ovale. First vaccination with Infanrix hexa, Prevenar and RotaTeq was given on [redacted]. On [redacted] the subject received 2nd dose of Infanrix hexa (unknown route and application site), 2nd dose of Prevenar (unknown route and application site), 2nd dose of RotaTeq (oral). In the

middle of [redacted], less than one week after vaccination with Infanrix hexa, Prevenar and RotaTeq, the subject experienced diarrhea, which was partly watery. Since [redacted] the subject had high fever up to 40 degC. The subject was vomiting once. On [redacted] the subject was hospitalised for 13 days and the regulatory authority reported that the events were life threatening. When admitted, the subject showed high fever, reduced general condition, good nutritional and nursing condition, pale skin colour, halonated eyes, centralised circulation with cool extremities, recapillarisation time 3 to 4 seconds, reduced vigilance, adequate reaction to pain stimuli, meteorism, redness of tonsillar ring and exsiccation, but otherwise normal pediatric state.. Diarrhea was greenish, watery and foul-smelling. Acute gastroenteritis was suspected and treatment with lactic-acid-producing organisms (Lactobacillus) and dextrose + electrolytes (Glucose + electrolytes) was started. Because of infection signs the subject received ceftriaxone (Ceftriaxon). Symptoms and laboratory values improved (tendency to normalisation) and fever decreased to 38 degC on [redacted]. On [redacted] the subject developed macular papular exanthema, at first on the extremities, which transiently disappeared on pressure. The subject was drinking well and intravenous treatment was stopped on [redacted]. Antibiotic was changed to cefpodoxime proxetil (Podomexef). On [redacted] fever, diarrhea and inflammatory parameters worsened. Despite good general condition, treatment was changed to cefepime (Maxipime) and vancomycin, with supporting dextrose + electrolyte infusion, because recurrent infective cause was suspected. On [redacted] exanthema expanded and partly became cockade-like. Further examinations for focus search showed negative findings. On [redacted] the subject further stabilised with decreasing temperatures and decreasing inflammatory parameters. On [redacted] the subject had intermittent restlessness with questionable pain, which was ascribed to diarrhea. In the morning of [redacted] the subject was pale and in bad condition, but stabilised after stimulation, with good recapillarisation. Heart and lung were auscultatory normal, liver was palpable 3 cm below the costal arch, spleen was not palpable and the abdomen was soft. In the afternoon the subject developed apnea on the mother's arm and became asystolic. Immediate cardio-pulmonary reanimation and emergency treatment with erythrocyte concentrate were without success. At 16:37 all measures were stopped. The subject was retrospectively diagnosed with sudden cardiac death, ventricular myocardial infarct, coronary arteritis and Kawasaki's disease, although the subject showed no diagnostic criteria for the latter besides fever and intermittent exanthema. A triggering by the recently administered rotavirus vaccine had to be examined. An autopsy was performed on [redacted]. Within Anamnesis the autopsy report mentioned that there was a highly positive EBV IgM and the suspect of severe connatal immune defect. Cause of death was a distinct coronaritis within the frames of Kawasaki syndrome, with beginning coronary arterial aneurysm and focal inflammatory affection of left-ventricular myocard, a complete lumen obliterating thrombus of Ramus interventricularis anterior and its branches (Ramus diagonalis) and a left ventricular myocardial infarction. Secondary findings included an accessory spleen of 1.5 cm diameter and ectopic endocrine pancreas tissue (1.1x1.0x0.3 cm) one cm aboral of papilla duodeni major. Follow-up information was received on [redacted]. Histopathological examination of the coronary vessel walls showed infiltration with CD4+, CD34+ and CD31+. No further information will be available.

Company comment: *Not confirmed Kawasaki disease. Patient who develop fever, diarrhoea and probable gastroenteritis less than a week after vaccination with Infanrix hexa, Pneumococcal vaccines (Non GSK), and Rotavirus vaccine (Non GSK). Patient get intermittent erythema, palpable liver 3 cm below costal arch, and high fever after hospitalization and treatment with antibiotics. Patient get a worst condition, with bad recapilarisation, and fever, and had apnea and sudden cardiac death. Medical conditions of this patient were persistent foramen ovale, and suspect of connatal immune defect. Autopsy report provides highly positive results of EBV IgM and the cause of death as a distinct coronarteriis within the frame of Kawasaki syndrome with beginning coronary arterial aneurysm and focal inflammatory affection of left ventricular myocardium, a complete lumen obliterating thrombus of Ramus interventribularis anterior and its branches and a left ventricular myocardial infarction. Kawasaki disease was suspected due to intermittent erythema and fever. Patient did have coronarteritis within the frames of Kawasaki disease. Due to the short time to onset after the vaccines, the events are temporally associated to vaccination. The autopsy report of Epstein Barr Virus higly positive IgM may have been a trigger to develop KD, although a causal relationship to vaccination cannot be excluded.*

[redacted]

This case was reported by a physician and described the occurrence of Kawasaki syndrome in a 3-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. This same case was also received from a [redacted] regulatory authority ([redacted]). On [redacted] the subject received the first dose of Infanrix hexa (0.5 ml, unknown). Less than one month post vaccination with Infanrix hexa, on an unknown date in [redacted], the subject experienced Kawasaki syndrome. The subject was hospitalised for an unknown period of time. At the time of reporting the outcome of the event was unspecified. Follow-up information was received on [redacted] from the reporting physician. Co-suspect vaccinations included pneumococcal vaccine (non-GSK) (Prevenar, Wyeth). The subject has no underlying or concurrent medical conditions or other risk factors. No concomitant medication has been reported. On [redacted] the subject received the first dose of Infanrix hexa (0.5 ml, intramuscular, unknown) and the first dose of Prevenar (0.5 ml, intramuscular, unknown). Approximately one day post vaccination with Infanrix hexa and Prevenar, on [redacted] the subject experienced therapy resistant fever, conjunctivitis, pharyngitis, cheilitis, macular exanthema, palmar plantar erythema and cervical lymphadenitis. The subject was hospitalised for an unknown period of time. The subject was treated with normal immunoglobulin (Immunoglobulin), antipyretic and, as thrombocytic antiaggregant, aspirin (ASS). After about seven days, on [redacted], the events were resolved. Platelet count was still increasing. At the time of reporting, on [redacted], the reporting physician considered that all events were resolved up to now. The vaccination courses with Infanrix hexa and Prevenar were discontinued. The reporting physician considered that the events were unlikely to possibly related to vaccination with Infanrix hexa and/or Prevenar. On [redacted] the case was also received from a [redacted]

regulatory authority ([redacted]). On [redacted] the subject received the first dose of Infanrix hexa (0.5 ml, intramuscular, unknown thigh) and the first dose of Prevenar (0.5 ml, intramuscular, unknown thigh), contralaterally in one thigh each. Between [redacted] and [redacted] the subject experienced Kawasaki syndrome. Less than one day post vaccination with Infanrix hexa and Prevenar, in the night between [redacted] and [redacted] the subject experienced high fever up to 39.5 degC. Despite of treatment with paracetamol (paracetamol) fever persisted over the next two days. On [redacted] the subject was treated by a physician for persistent fever. The physician suspected acute inflammation of the tonsils and the pharynx (tonsillopharyngitis) and started treatment with cefaclor (CEC Trockensaft). On [redacted] the subject experienced further increase of body temperature to up to 40 degC. The subject was hospitalised for an unknown period of time after visiting the emergency room of the hospital. The subject showed high inflammatory activity and persistent fever. The hospital physician(s) considered the possibility of beginning sepsis. Treatment with cefaclor was discontinued and treatment with cefotaxime (Cefotaxim), paracetamol and ibuprofen was started instead. By differential diagnosis measles, scarlet fever, sixth disease, pneumonia, meningitis and urinary tract infection have been excluded. On [redacted] the subject was diagnosed with Kawasaki syndrome due to the following criteria. Persistent fever for more than five days despite antipyretic and antibiotic treatment while showing inflammatory activity in serum examinations; macular, red-purple colored, confluent exanthema at the trunk and spread on the limbs; palmar plantar erythema; tonsillopharyngitis, conjunctivitis catarrhalis both sides and red lips; submandibular lymphadenitis of the neck (in sonography 1.7 cm large) and occipital lymph node swelling. The subject was treated with high-dose normal immunoglobulin (Privigen and Sandoglobulin) intravenously at a total dose of 2 g/kg distributed on two days from [redacted] to [redacted]. Fever was finally and completely resolved in the evening of [redacted] after starting treatment with high-dose immunoglobulin. Until [redacted] no signs of cardiac aneurysm formation could be observed. Laboratory examinations showed slow increase of platelet count. Around [redacted] Kawasaki syndrome was resolved. The reporting physician considered that the subject might experience life-threatening long-term sequelae. The vaccination courses with Infanrix hexa and Prevenar were discontinued. Follow-up information including hospital and examination reports was received on [redacted] from the [redacted] regulatory authority ([redacted]). On [redacted] the subject received the first dose of Infanrix hexa (0.5 ml, intramuscular, unknown) and the first dose of Prevenar (0.5 ml, intramuscular, unknown). The subject was born about two and a half week prior to expected date. Concurrent medical conditions included umbilical hernia which had not been surgically treated up to now. The subject's development was normal. Family anamnesis and social anamnesis were normal. Less than one day post vaccination with Infanrix hexa and Prevenar, in the afternoon of [redacted], the subject experienced high fever. Approximately three days post vaccination with Infanrix hexa and Prevenar, on [redacted], the subject was diagnosed with pharyngitis / tonsillitis. The subject was treated with cefaclor. Despite treatment with cefaclor the subject's condition worsened, high fever persisted and the subject experienced conjunctivitis and increasingly reduced intake of fluid up to refusal of food intake (anorexia). In the night between [redacted] and [redacted] the subject was hospitalised at an emergency ward. The subject was diagnosed with Kawasaki syndrome and anorexia. On admission

to hospital the subject was in reduced general condition and normal nutritional condition. The subject showed small spotted, confluent exanthema. Heart rhythmic, heart sounds were clear, 2/6 systolic murmur above point of maximal intensity at Erb´s point. Abdomen soft, bowel sounds existent, no pain on pressure, no palpatory increased organs, small hen egg-sized, well reponible umbilical hernia containing intestinal loop. Tympanic membrane right bland, tympanic membrane left blocked, throat congested with mucus and reddened, non-purulent conjunctivitis both sides. No signs of meningism. Body temperature 39.3 degC. The subject showed high fever, signs of anorexia (refusal of food intake) and severely increased inflammatory parameters (C-reactive protein (CRP): 200 mg/l; white blood cell count 10.24). Treatment included cefotaxime (Cefotaxim) and parenteral fluid substitution (infusion) with glucose-electrolyte solution. Fever up to 40 degC persisted. The subject showed polymorphous exanthema, increased cheilitis, palmar plantar erythema, as well as retro-mandibular lymphadenitis. Due to these symptoms and after exclusion of other infections, including measles, Epstein-Barr virus (EBV) and Streptococcus A, the subject was diagnosed with Kawasaki syndrome. The subject was treated with high-dose immunoglobulin at 1 g/kg body weight for two days which has been well tolerated. Fever was quickly resolved. Additionally the subject received aspirin (ASS) for thrombocytic aggregation inhibition. Laboratory examinations showed improvement of CRP and increase of platelet count: During further course of hospitalisation the subject was free if fever and clinically normal. Fluid intake normalised. Infusion therapy was discontinued.During course of hospitalisation no signs of myocardial or coronary involvement have been observed. On [redacted] the subject was discharged from hospital.50

Company comment: *Patient who develop Classic KD less than a month after vaccination with Infanrix hexa and Prevenar. It is not possible to exclude causal association to vaccines given, due to temporal association and due to the fact that the most common infectious diseases were excluded.*

[redacted]

This case was reported by a regulatory authority ([redacted]) and described the occurrence of viral infection in a 5-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Co-suspect vaccination included pneumococcal vaccines (non-gsk) (Prevenar, Wyeth Labs). The report included a hospital report, signed on [redacted] a pre-hospital report, signed on [redacted], and a filled-in form, signed on [redacted]. According to the hospital report, the subject was hospitalised from [redacted]. On [redacted] the subject received 3rd dose of Infanrix hexa. Since [redacted], 1 day after vaccination with Infanrix hexa, the subject developed increased temperature. From [redacted], body temperature was up to 39.8 degC, which could not be decreased by Paracetamol. Additionally, he coughed since 2 days prior to hospitalisation and his fluid intake was reduced. The subject's parents observed a yellow secretion at both eyes. Since 2 days prior to hospitalisation he had greenish mucous diarrhea and vomited once. On [redacted], the subject developed exanthema on trunk and went to see the doctor. Due to fever of unclear genesis, the subject was hospitalised. Both parents suffered from respiratory infection (sick person in

family). Examination on admission showed the subject with reduced general condition, eutrophic, and agitated. X-ray examination of thorax showed weak decreased transparency at left upper field, but this could not explain increased inflammation parameters. Urinary diagnosis was uneventfully. Therefore the subject's liquor was examined as diarrhea was mentioned only after puncture by the subject's parents. Liquor examination showed 16 cells/mcl. Shortly after puncture, the subject developed thin mucous and bloody stools. Therefore the subject was treated with cefotaxime (Cefotaxim) until [redacted] to medicate possible bacterial meningitis and Salmonella enteritis. Culture of blood was negative. Parallel the subject was treated with isotonic sodium chloride solution, then a mixture of electrolytes and glucose for 5 days for rehydration. He was treated symptomatically with sodium chloride (0.9% NaCl NT) and unspecified inhalations (inhalations). For mild conjunctivitis the subject was treated with kanamycin sulphate (Kanamytrex). For antipyresis and analgesia the subject was treated with paracetamol and ibuprofen. Control of vital signs was constantly uneventfully. Until [redacted], the subject suffered recurrently from fever with a body temperature up to 40 degC. He suffered from distinct gastroenteritis with regressive inconstant conjunctivitis. Transient exanthema faded after 2 days. Because fever was resolved on [redacted], previously suspected Kawasaki's disease was rejected. Blood picture showed no increase of leukocytes, CRP was 20 mg/dl. Overall picture with gastroenteritis, mild conjunctivitis, transient exanthema, peribronchitis and secondary meningitis argued for viral infection. Therefore, antibiotic therapy was not changed or enlarged. There were no pathogens in stool. Especially adenovirus could not be detected 2 times. Due to increase of fluid intake and improvement of consistency as well as reduction of frequency of stools, infusion was reduced. On [redacted], the subject was discharged from hospital in good general condition, but with subfebrile body temperatures (37.9 degC). According to pre-hospital report, the subject was examined on [redacted] to clarify recurrent subfebrile temperature. After discharge on [redacted], the subject suffered from subfebrile temperature. On [redacted] respectively the subject showed C-reactive protein with a value of 10 mg/dl and suffered from leukocytosis. Therefore, the subject was treated with cefaclor. Urinary examinations were uneventfully. During the night to [redacted], the subject developed fever with a body temperature up to 38.5 degC. Due to suspected possibly atypical Kawasaki's disease, the subject was readmitted to the hospital. Kawasaki's disease could not be clearly excluded and diagnosed respectively. According to filled-in form, previous vaccination included 1st dose of Infanrix hexa and 1st dose of Prevenar (unknown route and application site) given on [redacted]. Previous vaccination included 2nd dose of Infanrix hexa and 2nd dose of Prevenar (unknown route and application site) given on [redacted]. The subject had no adverse event following receipt of prior immunisation. On [redacted] the subject received 3rd dose of Infanrix hexa (intramuscular, left thigh) and 3rd dose of Prevenar (intramuscular, right thigh). On [redacted], 1 day after vaccination with Infanrix hexa and Prevenar, the subject experienced Kawasaki's disease (fever). The subject was hospitalised. At the time of reporting, the outcome of the events was unspecified. An appendix summarized the progress: On [redacted], the subject was vaccinated with Infanrix hexa and Prevenar. On [redacted], the subject went to see the doctor due to fever and diarrhea. He was in good general condition. Gastroenteritis and fever was diagnosed. On [redacted], the subject went to see the doctor again. He was in reduced general condition. He developed exanthema on trunk. The subject was

admitted to the children's hospital. From [redacted] the subject was hospitalised. On [redacted], body temperature increased again. He went to see the doctor again. He was in good general condition. C-reactive protein showed a value of 5 mg/dl. Cell count showed 14900 leucocytes and 957000 platelets. Culture of stool was negative for pathogens. His liver was measured with a size of 3 cm. There was no palmar and no plantar erythema. On [redacted], the subject was not febrile. C-reactive protein showed a value of 10 mg/dl. Cell count showed 14000 leucocytes and 885000 platelets. On [redacted], the subject was not febrile. On the eve, his body temperature was 38.6 degC. C-reactive protein showed a value of 5 mg/dl. Cell count showed 11000 leucocytes. The subject was admitted to the hospital. His liver was measured with a size of 4 cm. On [redacted], C-reactive protein showed a value of 5 mg/dl. Cell count showed 11300 leucocytes and 803000 platelets. The subject was admitted to the hospital again. According to written follow-up information, received on [redacted] by the regulatory authority, including one further hospital report, signed on [redacted]. The subject was hospitalised from [redacted] respectively [redacted] due to persistent fever. Since [redacted] the subject was treated with cefaclor preventively. On [redacted], echocardiographic recordings seemed to indicate incomplete Kawasaki's syndrome with coronary involvement. Suspected Kawasaki's syndrome was confirmed due to clearly ectatic coronary arteriae by echocardiography. On [redacted], the subject was treated with Octagam, ASS and Omeprazol. In the course, fever resolved. Echocardiographic recordings showed clear decrease of perivascular echogenicity of coronary arteriae. Values of C-reactive protein clearly decreased. On [redacted] the subject was discharged from hospital in good general condition. No further information will be available.

***Company comment**: Incomplete KD in patient who develop symptoms one day after vaccination with Infanrix hexa, and Pneumococcal vaccines. The patient had concurrent coughing, suspicion of meningitis and viral disease, so the aetiology of KD may have been triggered by an infectious disease.*

[redacted]

This case was reported by a physician, via a sales representative, and described the occurrence of kawasaki syndrome in a 4-month-old subject of unspecified gender who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. On an unspecified date the subject received 2nd dose of Infanrix hexa (unknown route and injection site). 3 days after vaccination with Infanrix hexa, the subject experienced kawasaki syndrome. At the time of reporting the outcome of the event was unspecified.

***Company comment**: Not confirmed KD case in patient of four months 3 days after vaccination with Infanrix Hexa. There is not enough clinical evidence to relate this event to vaccination with Infanrix Hexa.*

[redacted]

This case was reported by a [redacted] regulatory authority ([redacted] and described the occurrence of partial Kawasaki's disease in a 3-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Co-suspect vaccinations included pneumococcal vaccine (non-GSK) (Prevenar, Wyeth). On [redacted] the subject received the first dose of Prevenar (0.5 ml, unknown). On [redacted] the subject received the first dose of Infanrix hexa (0.5 ml, unknown). Approximately two days post vaccination with Infanrix hexa and approximately 30 days post vaccination with Prevenar, on [redacted], the subject experienced partial Kawasaki's disease. The subject was hospitalised for an unknown period of time. At the time of reporting, on [redacted], the event was unresolved. The vaccination courses with Infanrix hexa and Prevenar were discontinued. The vaccine was reported as diphtheria and tetanus toxoids and acellular pertussis vaccine (Infanrix, GlaxoSmithKline), but according to lot number the subject was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline). Follow-up information including a hospital report was received on [redacted] from the [redacted] regulatory authority ([redacted]). In hospital report vaccinations with pneumococcal vaccine (non-GSK) (Prevenar, Wyeth) was not reported. Familial risk factors included hay fever of the subject's mother, dust mite allergy and asthma of the subject's father, and asthma of the subject's grandfather on the father's side. Course of pregnancy, birth and development of the subject up to now have been normal. On [redacted] the subject received the first dose of Infanrix hexa. Approximately two days post vaccination with Infanrix hexa, on [redacted], the subject experienced partial Kawasaki's disease with high fever, severe generalised exanthema which has started at the belly button, severe abnormal crying, severe restlessness and reduced fluid intake. Despite treatment by a paediatrician the events did not resolve and fever was more than 40 degC. On [redacted] the subject was hospitalised for six days for high fever and severe generalized macular rash. In hospital the subject was diagnosed with partial Kawasaki's disease. On admission to hospital the subject was in reduced but stable general condition, good nutritional condition, showed rosy skin colouration and fontanels in level. The subject was crying severely and was very restless. Exanthema was very intense with middle and large maculae over the whole body including palms of the hands and soles of the feet. The subject showed serous rhinitis, tachycardia and soft but bloated abdomen. All other internal and neurological examinations were normal. Body temperature was 39.1 degC, blood pressure was 108/46 mmHg and heart rate was 162 /min. Laboratory examinations showed increased C-reactive protein (CRP) of up to 5.5 mg/dl, anemia due to infection and eosinophilia with 8%. Differential white blood cell count was otherwise normal. Blood electrolytes, blood metabolites, liver enzymes and urinalysis were normal. Blood cultures were sterile. Parvovirus serology was positive for IgG but negative for IgM. Mycoplasma antibodies were negative. Electrocardiograms (ECG), performed repeatedly, were normal. C-reactive protein (CRP) value decreased during course of hospitalisation. Treatment at hospital included infusion therapy with repeated antipyretic treatment, decongestive nasal drops, normal immunoglobulin (intravenous) for two days

for the treatment of Kawasaki's disease and aspirin (ASS) at 100 mg four times daily for two days, followed by 50 mg daily. Fever was resolved post treatment with immunoglobulin. Exanthema improved and became at first rosette-shaped and later on started to fade. Transitory the subject experienced mild conjunctivitis and discrete exfoliation of palms of hands. On [redacted] the subject was discharged from hospital without fever and in distinctly improved general condition. At the time of discharge from hospital partial Kawasaki's disease was improved, but anemia due to infection and eosinophilia were unresolved. The reporting physician considered that by differential diagnosis partial Kawasaki's disease might be causally related to vaccination with Infanrix hexa. No further information will be available.

Company comment: *Patient with Incomplete KD, 2 days after vaccination with Infanrix Hexa, Pneumococcal vaccines. There is temporal association with vaccination, but insufficient clinical evidence to relate this case to vaccination as other counfounders are present like 'anemia due to infection' are reported in the narrative.*

[redacted]

This case was reported by a physician and described the occurrence of Kawasaki syndrome in a 4-month-old female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Co-suspect vaccinations included pneumococcal vaccine (non-GSK) (Prevenar, Wyeth). On an unspecified date the subject received an unspecified dose of Infanrix hexa (0.5 ml, unknown route and application site) and an unspecified dose of Prevenar (0.5 ml, unknown route and application site). At an unspecified time post vaccination with Infanrix hexa and Prevenar, on an unknown date, the subject experienced Kawasaki syndrome. At the time of reporting, on [redacted], the outcome of the event was unspecified. Follow-up information including a hospital report was received on [redacted] from the reporting physician. The case was upgraded to serious. Concomitant medications included Antibiotics as needed. Recent family anamnesis included infection of the upper respiratory tract of the sister some days ago. On [redacted] the subject received the first dose of Infanrix hexa (0.5 ml, intramuscular, left thigh) and the first dose of Prevenar (0.5 ml, intramuscular, right thigh), contralaterally. Approximately three days post vaccination with Infanrix hexa and Prevenar, on [redacted], the subject experienced persistent fever up to 40 degC within the scope of Kawasaki syndrome: The subject showed no signs of infection. A pediatric emergency service determined increased C-reactive protein (CRP). On [redacted] the subject was hospitalised for 16 days. In hospital the subject was diagnosed with Kawasaki syndrome, interstitial pneumonia right, decreased fluid intake and diaper rash. Suspected meningitis was excluded. On admission to hospital the subject was in decreased general condition and good nutritional condition. Body temperature was 37.9 degC. The subject was crying and whimpering (crying abnormal). The subject apparently showed mild signs of meningeal disorder. The skin was pale and marbled, but otherwise normal. Otorhinolaryngologic, internal and pediatric examinations were normal. The subject was hospitalised for infection of unknown origin with high fever for monitoring

diagnostics and treatment. Initially suspected meningism was excluded by cerebrospinal fluid (CSF) examination which showed no pathologic findings. Laboratory examinations showed increased inflammatory parameters. In combination with clinical signs bacterial infection was suspected and intravenous antibiotic treatment with cefuroxime sodium (Cefuroxim) was started. Thoracic X-rays, performed on [redacted] and [redacted] showed interstitial pneumonia right lower lobe with spotted extensive pulmonary infiltration due to pneumonia in the lower right pulmonary field. Urinalysis was normal. Blood and cerebrospinal fluid (CSF) cultures were sterile. During course of hospitalisation general condition deteriorated further, laboratory infection parameters worsened and high fever up to 40.3 degC persisted. On [redacted] the subject experienced greenish stools. Test for occult blood, performed on [redacted] was positive one time, but follow-up tests for occult blood, performed on [redacted] were negative. Microbiological stool examinations, performed on [redacted] showed no pathologic findings. Abdominal and cranial sonography, performed on [redacted] was normal. Because of persistent high fever antibiotic treatment was changed to cefotaxime (Cefotaxim), netilmicin sulphate (Certomycin), erythromycin (Erythromycin) and ampicillin sodium + sulbactam sodium (Unacid), in combination with antimycotic prophylaxis with nystatin (Candio-Hermal). Due to intermittent exanthema, conjunctival injection, lip redness and lip tension (cracked lips), as well as antibiotic resistant fever the subject was diagnoses with possible Kawasaki syndrome. The subject was treated with normal immunoglobulin (Intratect) for two days from [redacted] to [redacted] and with aspirin (ASS). Antibiotic treatments were discontinued on [redacted]. Post treatment with immunoglobulin fever resolved and general condition improved. The subject showed increased skin exfoliation on hands and feet. Laboratory examinations showed distinct anemia, thrombocytosis and increase in liver values, which were seen within the scope of Kawasaki syndrome and treatment with aspirin. Multiple echocardiograms and electrocardiogram (ECG), performed for controls, showed no conspicuous findings. Due to decreased fluid intake the subject was fed by infusion and gastric tube until [redacted] Cardiopulmonary monitoring was stable at all times. The subject did never need oxygen supplementation. On [redacted] the subject was discharged from hospital in good general condition for ambulatory follow-up. According to the reporting physician, after about 16 days, on [redacted] all events were completely resolved. The vaccination courses with Infanrix hexa and Prevenar were discontinued, but vaccination with combined diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (non-GSK) (Pentavac; Sanofi Pasteur MSD), given on an unspecified date, was well tolerated. The reporting physician considered that the events were possibly related to vaccination with Infanrix hexa. The reporting physician did not specify the causal relationship of the events to vaccination with Prevenar. No further information will be available.

***Company comment**: Patient with Incomplete KD after 3 days with vaccination with Infanrix hexa and Pneumococcal vaccines. There is temporal association with vaccination, but not enough clinical evidence to relate this case to vaccination as there is also a diagnosis of Interstitial pneumonia that may have trigger the KD.*

[redacted]:

This case was reported by a physician via regulatory authority [redacted] and described the occurrence of Kawasaki's disease in a 4-month-old subject of unspecified gender who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Co-suspect vaccination included pneumococcal vaccines (non-gsk) (Prevenar 13, Pfizer) for prophylaxis. Previous vaccination with Infanrix given on [redacted] was well tolerated. On [redacted] the subject received 2nd dose of Infanrix (unknown route and application site). On [redacted], 4 days after vaccination with Infanrix, the subject experienced Kawasaki's disease. The subject was hospitalised for 7 days. At the time of reporting the outcome of the event was unspecified. Follow-up information was received on [redacted] from a physician. On [redacted] the subject received 1st dose of Infanrix hexa and 1st dose of Prevenar (unknown route and application site). On [redacted], 4 days after vaccination with Infanrix hexa and Prevenar, the subject was presented to a doctor with high fever. Laboratory test showed leucocyte count of 19.700. The subject was hospitalised. At hospital Kawasaki's disease was diagnosed. At the time of reporting the outcome of the events was unspecified. Follow-up information was received on [redacted] from the physician including completed questionnaire and hospital report. According to completed questionnaire, previous vaccination included 1st dose of Infanrix hexa (unknown route and application site) and 1st dose of Prevenar 13 (unknown route and application site) given on [redacted]. Concurrent medications included Zymafluor D 500. On [redacted] in the morning, the subject received 2nd dose of Infanrix hexa (intramuscular, left thigh) and 2nd dose of Prevenar 13 (intramuscular, right thigh). On [redacted], at approximately 18:00, 4 days after vaccination with Infanrix hexa and Prevenar 13, the subject experienced fever without signs of an infection. The subject was hospitalised due to white blood cell count of 17900 cells. At hospital Kawasaki's disease was diagnosed. The physician reported that the events were disabling (tagged with question mark) and life threatening (tagged with cross and question mark). At the time of reporting the outcome of the events were was unspecified. According to hospital report, signed on [redacted], the subject was hospitalised from [redacted]. Mucocutaneous lymph node syndrome (Kawasaki's disease) was diagnosed. On [redacted], the subject developed fever with a body temperature up to 39 degC. She did not develop cough, rhinitis, diarrhea or vomiting. Fluid intake was well. Laboratory examination showed leucocytosis. Therefore, the subject was hospitalised. Four days prior to hospitalisation, the subject was vaccinated. After that, she developed fever for 2 days with a body temperature up to 38 degC. Maternal concurrent medical condition included rheumatoid arthritis and psoriasis. On admission examination, her general condition was reduced. Her skin showed no exanthema. Skeleton, eyes, ears, oral cavity, heart, respiration, abdomen and genitals were without pathological findings. Central nervous system was without pathological finding despite of sensitiveness to touch and crying fits. The subject was hospitalised due to possible meningitis. Inflammatory values were increased. Urine was normal. X-ray of thorax showed no hints for pulmonary infiltrates. Stool was malodorous. By differential diagnosis, bacterial gastroenteritis and sepsis was suspected. The subject was treated with cefotaxime (Cefotaxim) for 2 days. Examination of stool showed no pathological germs and state of cerebrospinal fluid was

normal. On [redacted], the subject developed painful cervical lymph node swelling at right side. There were just solitary stipples at tonsils (angina follicularis). Treatment was changed to clindamycin and cefuroxime sodium (Cefuroxim) for 5 days. Due to recurrent tachycardia during sleep, electrocardiogram was performed. Despite of sinus-tachycardia, examination showed normal results. Also echocardiography and sonography of abdomen showed normal results. Values of C-reactive protein further increased. By computed tomogram of petrosa, mastoiditis was excluded. The subject was additionally treated with fosfomycin for 3 days. On [redacted], the subject developed small spot exanthema on trunk and dry chapped lips. Fever remained already since 5 days, which could not be resolved by antibiotics. Therefore, Kawasaki's syndrome was diagnosed. The subject was treated with normal immunoglobulin (Immunoglobulin) and aspirin (Acetylsalicylacid). General condition improved fast. By echocardiography, coronary ectasia was excluded. Thirty hours after treatment with immunoglobulin, the subject's general condition again decreased. The subject was treated with normal immunoglobulin (Immunoglobulin) for the second time. There were still no hints for coronary ectasia. Under arterial hypotension the subject was treated with human albumin (Human albumin 5%). On [redacted], the subject was transferred to another hospital for further medical care treatment. This case was also reported to [redacted] regulatory authority and Drug Commission of the German Medical Association. Follow-up information was received on [redacted] from the physician including hospital report, signed on [redacted]. The subject was hospitalised from [redacted]. First episode of Kawasaki vasculitis on 13 [redacted] and recurrent Kawasaki vasculitis on [redacted] as well as dysplastic pinna (right more than left sided) was diagnosed. On [redacted], the subject developed fever with a body temperature up to 39.5 degC. Due to increased inflammatory values, the subject was hospitalised by the paediatrician. Due to missing focus of inflammation, lumbar puncture was performed. On [redacted], she developed cervical lymph node swelling. Fever did not resolve despite of treatment with antibiotics. The subject developed small spot exanthema. Therefore, Kawasaki vasculitis was suspected. After treatment with immunoglobulin on [redacted], fever and increased values of C-reactive protein resolved. After 2 days, fever and values of C-reactive protein recurred. Therefore, the subject was transferred. On admission examination, small spot exanthema on trunk was improved. Heart and respiration were normal. Pharynx was dry and lips were chapped. She still suffered from cervical lymph nodes swelling at both sides. Due to anemia, the subject was treated with red blood cells (Erythrocyte transfusion). Fever resolved. Values of C-reactive protein halved within one day. On [redacted] the subject developed again fever and small spot exanthema on trunk. She developed glazed lips (lip disorder). Treatment with immunoglobulin resolved fever and decreased values of C-reactive protein. Treatment with aspirin (Acetylsalicylacid) was continued for altogether 8 days. On [redacted] fever and decreased general condition resolved. Platelet count increased up to 1500/mcl. Therefore, the subject was treated with clopidogrel additionally to reduced dose (25 mg total daily dose since [redacted] of aspirin (Acetylsalicylacid). On [redacted] the subject was discharged in good general condition. Written follow-up information was received on [redacted] from the regulatory authority [redacted]. This report was identified being a duplicate of [redacted]. Gender of subject was inconsistent in previous reports. According to provided batch number Infanrix must be Infanrix hexa. On [redacted] the subject received a dose of Infanrix and a dose of

Prevenar. On [redacted], 4 days after vaccination with Infanrix and Prevenar, the subject experienced Kawasaki's disease with concurrent conjunctivitis, exanthema, hy59

Company comment: *Not Confirmed KD case, 4 days after vaccination with Infanrix Hexa and Prevenar 13. It is not possible to exclude causality association with vaccines given, due to temporal association and exlusion of other infectious etiologies. Although meningitis and sepsis were suspected.*

[redacted]

This case was reported by a physician via regulatory authority [redacted]) and described the occurrence of Kawasaki syndrome in a 2-month-old female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. According to completed questionnaire, signed on [redacted], on [redacted] the subject received 1st dose of Infanrix hexa (intramuscular, left thigh). On [redacted], 3 days after vaccination with Infanrix hexa, the subject experienced Kawasaki's syndrome for several days. Diagnose was based on clinical symptoms and exclusion of other causes for fever after puncture of cerebrospinal fluid and urinary bladder. By differential diagnosis, sepsis, meningitis and urinary tract infection have been excluded. The subject was hospitalised and the reporter reported that the events were life threatening. In [redacted], the event was resolved. According to provided hospital report from paediatric unit, signed on [redacted], the subject was hospitalised from [redacted]. Kawasaki's syndrome and haemangioma were diagnosed. The subject's medical history included premature baby (after 34th weeks of pregnancy). She was a twin. Postpartal the subject developed streptococcal infection, which was treated. Concurrent medical conditions included congenital hemangioma at back and forehead. There were no concurrent medical conditions, no continuous medications and no known allergies. On [redacted] the subject received 1st dose of Infanrix hexa. On [redacted] in the evening, the subject experienced fever with a body temperature up to 39.3 degC. The subject was treated with paracetamol on [redacted] or [redacted] in the evening and on [redacted] or [redacted] in the morning. Since [redacted], the subject was sleeping a lot (sleepiness) and drinking less (fluid intake reduced). Blood examination showed increased value of C-reavtive protein (75 mg/L). By examination of urine via test strip, leucocytes were shown. The subject was hospitalised due to unclear highly febrile infection and suspected pyelonephritis. On admission examination, the subject was in reduced general condition. Skin coloration was mildly pale (paleness of skin). There were no signs for meningism. Values of inflammation were shown to be distinctly increased. Initially, urinary tract infection was suspected due to unusual urine test of urine bag. Puncture of bladder showed very low increased leukocyte count (15/mcl). Puncture of liquor showed also normal values. The subject was treated with cefotaxime (Cefotaxim) and mezlocillin. On the following day, the subject developed increasing exanthema on whole trunk and in further course non-purulent conjunctivitis, erythema at palmar and and plantar as well as a distinct enanthema with chapped lip and hypertrophy of tongue papillae. During treatment with antibiotics, fever remained. Due to clinical signs and fever, Kawasaki's syndrome was suspected. The subject was treated with normal immunoglobulin (Immunoglobulin) two times (2 g/kg body weight).

Treatment with antibiotics was discontinued. Symptoms improved, fever resolved. By echocardiography, no coronary aneurism could be detected. The subjected was treated with aspirin (ASS, 3-5 mg/kg body weight/d) for prophylaxis. During hospitalisation, small haemangioma at forehead and a bigger one at back were treated with cryosurgery (Cryotherapy). Symptoms resolved and subject was discharged in good general condition. According to provided CIOMS report, a 10-week-old female was vaccinated with Infanrix Hexa (batch-no.: A21CA958B) for prophylactic vaccination on [redacted]. Past medical history included preterm birth (gestational age 34 weeks), twin birth, postpartal streptococcal infection, haemangiomas localised at the back and the forehead. 3 days after vaccination the patient developed fever with signs of infection (C-reactive protein increased to 75 mg/l). Since an urine stix test revealed an increased leukocyte count, pyelonephritis was suspected. The patient was hospitalised to undergo further examinations. Inflammatory parameters (leukocytes in serum, CRP) were increased. Urinary tract puncture was performed which confirmed an increased urine leukocyte count (15/µl). Lumbar puncture was performed and CSF analysed. Protein in CSF was slightly increased, other parameters were within reference values. Via echocardiography, a persistent foramen ovale and mild aortic valve insufficiency were detected. The girl was treated with antibiotic therapy (Cefotaxim and Mezlocillin). The very next day the girl developed a spreading exanthema at thorax and abdomen and in the further course purulent conjunctivitis, palmar and plantar erythema as well as an enanthema with chapped lips and hypertrophic papillas of the tongue. Despite antibiotic therapy the patient still had a subfebrile body temperature. Due to these clinical signs and persisting fever without focus Kawasaki's disease was suspected. In the further course the patient was treated with immunoglobulins (2g/kg body weight). Antibiotic treatment was discontinued. Already after the first administration of immunoglobulins symptoms were declining and body temperature normalised. in the further course no fever, no exanthema and declining conjunctivitis. Echocardiography was repeated twice with no evidence of coronar aneurysma. Prophylactic therapy with ASS was started (3-5 mg/kg body weight/day) and a cardiologic examination within two weeks was recommended. A small haemangioma at the forefront as well as a bigger haemangioma at the back were treated with cryotherapy. No further information will be available.

Company comment: *Patient with Classic KD, 3 days after vaccination with Infanrix Hexa. Concomitant Pyelonefritis was diagnosed. There is temporal association with vaccination although an infectious cause may have been the trigger of KD.*

[redacted]

This case was reported by a regulatory authority [redacted] and described the occurrence of atypical kawasaki disease in an nearly 12-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Co-suspect vaccination included pneumococcal vaccines (non-gsk) (Prevenar 13, Pfizer). Previous vaccination included 1st dose of Infanrix hexa and Prevenar 13 (each unknown route and application site) given on [redacted], which was well tolerated. On [redacted] the

subject received 2nd dose of Infanrix hexa and 2nd dose of Prevenar 13 (each unknown route and application site). At an unspecified after 2nd vaccination with Infanrix hexa and Prevenar 13, the subject experienced fever with a body temperature up to 38.2 degC. On [redacted] the subject received 3rd dose of Infanrix hexa and 3rd dose of Prevenar 13 (each unknown route and application site). On [redacted], 3 days after 3rd vaccination with Infanrix hexa and Prevenar 13, the subject experienced atypical Kawasaki disease. The subject developed fever with body temperatures up to 40 degC. On [redacted], the subject developed exanthema on abdomen and back. Exanthema of mycotic cause was suspected. The subject was treated symptomatically with antipyretic (Antipyretics). On [redacted], the subject's fluid intake was reduced. His general condition was reduced. The subject was treated with cefpodoxime. Symptoms did not improve. On [redacted] the subject was hospitalised. Atypical Kawasaki syndrome, secondary meningitis and pericarditis were diagnosed. He showed maculo-papular exanthema at trunk, arms, legs and face. His lips and palms were reddened. Cervical lymph nodes were enlarged. His body temperature was up to 40.3 degC. Initially, there were clearly increased parameters for an infection (signs of infection) as well as distinct exanthema. Culture of blood and liquor were uneventfully. Due to abnormal midstream urine, the subject was treated with cefuroxime sodium (Cefuroxim). Fever did not resolve. On [redacted] the subject still suffered from fever. He showed chapped lips, palmar erythema, leukocytosis and mild cervical lymphadenopathy. Kawasaki's disease was suspected. The subject was treated with normal immunoglobulin (Immunoglobulin) and aspirin (Acetylsalicylacid). Fever resolved and general condition improved. On [redacted] echocardiography showed pericarditis and mitral insufficiency. On [redacted], the subject was discharged from hospital after 12 days. At the time of reporting atypical Kawasaki disease was unresolved. The reporter reported that the events were life threatening. No further information will be available.

Company comment: *Patient with Classic KD, although in the narrative it states Incomplete KD (Atypical) after 3 days of Infanrix Hexa, and Pneumococcal vaccines. There is temporal association with given vaccines, but infectious etiology may have trigger KD (narrative states infectious origin and secondary meningitis and pericarditis were diagnosed)*

[redacted]

This case was reported by a physician via a regulatory authority ([redacted]) and described the occurrence of Kawasaki disease in a 12-week-old female subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline), pneumococcal vaccines (non-gsk, Prevenar 13) and rotavirus vaccine (non-gsk, RotaTeq) for prophylaxis. The following narrative was provided by the regulatory authority: "A 12-week-old female, born on [redacted], was vaccinated with Prevenar 13 (batch-no.: PAA012842, i.m., vaccination site: left thigh), Infanrix Hexa (batch-no.:A21CB162B, i.m., vaccination site: right thigh) and RotaTeq (batch-no.:0074AA, oral administration) for prophylaxis on [redacted]. Medical history was not provided. On the very same day, the patient developed fever. On

[redacted] the child was admitted to hospital due to suspicion of meningitis. At admission, C-reactive protein and thrombocyte count were increased. During the further course, C-reactive protein, leukocyte and thrombocyte count were still increasing whereas hemoglobin was decreasing. Norovirus stool test was positive. ECG performed on [redacted] was without pathological findings. Echocardiography showed a mild pericardial effusion as well as enlargement of the right and left coronary arteries. Thus atypical Kawasaki's disease with coronary aneurysms was suspected. In addition, norovirus gastroenteritis with exsiccosis was diagnosed. MR angiography performed on [redacted] detected enlargement of the A. axillaris and ectasy of the left renal artery. As secondary finding, splenic infarction was diagnosed. The patient was treated with intravenous fluids and received antibiotic treatment with ampicillin and tobramycin. In addition, antipyretics were administered. Since fever was persisting and echocardiography showed evidence of coronary aneurysms, intravenous immunoglobulins as well as enoxaparin were given. In addition, ASS was administered to inhibit thrombocyte aggregation. Subsequently, the fever resolved. Necrosis of the distal part of the left little finger was observed. The patient was discharged from hospital in good medial condition (afebrile, lab parameters including thrombocyte count were normalising) on [redacted], but she had not completely recovered at the date of reporting. The attending physician is of the opinion that the above described events had been life-threatening and might potentially result in a sequel. Control echocardiography was scheduled to be performed 6 to 8 weeks after discharge from hospital. In addition, control of the lab parameters was scheduled to be performed 2 to 3 months after discharge from hospital." Follow-up-information was received on [redacted] via the regulatory authority by means of a preliminary hospital report (nearly identical with the final hospital report which had been provided previously) and some updated structured information and lab text. According to structured information the patient also developed aneurism and worsening of general condition (on [redacted]). The following information was added to the lab text: By means of echocardiogram ([redacted]) aneurism-like dilation of left coronary artery was detected. Atypical Kawasaki syndrome was strongly suspected. By means of Doppler sound scan (date unspecified) there was identified suspected arterial perfusion disorder of left hand and no changes or mild worsening of aneurism of coronary arteries. The following information was added the narrative: "The patient was treated with Ampicillin, Tobramycin, Antipyretics, twice i.v., Immunglobulins and one week antikoagulation with Enoxaparin, ASS. The patient was discharged from hospital in good condition." Follow-up information was received on [redacted] via the regulatory authority: According to a physician's letter (date: [redacted]) two days after vaccination, on [redacted], the subject presented with vomiting, fever, abnormal respiration and increased c-reactive protein. The subject was hospitalized for clarification of the origin of fever. At the hospital the subject developed diarrhea. On the third day at the hospital, probably on [redacted], the subject developed swelling of the back of both hands. At the time of reporting the subject had not recovered. There was still coronary aneurism of 4 mm.

Company comment: *Not Confirmed KD, that developped symptoms on the same day after vaccination with Infanrix Hexa, Pneumococcal vaccines and Rotavirus Vaccine (Non GSK). Norovirus infection positive in stool. Infectious etiology may have trigger KD.*

[redacted]

This case was reported by a physician and described the occurrence of kawasaki syndrome in an 2-month-old male subject who was vaccinated with live attenuated human rotavirus vaccine (Rotarix liquid formulation, GlaxoSmithKline) for prophylaxis. On [redacted] the subject received a dose of Rotarix liquid formulation. Less than one month after vaccination with Rotarix liquid formulation the subject developed kawasaki syndrome. At the time of reporting the outcome of the event was unspecified. Follow-up information was received on [redacted] from the reporting physician by means of a completed questionnaire: Co suspect vaccinations included combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa) and pneumococcal vaccines (non-gsk, Prevenar 13). There was no relevant concurrent medication. On [redacted] the subject received the first dose of Rotarix liquid formulation (oral), the first dose of Infanrix hexa (intramuscular) as well as the first dose of Prevenar 13 (intramuscular). On [redacted], eight days after vaccination with Rotarix, Infanrix hexa and Prevenar 13 the subject developed kawasaki syndrome. The subject was hospitalised and treated with normal immunoglobulin (Immunoglobulin) and aspirin (ASS). On [redacted], the event was resolved. The physician considered the event was life threatening. The physician considered the event was "possibly/probably" related to vaccination with Rotarix liquid formulation, Infanrix hexa and Prevenar 13. Follow-up information was received on [redacted] via the [redacted] regulatory authority ([redacted]. The original reporter had reported to the [redacted] directly as well as via the drug commission of the [redacted] medical association ([redacted]. According to the report issued to the [redacted] directly, the following differential diagnosis were excluded: Cytomegalovirus, Epstein-Barr-virus, other bacterial infections (Serology negative). Abdominal ultra sound was normal. There was no coronary involvement. Diagnosis of Kawasaki's syndrome was confirmed by the associated symptoms of fever despite antibiosis, exanthema, conjunctivitis, and lymphadenitis as well as increased levels of c-reactive protein and liver enzymes. The event resolved after nine days. Otherwise information was identical to the report previously provided. According to the report issued via the drug commission of the [redacted] medical association, the onset of the events Kawasaki's syndrome, fever despite antibiosis, exanthema, conjunctivitis, and lymphadenitis was on [redacted] (previously reported: [redacted]) and resolved after nine days. Otherwise information was identical to the reports previously provided. In the latter report the physician considered the events were related to vaccination with Rotarix liquid. Follow-up information was received on [redacted] via the [redacted] regulatory authority [redacted] and included two questionnaires and one hospital report. According to the report issued to the [redacted] directly, the following differential diagnosis were excluded: Sepsis, lymphadenitis and conjunctivitis. Diagnosis of Kawasaki's syndrome was confirmed by the associated symptoms of increased levels of c-reactive protein, fever, exanthema, conjunctival infection, enlarged lymph nodes on sides in cervical region and chapped lip. According to the other questionnaire, the physician considered the event, Kawasaki syndrome was related to vaccination with Rotarix liquid formulation. According to the hospital report, dated on [redacted], the subject was hospitalised from [redacted] to [redacted]

Admission to hospital was due to a cervical lymphadenitis on the right side. At first the patient was treated with ampicillin intravenous. The laboratory inflammatory parameters increased and the subject developed on the second day of hospitalisation an exanthema at the trunk and extremities. An allergic reaction due to treatment with antibiotics was suspected and treatment with ampicillin was changed to Cefuroxim. On [redacted], fever could not be reduced and in addition the c-reactive protein level increased. Kawasaki-syndrome was suspected as diagnosis. Therefore a therapy with acetylsalicaylacid and immunoglobulin was started and the symptoms resolved. The patient was discharged from hospital on [redacted]. On [redacted], a laboratory test for cytomegalovirus IgG was positive and for IgM negative.

Company comment: *Patient with Classic KD eight days after vaccination with Rotavirus vaccine, Infanrix hexa, and Pneumococcal vaccines. Causality association can not be excluded due to the fact that bacterial serology was negative and viral tests for some virus were negative too.*

[redacted]

This case was reported by a regulatory authority ([redacted]) and described the occurrence of atypical Kawasaki disease in a 3-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. There was no relevant medical history. Co-suspect vaccinations included pneumococcal vaccines (non-gsk) (Prevenar 13, Pfizer) and rotavirus vaccine (non-gsk) (RotaTeq, other manufacturer). On [redacted] the subject received unspecified dose of Infanrix hexa (unknown route and application site), unspecified dose of Prevenar 13 (unknown route and application site), unspecified dose of RotaTeq (unknown route and application site). On [redacted], 49 days after vaccination with Infanrix hexa, Prevenar 13 and RotaTeq, the subject experienced atypical Kawasaki disease. The subject was hospitalised and the event was life threatening with intermittent severe impact on the subject. Echocardiogram showed threshold wideness left coronary artery at first, but was normal in further course. The subject was treated with antibiotics (Antibiotic), but the event showed therapy resistance to this. Treatment then included normal immunoglobulin (Immunoglobulin) and acetylsalicylic acid (ASS). After 13 days the event was resolved. The reporting podiatrist considered that the event was related to vaccination with Infanrix hexa, Prevenar 13 and RotaTeq. Follow-up information was received on [redacted] via the [redacted] regulatory authority [redacted]. On [redacted], 49 days after vaccination with Infanrix hexa, Prevenar 13 and RotaTeq, the subject experienced atypical Kawasaki disease, respiratory acidosis, bronchitis, fever, rash on skin, exsiccation and fluid intake reduced. On [redacted] conjunctivas were severely red and purulent. The subject was treated with normal immunoglobulin (Immunoglobulin) and acetylsalicylic acid (Aspirin). Follow-up information was received on [redacted] via the [redacted] regulatory authority [redacted], including a hospital report. The subject was hospitalised from [redacted] to [redacted] According to the hospital report, concurrent medications included Vitamin D + fluoride. The subject's older brother had a cold. On [redacted] the subject

developed fever up to 39 degC. There was increasing cough and bad drinking behaviour. On [redacted] the subject developed skin rash, beginning on the legs and expanding to arms and face. Before hospitalisation, the subject had received treatment with paracetamol. On [redacted] the paediatrician admitted the subject to hospital. When admitted, the subject showed reduced general condition and good nutritional condition. The subject showed breathing sounds, red throat, red conjunctiva at both sides with pus, but no meningism, no petechiae, no lymph node swelling, no abnormal heart sounds and no enanthema. Vasculitis was suspected first. The subject had high fever, generalised exanthema, bronchitis, reduced fluid intake, exsiccation (ketonuria) and metabolic acidosis. Treatment with acetate containing infusion, ofloxacin (Floxal) eye drops, nasal drops, inhaled sodium chloride (NaCl), paracetamol and ibuprofen was started. Because of increased inflammatory parameters, the subject received antibiotic treatment with azithromycin and cefuroxime sodium (Cefuroxim). On [redacted] the subject still had fever and additionally the coronary artery was threshold dilated in echocardiogram. As clinical picture showed atypical kawasaki disease, treatment with immunoglobulin and Acetylsalicylic acid was started. This was well tolerated and fever quickly regressed and general condition improved. The subject drank better. Control echocardiogram on [redacted] showed improvement and on [redacted] the results were normal. Intermediate ST segment elevation in electrocardiogram (ECG) had resolved at the time of discharge. No further information will be available.

Company comment: *Patient with Incomplete KD, 49 days after vaccination with Infanrix Hexa, Pneumococcal vaccines and Rotavirus vaccine (Non GSK), there was a concomitant bronquitis. There is no temporal association as the TTO is more than 30 days, an infectious disease may have trigger KD.*

[redacted]

This case was reported by a regulatory authority ([redacted]) and described the occurrence of Kawasaki's syndrome in a nearly 19-week-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine. (Infanrix hexa, GlaxoSmithKline), live attenuated human rotavirus vaccine (Rotarix liquid formulation) and pneumococcal vaccines (Prevenar, non-GSK) for prophylaxis. On [redacted], the subject received the first dose of Infanrix hexa (reported as Infanrix, but identified as Infanrix hexa upon review of batch number) (unknown route, upper thigh), the first dose of Rotarix liquid formulation (oral), and the first dose of Prevenar (unknown route, upper thigh). On [redacted] 28 days after vaccination, the subject experienced Kawasaki's syndrome, and suspected pyelonephritis that was unresponsive to antibiotic therapy. Clinical symptoms included conjunctivitis and skin involvement. The subject was hospitalised. Cerebrospinal fluid examination revealed no pathologic findings. No pyelonephritis-causing pathologic germs were identified. At the time of reporting, the events were unresolved. A discharge summary was provided, covering the subject's hospitalization from [redacted] to [redacted]. The subject was previously admitted to another clinic on an unspecified date. Concurrent medical conditions included duplex kidneys on the right side. At an unspecified date, prior to hospitalization, the subject experienced bilateral purulent conjunctivitis. Treatment with antibiotic eye drops was three times unsuccessful. The

subject was treated with decongestant nose drops and the event improved. On [redacted], the subject developed high fever, high inflammatory parameters, and macroscopically "suspicious" urinalysis results. Pyelonephritis was suspected. Antibiotic treatment with cefotaxime (Cefotaxim) was initiated. No pathological germs were found in the initially suspicious urine sample. Fever and leukocytosis persisted, and C reactive protein (CRP) increased. Intravenous ampicillin (Unacid) was added as an antibiotic treatment on [redacted]. Clinical condition improved and CRP was half of its previous value. On [redacted], urinary culture revealed Enterococcus faecalis sensitive to vancomycin, and candida. Treatment with fluconazold (Fluconazol) was initiated. Antibiotic treatment was changed to gentamicin sulphate (Gentamycin) and ampicillin on [redacted]. Cefotaxime was discontinued. Due to the prolonged course of event, renal fistula at the hydronephrotic caudal pole of the left kidney was created and a central line was inserted on [redacted]. A renal urine sample drawn in sterile setting showed no pathological germs. Despite treatment with vancomycine and ampicilline, inflammatory parameters increased. Ampicillin was discontinued on [redacted] and meropenem was added. Blood culture was negative. Rotavirus was found in stool culture following oral vaccination, but was negative on repeated culture. Relevant tests included ultrasound of head and abdomen, echocardiography, and cerebrospinal fluid examination (due to unspecified meningeal symptoms), which were all negative. The subject was transferred to reporting clinic. On admission, on [redacted], the subject appeared sensitive to light, and somewhat stiff and painful in thoracic spine area from cerebrospinal fluid collection. The subject had no exanthema. Treatment with meropenem and vancomycine was continued. On [redacted], blood culture was negative for bacteria and fungi. Abdominal ultrasound on [redacted] showed possible high echogenic urine, but revealed no abdominal abscess. High volume of urine was excreted from renal fistula, and a permanent catheter was inserted to avoid reflux. Abdominal ultrasound on [redacted] was unremarkable for inflammatory focus. The subject was a bit exhausted and slept more. Also, the subject experienced isolated cough attacks and intermittent hoarseness. On [redacted], CRP and leukocytes increased. On [redacted], the subject experienced thrombocytosis which was assessed as parainfectious. The subject also experienced anemia, which was considered as iatrogenic due to the almost daily blood drawals. In the evening of [redacted], a small palmar desquamation was noticed. Upon review of all findings, a differential diagnosis of Kawasaki syndrome was suspected. When being asked directly, the subject's mother remembered a fluctuating exanthema on subject's trunk, which had occurred during the previous hospitalization. The subject also had dry lips at that time. Due to suspicion of incomplete Kawasaki syndrome, an echocardiography was performed on [redacted] and revealed an aneurysm of the right coronary artery, with a widening of approximately 4 mm in diameter. An electrocardiogram (EKG) on [redacted] was unremarkable. The subject was treated with acetylsalicylic acid (ASS) and immune globulins and fever resolved on the next day. The subject slept more due to anemia. In the further course, palmar skin desquamation became more clearly visible. Antibiotic and antifungal treatments were continued until [redacted], and central line was removed subsequently. On [redacted], voiding cystouretrography confirmed vesicoureteral reflux grade III. Nephrostomy was removed on [redacted]. Permanent catheter was removed on [redacted] and the subject was treated with oral trimethoprim (Trimetoprim) and sulbactam. On [redacted], the subject still

showed an increased blood sedimentation rate and leukocytosis. The subject was discharged home on [redacted], with decreasing blood sedimentation rate and decreasing leukocyte count. Final diagnoses included incomplete Kawasaki syndrome, and pyelonephritis with differential diagnosis of pyuria. Symptoms also included irritability. No lymphadenopathy was found. Treatment during hospitalisation also included infusion therapy. The regulatory authority reported that the events anemia, coronary artery aneurysm, Kawasaki syndrome, leukocytosis, thrombocytosis and light sensitivity started on [redacted] Information received from a physician on [redacted]: At an unspecified time after first vaccination with Rotarix, the subject experienced fever and suspected urinary tract infection and was hospitalised. Symptoms worsened and the subject was transferred to another hospital, where Kawasaki syndrome was diagnosed. At the time of reporting, the subject's condition was improved. Written follow-up information received from the physician on [redacted]: The physician reported that the event incomplete Kawasaki Syndrome was possibly related to vaccination with Rotarix liquid formulation.

Company comment: *Patient with Incomplete KD, 28 days after vaccination with Infanrix Hexa, Rotavirus, and Pneumococcal vaccines (Non GSK), Patient with Pyelonefritis and renal complications (vesicouretral reflux grade III, cystouretrography) Renal infectious etiology may have trigger KD.*

[redacted]

This case was reported by a physician via a [redacted] regulatory authority [redacted] and described the occurrence of Kawasaki's disease in a 4-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) and 10 valent pneumococcal conjugate vaccine (Synflorix, GlaxoSmithKline) for prophylaxis. The subject was born on [redacted] at 08:00 (spontaneous, 24 hours post premature rupture of the amnion) with pH of umbilical cord blood at birth: 7.28; birth weight: 2330 g; birth height: 46 cm; head circumference at birth: 32 cm and Apgar score of 7/8/9. The subject's medical history included premature baby 26 to 32 weeks (32+5 weeks), hospitalization post birth, neonatal hypoglycemia, poor neonatal adaptation syndrome with neonatal respiratory failure and transitory tachypnea of newborn, sucking weakness (fluid intake reduced), neonatal bradycardia, bilateral mucopurulent conjunctivitis as well as mechanical ventilation (CPAP) for 20 hours after birth and need of oxygen supplementation for about two hours (oxygen saturation after birth was only 82% without CPAP). Concomitant medication was not reported. On [redacted] the subject received the first dose of Infanrix hexa (0.5 ml, unknown, left thigh) and the first dose of Synflorix (0.5 ml, unknown, right thigh), contralaterally. Approximately one day post vaccination with Infanrix hexa and Synflorix, on [redacted], the subject experienced Kawasaki's disease. The subject was hospitalised for an unknown period of time. The event was confirmed by clinical course. Sepsis and meningitis have been excluded by differential diagnosis. At the time of reporting, on [redacted], the event was unresolved. The vaccination courses with Infanrix hexa and Synflorix were discontinued. Follow-up information was received on [redacted] from the [redacted] regulatory authority [redacted]. The reporting physician confirmed that the subject was

vaccinated with Infanrix hexa and Synflorix but did not receive vaccination with any Rotavirus vaccine. Follow-up information received on [redacted] from the [redacted] regulatory authority ([redacted]), contained no new data. No further information will be available.

Company Comment: *Not Confirmed KD, one day after vaccination with Infanrix Hexa, and Synflorix. There is temporal association with the administered vaccines. It is not possible to conclude or exclude causality association with this KD event (not enough clinical evidence).*

APPENDIX 7B.7 : Rash and Rash maculo-papular

BACKGROUND

[redacted] health authorities received a report of adverse reactions suspected to be associated with the use of Infanrix-HEXA Vaccine [redacted] [Batch no. A21CB398A; DoE 9/2014] and Rotarix Vaccine [Batch no. AROLA954BB; DoE 5/2016]. The adverse reactions reported included itchy rash in the thighs, face and whole body (GSK global case ID of index case: [redacted].

Question No. 1

A soft copy of the Product Monographs of Infanrix-HEXA Vaccine ([redacted]) and Rotarix Vaccine

Company response

Provided by GSK [redacted] local operating company.

Question No. 2

Global data on the report of similar adverse events received in relation to the above-mentioned batch of vaccines

Company response

A search in the global GSK safety database of spontaneously reported adverse event cases associated with batches A21CB398A and AROLA954BB was performed (data lock point 25 September 2014). In addition to the index case ([redacted], one other case was reported for Rotarix batch AROLA954BB (Table 1). No other cases were received for Infanrix hexa batch [redacted].

Table 1 Cases reported for batches A21CB398A and AROLA954BB

Case ID Country	Vaccine	Batch	Events	Date received by GSK	Serious-ness	Age
[redacted]	Rotavirus vaccine	AROLA954BB	Vomiting, Underdose	04/09/2014, 05/09/2014	Not serious	2 Months
	Infanrix hexa, Rotavirus vaccine, Pneumococcal vaccines (Non-GSK)	A21CB398A, AROLA954BB	Rash pruritic, Pyrexia	12/09/2014, 15/09/2014, 17/09/2014	Serious	2 Months

- [redacted] **Vomiting, Underdose**

  This case was reported by a nurse via a sales representative and described the occurrence of vomiting in a 2-month-old male who was vaccinated with Rotarix (liquid formulation). Concurrent vaccination included unspecified doses of Infanrix IPV/Hib (diphtheria, tetanus, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine and Prevenar 13 (pneumococcal vaccine, non-GSK) given on [redacted]. On the same day, the subject received 1st dose of Rotarix liquid formulation (oral). On [redacted], immediately after vaccination with Rotarix liquid formulation, the subject vomited out with milk curd. On [redacted], vomiting was resolved after 20 minutes and revaccination was performed uneventfully.

  Company comment: Non-serious listed event that resolved quickly. Vomiting, which occurred immediately after Rotarix administration, is suggestive of spitting or regurgitation of the vaccine which is frequent and benign in young infants.

- [redacted] **Rash pruritic, Pyrexia**

  This is the index case and was reported by a physician and pharmacist via a sales representative and described the occurrence of itchy rash in a 2-month-old female who was vaccinated with a first dose of Infanrix hexa, Rotarix (liquid formulation) and Prevenar 13 (pneumococcal vaccine, non-GSK) on [redacted]. Five to six hours after vaccination, in the night, the subject experienced fever. On [redacted], 10 hours after vaccination, the subject experienced itchy rash on the

thighs. On [redacted], the rash spread to the rest of the body and face. Fever subsided when rash appeared. Hospitalisation was not required. The subject was treated with chlorpheniramine maleate (Piriton). At the time of reporting, the outcome of itchy rash was unspecified.

Company comment: Time to onset was 5-6 hours post vaccination with Infanrix hexa, Prevenar 13 and Rotarix liquid formulation. Initial fever was followed by development of widespread itchy rash covering thighs, body and face about 10 hours post vaccination. The infant was not hospitalised but required treatment with chlorpheniramine. No other clinical details are available for this case. Rash is listed for Infanrix hexa and Prevenar. Rash is not a listed event for Rotarix, but hypersensitivity and dermatitis are listed for Rotarix.

Question No. 3

Data on local and global trend on any increase in the incidence of the mentioned reaction(s) (if any)

Company response

1. INFANRIX HEXA

The GSK worldwide safety database was searched using the following criteria:

- **Data lock point:** 22 September 2014
- **Report types**: All spontaneous reports
- **Suspect vaccine**: Infanrix hexa
- **MedDRA preferred terms**: Rash, Rash generalised, Rash pruritic
  Preferred terms related to the verbatim terms '*itchy rash in the thighs, face and whole body*' were selected by reviewing a cumulative summary of adverse events for Infanrix hexa.

Globally
The above search of the global GSK Safety Database retrieved 337 spontaneous cases. All included the PT 'Rash', three included the PT 'Generalised rash' (in addition to 'Rash'), and one included the PT 'Rash pruritic' (in addition to 'Rash'). Most were from European countries such as Italy (42.3%), Germany (11.6%) and the Netherlands (11.6%). The median age (5 months) and dose number were in line with the Infanrix hexa age indication for primary vaccination (first year of life). Both genders were equally distributed. The median time to onset was 2.5 hours after the last Infanrix hexa dose. The outcome was reported as resolved, resolved with sequelae or improved in 70% of cases. Most (65.5%) cases were non-serious and reported as co-administered with other vaccines.

Figure 1 shows the number of cases including the PTs Rash, Rash Generalized and/or Rash Pruritic by calendar year (using vaccination date, not case receipt date) since first marketing authorization in 2000 (left axis). The red line (and right axis) represents the number of doses distributed by calendar year. Note that the data for 2014 does not cover the entire year since the data lock point was 22 September 2014. Overall, the number of cases including the PTs Rash, Rash Generalized and/or Rash Pruritic received by the Company increased over time, as did the number of doses distributed.

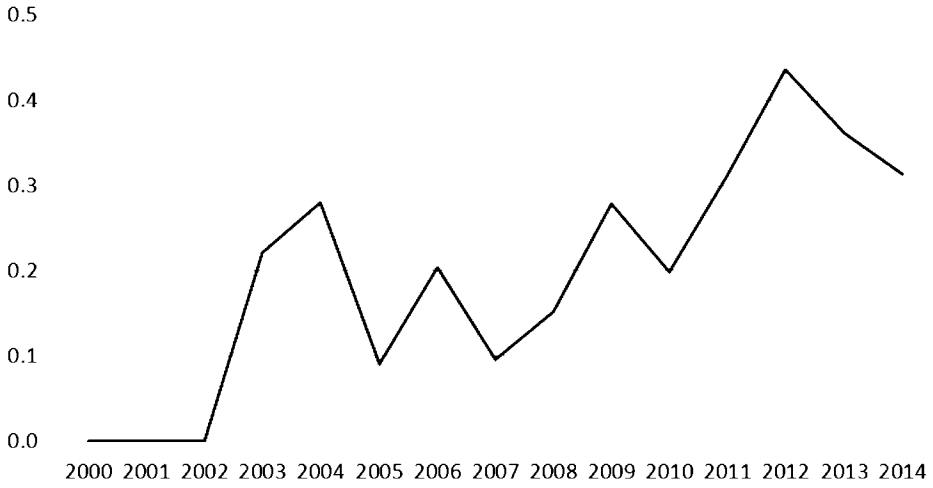
Figure 2 shows the worldwide reporting frequency of Infanrix hexa cases including the PTs Rash, Rash Generalized and/or Rash Pruritic per 100,000 doses distributed by calendar year (using vaccination date, not case receipt date). This reporting frequency varied between 0.10 and 0.30 cases per 100,000 doses distributed, and peaked at 0.44 in 2012. This increased reporting rate was mainly driven by the Netherlands and Italy (see Figure 1).

The Dutch overall (regardless of event) case reporting frequency is the highest among countries where Infanrix hexa is distributed (54 cases per 100 000 doses distributed). Thus Dutch reporting has a high impact on the global reporting frequency for Infanrix hexa. Special attention might have further impacted the Dutch reporting frequency due to extension of the target population for Infanrix hexa vaccination from only children at risk for hepatitis B infection in 2006, to children with Down syndrome as of 2008 and finally all new-borns as of 2011.

In Italy the increase was due to an increased attention of health care providers to report AEs as encouraged by the Italian Drug Agency (AIFA). Since 2008 there has been a steady increase in the Italian overall case reporting frequency, regardless of event.

Figure 1 Worldwide reporting of spontaneous Infanrix hexa cases including the PTs Rash, Rash Generalized and/or Rash Pruritic by calendar year

Figure 2 **Worldwide reporting frequency of spontaneous Infanrix hexa cases including the PTs Rash, Rash Generalized and/or Rash Pruritic per 100,000 doses distributed by calendar year**



Hong Kong

Among the above 337 spontaneous Infanrix hexa cases, four were reported from [redacted] including the index case (Table 2). Only the index case was serious and the only other event co-reported was pyrexia. The time to onset (when reported) did not exceed one day and the outcomes were either unresolved at the time of reporting or unknown.

Table 2 Line listing of spontaneous Infanrix hexa cases including the PTs Rash, Rash Generalized and/or Rash Pruritic reported from [redacted]

Case ID + Country Of Reporter + GSK Receipt date	Age + Gender	Suspect Drugs PT Comma Sep	Dose Number	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted] 12 Dec 2012	Infant Unknown	Infanrix hexa, Rotavirus vaccine	Unknown	0 Days	Rash	Not serious	Unknown
[redacted] 6 Aug 2012	Infant Unknown	Infanrix hexa, Rotavirus vaccine	2	1 Day	Rash, Pyrexia	Not serious	Unresolved
[redacted] 05 Feb 2013	Infant Unknown	Infanrix hexa	Unknown	Unknown	Rash	Not serious	Unknown
[redacted]	2 Months Female	Infanrix hexa, Rotavirus vaccine	1	5 Hours	Rash pruritic, Pyrexia	Serious	Unknown

2. ROTARIX

The GSK worldwide safety database was searched using the following criteria:

- **Data lock point:** 23 September 2014
- **Report types**: All spontaneous reports
- **Suspect vaccine**: Rotarix

MedDRA preferred terms: Rash, Rash generalised, Rash pruritic
Preferred terms related to the verbatim terms '*itchy rash in the thighs, face and whole body*' were selected by reviewing a cumulative summary of adverse events for Rotarix.

Globally
Search of the GSK Safety Database revealed 203 spontaneous cases of rash, of which 22 were reported in Asian countries such as the Philippines, Korea, Brunei, Singapore, Vietnam, Hong Kong and Indonesia. The highest frequency of cases were from Japan, (23 cases), Brazil (26 cases) and Germany (19 cases). One hundred and fifty (150) cases included the PT 'Rash', 49 cases included the PT 'Generalised rash', and 4 cases included the PT 'Rash pruritic'.

Ninety three (93) spontaneous cases were male, 89 cases were female, and in 21 cases gender was not reported. The range of ages was 1 month to 28 months. The range of times to onset was 'zero minutes' to 14 months.

144 (71%) cases were non-serious, and 117 (58%) cases were reported as co-administered with other vaccines.

Figure 3 shows the number of spontaneous cases of rash (as defined in the previous sections) reported in association with Rotarix by year. There is a rise in the frequency of reports over the first 7 years of marketing, with a peak of reports in 2011, which predictably corresponds to the widening use of the vaccine around the world.

Figure 3 Worldwide reporting of spontaneous Rotarix cases including the PTs Rash, Rash Generalized and/or Rash Pruritic by calendar year

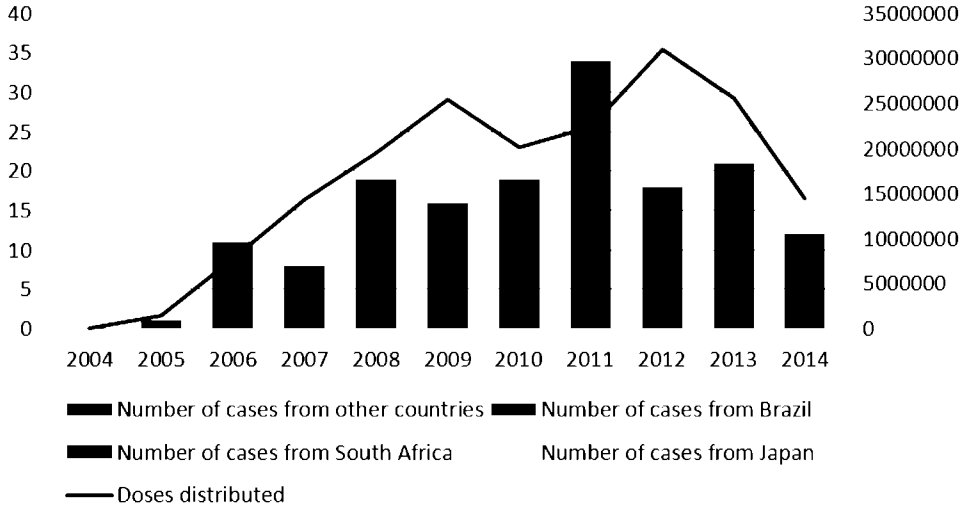


Figure 4 shows the rash adverse drug reactions (ADRs) associated with Rotarix as a proportion of sales per year. After an initial rise over the first 2 years after initial marketing authorisation, the reporting frequency rises to a peak in 2011, and then decreases in line with less annual sales. The proportion varies between 0.06 and 0.16 cases per 100,000 doses distributed between 2005 and 2014. Of note marketing in certain countries produces larger increases in the number of reports, which increases the reporting ratio of ADRs overall. A large part of the peak in reports was due to reports coming from Brazil in 2010 and 2011. Reporting for all ADRs from Brazil increased between 2009 and 2012, before decreasing again. This is attributed to the launch of a local pharmacovigilance regulation in 2009, in addition to new regulations over subsequent years addressed to Health Care Professionals which required compulsory notification of specific adverse events (including post vaccination). These account in part for the increased awareness and reporting among Brazilian HCPs over this period, and also the fall in reports after the initiatives were completed. Another part of the peak in reports observed was due to the approval of Rotarix Japan in 2011 (Figure 3).

Figure 4 **Worldwide reporting frequency of spontaneous Rotarix cases including the PTs Rash, Rash Generalized and/or Rash Pruritic per 100,000 doses distributed by calendar year**

[redacted]

There were 6 spontaneous cases identified using these preferred terms.

Only one of these cases met the criteria for seriousness. Of note no other events are reported with these rashes.

Gender was reported in 2/6 of these cases (female), and was unknown in the rest. Age was reported in 4 cases (1 case was 2 months old, and 3 cases were 4 months old).

The event time to onset was reported in only 4/6 of these cases, and was reported as 0 days in 2 cases, 1 day in 1 case, and 5 hours in one case.

In all of these cases causality assessment was confounded by concomitant vaccination with other vaccines. In 3 cases with Infanrix-Polio-Hib, and in 3 cases with Infanrix hexa (see Table 2).

Question No. 4

Other adverse effects or events reported locally in relation to the vaccines

Company response

Provided by GSK [redacted] local operating company.

Question No. 5

View or opinion of or scientific finding(s) by your company in accounting for the emergence of this adverse event

Company response

1. INFANRIX HEXA

Review of batch A21CB398A
The review of the available safety data for batch A21CB398A did not highlight a safety issue (see Question No. 2), the events reported are unlikely related to a batch quality issue from manufacturing origin.

Global data and trends
The spontaneous reporting rate varied between 0.10 and 0.30 cases per 100,000 doses distributed between 2002 and 2011, and peaked at 0.44 in 2012. This increased reporting rate was mainly driven by the Netherlands and Italy.

The Dutch overall (regardless of event) case reporting frequency was the highest among countries where Infanrix hexa is distributed (54 cases per 100 000 doses distributed). Thus Dutch reporting has a high impact on the global reporting frequency for Infanrix hexa. Special attention might have further impacted the Dutch reporting frequency due to extension of the target population for Infanrix hexa vaccination from only children at risk for hepatitis B infection in 2006, to children with Down syndrome as of 2008 and finally all new-borns as of 2011.

In Italy the increase was due to an increased attention of health care providers to report AEs as encouraged by the Italian Drug Agency (AIFA). Since 2008 there has been a steady increase in the Italian overall case reporting frequency, regardless of event.

There were no abnormal trends in the reporting of rash events in association with Infanrix hexa, neither in [redacted], nor globally. Rash is an adverse event listed in the reference safety information (RSI) of Infanrix hexa. The incidence as observed in clinical trials is 'rare', i.e. ≥ 1/10000 to < 1/1000. Reporting of rash in post-marketing settings is therefore expected. The benefit risk balance of Infanrix hexa continues to be positive.

2. ROTARIX

Review of batch AROLA954BB
The review of the available safety data for batch AROLA954BB did not highlight a safety issue, the events reported are unlikely related to a batch quality issue from manufacturing origin.

Global data and trends

A total of 203 cases of rash ('Rash', 'Rash generalised', or 'Rash pruritic') have been identified in the GSK safety database. Review of spontaneous cases showed no abnormal trends in terms of geography, gender or age clustering.

Rash ADRs were reported often with few clinical details. This made individual case assessment difficult and therefore precluded extensive causality assessment. Where clinical details are available, the causality was predominantly confounded by the co-administration of several other vaccines.

Global figures showed an increase in the number of reports over time peaking at 2011, which reflects increasing marketing of the product globally, and the predictable increased awareness of the product. The figures were also impacted by new local regulations of ADR reporting in Brazil, and the launch of Rotarix in Japan in 2011, which made a major contribution to the peak of reporting of rash ADRs in 2011.

There were no abnormal trends in the reporting of rash events in association with Rotarix neither in [redacted] nor globally.

The company's view is that this is not a signal, and the benefit risk balance of Rotarix continues to be positive.

APPENDIX 7B.8a : Myocarditis

Background of the request

Health Canada is undertaking a review of myocarditis following administration of diphtheria and tetanus toxoids-containing vaccines. One case of myocarditis has been reported to the Canadian vigilance group ([redacted]) and there is a difference in diphtheria and tetanus toxoids-containing vaccine labels from different manufacturers, i.e. myocarditis is included in the Adacel™ (Sanofi) label under post-marketing adverse drug reactions, but not listed for Boostrix (GSK), Boostrix-Polio (GSK) and Infanrix-hexa (GSK). Therefore Health Canada requested GSK to perform a safety evaluation of adverse drug reactions (serious and non-serious) pertaining to Boostrix, Boostrix-Polio and Infanrix-hexa, including the following:

Question No. 1

A clear clinical definition of the adverse event of interest

The Company's response

Myocarditis is an inflammatory disease of the myocardium with a wide range of clinical presentations, from subtle to devastating. More specifically, it is described as "an inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes" [Aretz, 1987]. Myocarditis usually manifests in an otherwise healthy person and can result in rapidly progressive (and often fatal) heart failure and arrhythmia. It is diagnosed by established histologic, immunologic, and immunochemical criteria.

Lieberman [1991] further classified myocarditis as follows:

- **Fulminant** myocarditis - Follows a viral prodrome; distinct onset of illness consisting of severe cardiovascular compromise with ventricular dysfunction and multiple foci of active myocarditis; either resolves spontaneously or results in death
- **Acute** myocarditis - Less distinct onset of illness, with established ventricular dysfunction; may progress to dilated cardiomyopathy
- **Chronic active** myocarditis - Less distinct onset of illness, with clinical and histologic relapses; development of ventricular dysfunction associated with chronic inflammatory changes (including giant cells)
- **Chronic persistent** myocarditis - Less distinct onset of illness; persistent histologic infiltrate with foci of myocyte necrosis but without ventricular dysfunction (despite symptoms, eg, chest pain, palpitations)

For the purpose of this evaluation the case definition for **acute** myocarditis by Morgan [2008] was applied, including a risk period up to 30 days for symptom onset after Boostrix, Boostrix-Polio or Infanrix-hexa vaccination (Table 1). Use of a 30 day risk period is in line with the results of a literature search for individual case reports performed regardless of causality assessment by Barton [2008] who reported that time to disease onset after immunization ranged from 1 to 30 days. The same risk period was applied by Halsell [2003] and Arness [2004] to study post-vaccination (smallpox) myocarditis among US military personnel.

Table 1 Case definition of myocarditis, for surveillance of adverse events after smallpox vaccination in the United States, 2003

Level of diagnostic certainty for acute myocarditis	Signs and symptoms	Cardiac enzymes	Electrocardiogram findings (beyond normal variants) not previously documented	Imaging studies[a]	Histopathology
Suspected	Dyspnea, palpitations, and chest pain of probable cardiac origin, in the absence of evidence of any other likely cause of symptoms	Not performed or normal	ST-segment or T-wave abnormalities, paroxysmal or sustained atrial or ventricular arrhythmias, atrioventricular nodal conduction delays, or intraventricular conduction defects; continuous ambulatory electrocardiographic monitoring that detects frequent atrial or ventricular ectopy	Evidence of diffuse or focal depressed left ventricular function of indeterminate age	Not performed or normal
Probable	Dyspnea, palpitations, and chest pain of probable cardiac origin, in the absence of evidence of any other likely cause of symptoms	Elevated troponin I or T or creatine kinase–myocardial band; a troponin is preferred	Not performed, normal, or abnormal	Evidence of focal or depressed left ventricular function that is documented to be of new onset or increased severity, in the absence of a new or study findings of depressed left ventricular function, considered of new onset if no known studies; these findings may be evidence of myocardial inflammation	Not performed or normal
Confirmed	Dyspnea, palpitations, and chest pain of probable cardiac origin, in the absence of evidence of any other likely cause of symptoms	Not performed, normal, or elevated	Not performed, normal, or abnormal	Not performed, normal, or abnormal	Evidence of myocardial inflammatory infiltrate with necrosis and myocyte damage

Question No. 2

A description of the search strategy used to retrieve the cases

The Company's response

To retrieve cases of myocarditis following vaccination with Boostrix, Boostrix-Polio or Infanrix-hexa, the GSK worldwide safety database was searched on 18th March 2013 using the following criteria:

- **Data lock point:** 17th March 2013
- **Report types:** All spontaneous reports, post-marketing surveillance reports, and unblinded serious clinical trial reports (attributable and non-attributable)
- **Suspect vaccines:** Boostrix, Boostrix-Polio and Infanrix-hexa
- **MedDRA preferred terms (PTs in MedDRA Version 15.1):** PTs were selected by reviewing a cumulative summary of adverse events cumulatively reported for the three vaccines above. Among all PTs cumulatively reported for these vaccines the following were retained for the present query of the GSK safety database: Myocarditis, Myopericarditis and Pericarditis.
  Note: A query performed with the high level terms (HLTs) 'Infectious myocarditis[1]' and 'Noninfectious myocarditis[2]' retrieved only a subset of the cases retrieved with the three above PTs because 'Infectious myocarditis' does not include the PT Myocarditis nor Pericarditis, and because 'Non-infectious myocarditis' does not include the PT Pericarditis.

[1] The HLT '**Infectious myocardits**' includes the following PTs: Coxsackie carditis, Coxsackie myocarditis, Cytomegalovirus myocarditis, Malarial myocarditis, Myocardiac abscess, Myocarditis bacterial, Myocarditis helminthic, Myocarditis infectious, Myocarditis meningococcal, Myocarditis mycotic, Myocarditis septic, Myocarditis syphilitic, Myocarditis toxoplasmal, Viral myocarditis.

[2] The HLT '**Noninfectious myocardits**' includes the following PTs: Allergic myocarditis, Autoimmune myocarditis, Eosinophilic myocarditis, Lupus myocarditis, Myocarditis, Myocarditis post infection.

Question No. 3

A detailed summary analysis for all cases. Information should include, but should not be limited to:

a. tabulation of all events;

b. market authorization holder's comments on the cases;

c. summary analysis of the temporal relationship between drug administration and the occurrence of the events;

d. summary analysis of possible risk factors and confounding variables.

The Company's response

a. Tabulation of all events

The query described in answer to Question No. 2 retrieved 3 cases associated with Boostrix, no case associated with Boostrix-Polio and 4 cases associated with Infanrix hexa. These cases are listed in Table 3 and Table 4, including diagnosis certainty level for acute myocarditis according to Morgan [2008], as well as GSK causality assessments.

Six out of these seven cases were received from Germany. All were reported spontaneously, no case from clinical trials or post-marketing surveillance studies was received.

Causality
Myocarditis is probably caused by a wide variety of infectious organisms, autoimmune disorders, and exogenous agents, with genetic and environmental predisposition (see Table 2 and reviews by Feldman [2000], Cooper [2009] and Durani [2010]). Most cases are presumed to be caused by a common pathway of host-mediated, autoimmune-mediated injury, although direct cytotoxic effects of the causative agent and damages due to cytokine expression in the myocardium may play some role in myocarditis aetiology. **In adults**, myocarditis most often results from common viral infections; less commonly, specific forms of myocarditis may result from other pathogens, toxic or hypersensitivity drug reactions, giant-cell myocarditis, or sarcoidosis (Table 2). **In children**, the most common cause is idiopathic [Durani, 2009].

For the purpose of this evaluation, hypersensitivity myocarditis is the most plausible mechanism for a causal association to vaccination because allergic reactions have been associated with vaccination [Halsell, 2003; Mora, 2009]. Hypersensitivity myocarditis is an inflammatory disease of the myocardium, usually related to drug allergy [Fenoglio, 1981; Taliercio, 1985]. The nature of the inflammatory infiltrate present in myocardial tissue biopsy is a key for differentiating aetiology. The finding of an eosinophilic infiltrate on myocardial biopsy suggests a hypersensitivity phenomenon, as opposed to a lymphocytic infiltrate, characteristic of viral aetiology [Barton, 2008].

Vaccinations are usually well tolerated and vaccination-associated myocarditis has rarely been reported. A literature review by Barton [2008] identified 269 subjects with myocarditis or pericarditis after immunization, of which 251 were related to smallpox

vaccine. Although the real background rate of myo(peri)carditis in the general population is unknown, a causal association between the vaccinia vaccine and myo(peri)carditis is certainly suggested, and most of the medical community has accepted it [Halsell, 2003; Mora, 2009].

For other vaccines, myocarditis or pericarditis cases have been reported sporadically in temporal association with immunization. Among those identified by Barton's literature review [2008], 9 were temporally related to influenza vaccine, 2 pericarditis (zero myocarditis) cases were associated with hepatitis B vaccine, and one case was reported for each of the following vaccines: diphtheria-tetanus-polio, DTP and oral polio (probably whole cell DTP since reported in 1986), yellow fever, cholera, anti-catarrh and rabies/tetanus vaccine. There was also one case of myocarditis following multiple vaccines (DTPa booster, hepatitis A vaccine and meningococcal conjugate vaccine). A clear statement regarding acceptance of a causal association of myocarditis with vaccines other than smallpox could not be found.

The outcome of the often dramatic presentation of post-vaccination acute myocarditis was concluded to be usually benign [Thanjan, 2007; Barton, 2008].

Table 2 Causes of myocarditis

Infectious	
Bacterial	brucella, *Corynebacterium diphtheriae*, gonococcus, *Haemophilus influenzae*, meningococcus, mycobacterium, *Mycoplasma pneumonia*, pneumococcus, salmonella, *Serratia marcescens*, staphylococcus, *Streptococcus pneumoniae*, *Strep. pyogenes*, *Treponema pallidum*, *Tropheryma whippelii*, and *Vibrio cholerae*
Spirochetal	borrelia and leptospira
Fungal	actinomyces, aspergillus, blastomyces, candida, coccidioides, cryptococcus, histoplasma, mucormycoses, nocardia, and sporothrix
Protozoal	*Toxoplasma gondii* and *Trypanosoma cruzi*
Parasitic	ascaris, *Echinococcus granulosus*, *Paragonimus westermani*, schistosoma, *Taenia solium*, *Trichinella spiralis*, visceral larva migrans, and *Wuchereria bancrofti*
Rickettsial	*Coxiella burnetii*, *Rickettsia rickettsii*, and *Rick. tsutsugamushi*
Viral	**coxsackievirus**, cytomegalovirus, dengue virus, echovirus, encephalomyocarditis, Epstein–Barr virus, hepatitis A virus, hepatitis C virus, herpes simplex virus, herpes zoster, **human immunodeficiency virus**, influenza A virus, influenza B virus, Junin virus, lymphocytic choriomeningitis, measles virus, mumps virus, parvovirus, poliovirus, rabies virus, respiratory syncytial virus, rubella virus, rubeola, vaccinia virus, varicella–zoster virus, variola virus, and yellow fever virus
Immune mediated	
Allergens	acetazolamide, amitriptyline, cefaclor, colchicine, furosemide, isoniazid, lidocaine, methyldopa, penicillin, phenylbutazone, phenytoin, reserpine, streptomycin, tetanus toxoid, tetracycline, and thiazides
Alloantigens	heart-transplant rejection
Autoantigens	**Chagas' disease**, *Chlamydia pneumoniae*, Churg–Strauss syndrome, inflammatory bowel disease, giant-cell myocarditis, insulindependent diabetes mellitus, Kawasaki's disease, myasthenia gravis, polymyositis, **sarcoidosis**, **scleroderma**, **systemic lupus erythematosus**, thyrotoxicosis, and Wegener's granulomatosis
Toxic myocarditis	
Drugs	amphetamines, **anthracyclines**, catecholamines, cocaine, cyclophosphamide, **ethanol**, fluorouracil, hemetine, interleukin-2, lithium, and trastuzumab
Heavy metals	copper, iron, and lead
Physical agents	electric shock, hyperpyrexia, and radiation
Miscellaneous	arsenic, azides, bee and wasp stings, carbon monoxide, inhalants, phosphorus, scorpion bites, snake bites, and spider bites

The most common causes are shown in boldface type. Extracted from Feldman [2000].

Table 3 Tabulation of all cases reported after Boostrix vaccination

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness FDA/ Case Outcome	Acute Myocarditis diagnosis certainty*	Causality assess-ment
[redacted]	15 Years Male		Boostrix		Same day	Sudden death, Pyrexia, Headache, Cardiac arrest, Myocarditis, Skin lesion, Hypersensitivity	Serious/ Fatal	Confirmed	Insufficient evidence to confirm or exclude causality
	17 Years Male	Seasonal allergy	Boostrix		3 Days	Myocarditis, Pyrexia, Chest discomfort, Chest pain	Serious/ Improved	Probable	Insufficient evidence to confirm or exclude causality
	16 Years Male	Herpes simplex	Boostrix, Diphtheria + poliomyelitis vaccine + tetanus vaccine (Non-GSK)		1 Days	Myopericarditis, Myocarditis, Pericarditis, Pleurisy, Painful respiration, Pyrexia, Pericardial effusion, Pleural effusion, Fatigue, Cough	Serious/ Improved	Suspected	Unlikely related due to underlying HSV infection

*Morgan (2008)

Table 4 Tabulation of all cases reported after Infanrix hexa vaccination

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness FDA/Case Outcome	Acute Myocarditis diagnosis certainty*	Causality assess-ment
[redacted]	16 Months Male	Bronchitis chronic, Pneumonia, Otitis media, Tonsillitis, Caesarean section, Placental insufficiency, Parvovirus infection	Infanrix hexa	Infanrix hexa	2 Days	Myocarditis, Cardiac failure, Ill-defined disorder, Pericardial effusion, Pneumonia, Tachypnoea, Metabolic acidosis, Atelectasis, Pleural effusion, Pallor, General physical health deterioration	Serious/ Improved	Suspected	Unlikely related due to underlying parvovirus infection and recurrent bronchitis
	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)		3 Hours	Cardiac failure acute, Pulmonary oedema, Sudden death, Cardiopulmonary failure, Respiration abnormal, Tachypnoea, Myocarditis, Myocardial infarction, Haemostasis	Serious/ Fatal	Confirmed	Unlikely related due to lympho-cytic infiltrate

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness FDA/Case Outcome	Acute Myocarditis diagnosis certainty*	Causality assess-ment
[redacted]	12 Weeks Male		Synflorix, Infanrix hexa		7 Days	Respiratory tract inflammation, Pneumonitis, Myocarditis, Bacterial tracheitis, Pyrexia	Serious/ Fatal	Confirmed	Unlikely related due to underlying *Staphylo-coccus* infection
	12 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)		3 Days	Kawasaki's disease, Meningitis, Leukocytosis, Pericarditis, Mitral valve incompetence, Pyrexia, Fluid intake reduced, General physical health deterioration, Rash maculo-papular, Fungal skin infection, Cheilitis, Chapped lips, Palmar erythema, Lymphadenopa	Serious/ Unresolved	Not myocarditis	Unlikely due to Kawasaki's disease and the event resolved after treatment with immune-globulins and aspirin

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b. Market authorization holder's comments on the cases

- [redacted] ([redacted]) **Sudden death, Pyrexia, Headache, Cardiac arrest, Myocarditis, Skin lesion, Hypersensitivity**

  This case was reported by a regulatory authority ([redacted]) and described the occurrence of sudden death in a 15-year-old male subject who was vaccinated with an unspecified dose of Boostrix on [redacted] 24 hours after vaccination, the subject experienced fever and headache, lasting 2-3 days. On [redacted] the subject was feeling better. On [redacted] around 11:30 AM the subject was found dead on his bed. An autopsy was performed and showed cervical adenopathy, lung congestion and splenomegaly. The pathology did not find any evident cause to explain the death. The pathologist was more oriented towards an infectious cause because the teen presented splenomegaly, cervical adenopathy and pulmonary congestion. Culture results were negative for *Streptococcus* Group A. Microscopy results were pending. The Boostrix vaccine lot AC37B031CC was produced in compliance with the Good Manufacturing Practices. No deviation that could have impacted the quality of the product was highlighted during the investigation. No incident during distribution and no cold chain deviation that could have been linked to the adverse event were recorded. The final autopsy report identified severe active myocarditis with acute changes and chronic lesions. The precise aetiology could not be determined. Viral cultures and other cultures were negative and the toxicology was negative for alcohol, drugs and medication. The subject's medical history was negative. The physician reported that the subject had received all required vaccines since 1993. It could not be excluded that the acute myocarditis was due to a hypersensitivity reaction. It was suspected that the lesions were due to hypersensitivity since they were 2-5 days old which was around the time of the vaccination. The cause was not viral since all cultures came back negative. The physician considered the acute myocarditis was possibly related to vaccination with Boostrix. The subject died on [redacted] from acute myocarditis.

  *Company comment: This case describes a 15-year-old male who experienced sudden death 4 days after vaccination with Boostrix. Twenty-four hours after vaccination, the subject experienced fever and headache, lasting 2-3 days. The subject's medical history was negative. The final autopsy reported severe active myocarditis with acute changes and chronic lesions. This case fulfils a '**confirmed**' level of diagnostic certainty of acute myocarditis criteria [Morgan, 2008]. Viral cultures and other cultures were negative and the toxicology was negative. It was suspected by the pathologist that the lesions were due to hypersensitivity since they were 2-5 days old which was around the time of the vaccination. The reporting physician considered the acute myocarditis was possibly related to vaccination with Boostrix. No details on the type of infiltrate are provided, no signs or symptoms of hypersensitivity were reported, no information on treatment or possible infection. Although there is a temporal association to vaccination, there is insufficient clinical evidence to confirm or exclude causality.*

- [redacted] ([redacted]) **Myocarditis, Pyrexia, Chest discomfort, Chest pain**

  This case was reported by a physician via a sales representative and described the occurrence of myocarditis in a 17-year-old male subject who was vaccinated with first dose of Boostrix on [redacted].The subject's medical history included pollinosis. There were no concurrent drugs. The subject received several former vaccinations with vaccines from other manufacturers. Approximately three days post vaccination with Boostrix, in the morning of the [redacted], the subject woke up with fever and chest pressure. During the day the symptoms improved and the subject was riding bike. At about 17:00 the subject developed chest pain and was hospitalised. On admission the subject had fever up to 38.4°C. The lung showed vesicular breath sound, sonorous percussion sound and no rattling. There were no pathologic heart sounds. Neurological examination was reportedly normal. Laboratory tests showed increased creatine kinase, troponin T and C-reactive protein. An electrocardiogram (ECG) showed increased ST take-off in II, III aVF and V4-V6. An echocardiogram showed mitral insufficiency with decreased function of the left ventricle. A chest radiograph on [redacted] was without pathologic findings. A magnetic resonance tomogram (MRT) on [redacted] showed good function of the left ventricle, an indication for anterior hyperkinesias, no indication for myocardial edema, a mild pericardial effusion without haemodynamic effect and a mild pleural effusion at the right side. There were no clear signs of myocarditis, but in case of a skeletal muscle damage by tetanus toxoid a damage of myocardium was considered to be possible. No scars or fibroses were visible. Drug-induced myocarditis was diagnosed. The subject was treated with metoprolol succinate (Beloc-Zok mite) and ramipril (Delix). The laboratory values and ECG findings normalised. On [redacted] the subject was discharged from hospital. The clinical symptoms had resolved on [redacted].

  *Company comment: This case describes a 17-year-old male subject who developed fever and chest pain 3 days after vaccination with Boostrix. Drug-induced myocarditis was diagnosed. The subject's medical history included pollinosis. Laboratory tests showed increased CK, troponin T and C-reactive protein. An electrocardiogram (ECG) showed increased ST segment. An echocardiogram showed mitral insufficiency with decreased function of the left ventricle. MRT showed a mild pericardial effusion without haemodynamic effect and a mild pleural effusion at the right side. There were no clear signs for myocarditis, but in case of a skeletal muscle damage by tetanus toxoid a damage of myocardium was considered to be possible. This case fulfils a '**probable**' level of diagnostic certainty of acute myocarditis criteria [Morgan, 2008] although it has to be noted MRT does not seem to confirm myocarditis. A myocardial tissue biopsy was not reported to be performed. Although there is a temporal association to vaccination, there is insufficient clinical evidence to confirm or exclude causality. The events resolved within 2 weeks.*

- [redacted] **Myopericarditis, Myocarditis, Pericarditis, Pleurisy, Painful respiration, Pyrexia, Pericardial effusion, Pleural effusion, Fatigue, Cough**

  This case was reported by a [redacted] regulatory authority ([redacted]) and described the occurrence of perimyocarditis in 16-year-old male subject who was vaccinated with an unspecified dose of Boostrix on 10 July 2009. Co-suspect vaccinations included diphtheria + poliomyelitis vaccine + tetanus vaccine (Revaxis, Sanofi Pasteur MSD). Concurrent medical conditions included Herpes simplex virus (HSV) infection. Approximately one day post vaccination with Boostrix and Revaxis, on [redacted], the subject experienced perimyocarditis (myocarditis and pericarditis) and pleuritis. In the evening of [redacted] the subject experienced persistent pain in thorax upon breathing left parasternal with protective shallow breathing and fever of 38.7°C. On the next day, on [redacted], the subject was hospitalised for persistent thoracic pain for nine days. On admission to hospital the subject showed fatigue and was only coughing slightly and cautiously. The subject showed no palpable lymph nodes. The oral cavity was normal. The medial part of the sternum was sensitive to pressure. Lungs: Percussion sound of lungs sonorous, lower limit of lungs normal and well adjustable by breathing, vesicular respiration, no pleural friction rub. Heart: regular, rate 104 /min, heart sounds clear, blood pressure 140/90 mmHg. Abdomen: palpatory and auscultatory normal. Transthoracic echocardiogram showed mild pericardial effusion dorsal and minor pleural effusion left. Electrocardiogram (ECG) showed elevated ST segment on admission, followed by negative T waves since [redacted]. Serology showed Herpes simplex virus 1 (HSV-1) and Herpes simplex virus 2 (HSV-2) infection with increased IgG levels. C-reactive protein (CRP) was increased. The hospital physician(s) considered that the cause of the events was unknown. The reporting physician considered that the events were temporally related to vaccination with Boostrix and Revaxis, but considered that a causal relationship of the event to vaccination with Boostrix and Revaxis was most questionable. The reporting physician also considered that the causal relationship of the events to Herpes simplex virus (HSV) infection stayed unclear. The presence of IgG antibodies speaks for a former infection with HSV, because seroconversion post infection in average needs about eight weeks. Furthermore myocarditis was a very atypical event associated with HSV infection. Epstein-Barr virus (EBV) infection was mainly excluded because of antibody titre and missing typical symptoms like lymph node enlargement or splenomegaly. The subject received no antiviral medication because the events were already very much improved. On [redacted] the subject was discharged from hospital. At the time of writing the reports, on [redacted] the events were unresolved, but distinctly improved.

  Company comment: *This case describes a 16-year-old male subject who was diagnosed with perimyocarditis and pleuritis starting approximately 1 day post vaccination with Boostrix and Revaxis (i.e. overdose). Concurrent medical conditions included Herpes simplex virus (HSV) infection. The subject experienced persistent pain in thorax and fever of 38.7°C. Transthoracic echocardiogram showed mild pericardial effusion dorsal and minor pleural effusion left. Electrocardiogram (ECG) showed elevated ST segment on admission, followed by negative T waves. C-*

*reactive protein (CRP) was increased. The presence of IgG antibodies speaks for a former infection with HSV and myocarditis is a very atypical event associated with HSV infection. This case fulfils a 'probable' level of diagnostic certainty for pericarditis criteria and 'suspected' for myocarditis criteria [*Morgan, *2008]. An MRI or myocardial biopsy was not reported to have been performed. The reporting physician considered that the events were temporally related to vaccination with Boostrix and Revaxis, but considered that a causal relationship of the event to vaccination with Boostrix and Revaxis was most questionable. Although there is a temporal association to vaccination, there is insufficient clinical evidence to confirm or exclude causality. The events had improved after 9 days.*

- [redacted]**Myocarditis, Cardiac failure, Ill-defined disorder, Pericardial effusion, Pneumonia, Tachypnoea, Metabolic acidosis, Atelectasis, Pleural effusion, Pallor, General physical health deterioration**

  A physician reported the occurrence of myocarditis in a 16-month-old male who was vaccinated with the fourth dose of Infanrix hexa on [redacted]. Former vaccinations were well tolerated. No concurrent medications were reported. The subject's parents had allergies. The subject's further family anamnesis was uneventful. Birth anamnesis revealed that the subject was born after placental insufficiency via caesarean section in the 37th week of gestation. Birth weight was 2370 g and APGAR was 9/9. The subject had pneumonia when he was six weeks old (in [redacted]) and further pneumonias in [redacted], [redacted] and [redacted] The subject had otitis media in [redacted] and tonsillitis in [redacted]. Five weeks prior to hospitalisation, on an unknown date in [redacted], the subject had a parvovirus infection. Current medical conditions included recurrent obstructive chronic bronchitis. The subject was under treatment of the reporting physician since [redacted]. The reporting physician administered the third and fourth Infanrix hexa doses. The reporting physician did not know whether the first two vaccinations were done with Infanrix hexa. The third vaccination was administered with delay due to frequent bronchitis. The subject was healthy at the time of the fourth vaccination and there was no evidence for an infection. Two days post vaccination on [redacted] the subject started to drink not well. There was no fever and no cough. Some days prior to hospitalisation, the subject developed tachypnea and he was pale. The subject was brought to the hospital due to his reduced general condition. The subject was hospitalised on [redacted] as pneumonia was suspected. The subject received antibiotic treatment. In hospital, the subject developed metabolic acidosis. Echocardiogram showed dilatative cardiomyopathy. Myocarditis with global heart failure was suspected. Auscultation showed low-frequent proto-mesosystoles with puncto maximum over the fourth intercostal area, left parasternal. Electrocardiogram showed sinus rhythm with a frequency of 170/min. There was low voltage. There were no clear signs for hypertrophy. Biventricular excitation disturbances were found. Echocardiography revealed an increased left atrium, dilated right and left ventricle with clearly restricted systolic function, mild mitral valve insufficiency, bilateral pleural effusion and mild pericardial effusion. According to the reporting physician, myocarditis started on [redacted], two days post vaccination. X-ray of the thorax revealed enlarged left side of the heart, a vessels pattern in the lung and

pleural effusion. Laboratory examinations showed the following values: leukocytes 13.4/nl, hemoglobin 9.0 g/dl, electrolytes were normal, C-reactive protein 6.0 mg/dl (maximal 16.2 mg/dl), creatinine and urea were normal, lactate dehydrogenase 528 U/l (maximal value 1.762 U/l), glutamic pyruvic transaminase (GPT) maximal 838 U/l, glutamic oxaloacetic transaminase (GOT) maximal 1023 U/l, creatine kinase 206 U/l, creatine kinase MB 33 U/l, Quick's value 34%, partial thromboplastin time 41 seconds and antithrombin III 62%. Blood gas analysis showed pH 7.25, base excess - 13 and bicarbonate 14 mmol/l.Serological tests for cardiotropic viruses showed positive immunoglobulin G (IgG) and negative IgM antibodies to parvovirus B19; the other values were normal. Irregular anti-Lua antibodies were found. Increasing hemodynamic disturbance and tachypnea/dyspnea led to intubation and artificial respiration. The subject also received intensive diuretic therapy, adrenaline (Suprarenin) and milrinone until [redacted]. On [redacted], right pleural effusion was emptied (100 ml clear pleural secretion). The subject developed pneumonia with atelectasis of the right upper lung lobe. Haemophilus influenzae was detected in tracheal secretion, and Enterobacter cloacae was detected in throat swab. The subject was treated with imipenem, vancomycin and physiotherapeutic therapy. The subject's condition improved and laboratory infectious parameters normalised. Laboratory signs of heart failure normalised and liver and blood clotting values normalised. The subject was extubated on [redacted]. The subject was clinical cardial compensated under anticongestive medication and was discharged from hospital after 26 days, on [redacted]. In the hospital report, the vaccination was not mentioned; it was mentioned that parvovirus infection was the suspected cause for myocarditis. The reporting physician also considered that myocarditis was unrelated to the vaccination. The outcome of myocarditis was reported as improved.

*Company comment: This case describes a 16-month-old male who developed myocarditis 2 days after vaccination with the 4th dose of Infanrix hexa. Five weeks prior to hospitalisation, the subject had a parvovirus infection. Current medical conditions included recurrent obstructive chronic bronchitis. Echocardiography revealed an increased left atrium, dilated right and left ventricle with clearly restricted systolic function, mild mitral valve insufficiency, bilateral pleural effusion and mild pericardial effusion. This case fulfils a '**suspected**' level of diagnostic certainty of acute myocarditis criteria [*Morgan, *2008]. Serological tests for cardiotropic viruses showed positive immunoglobulin G (IgG) and negative IgM antibodies to parvovirus B19. The subject developed pneumonia with atelectasis of the right upper lung lobe. Haemophilus influenzae was detected in tracheal secretion, and Enterobacter cloacae was detected in throat swab. A causal role of the vaccination is considered unlikely, there are other alternative factors that may have likely contributed to the occurrence of this event, including recurrent bronchitis and parvovirus infection. The events were reported to have improved.*

- [redacted]**Cardiac failure acute, Pulmonary oedema, Sudden death, Cardiopulmonary failure, Respiration abnormal, Tachypnoea, Myocarditis, Myocardial infarction, Haemostasis**

  This case was reported by a physician and described the occurrence of acute cardiac failure in a 5-month-old male subject who was vaccinated with the 3rd dose of Infanrix hexa on [redacted]. Co-suspect vaccination included 3rd dose of Prevenar (Wyeth). According to subject's mother, the subject developed breathing not normal since the day of vaccination. At examination during doctor visit saturation and pulse were normal. Previous vaccinations with Infanrix hexa and Prevenar were well tolerated. The baby was vaccinated in the morning in good status of health. 8 hours after vaccination the patient presented with sudden infant death. Subject's sibling also died suddenly of fulminant cardiomyopathy at the age of 5 months. The sibling has received the last vaccination 2.5 months prior to date of death. Subject's brother showed same symptoms of abnormal breathing on [redacted] after unspecified vaccination on [redacted]. The sibling died from cardiomegaly on [redacted] in hospital. The physician did not see a relation to vaccination. Subject's parents consulted genetic advice, but a cause was not found. The subject was vaccinated at 9:00 AM at a wide-awake general condition. At about 12:00 AM the parents presented again in the practice claiming that the baby was tachypnoeic. The paediatrician found the baby in good status of health and sent them home. At 15:00 PM the parent presented again in the practice and the baby was found a little bit tachypnoeic but in good conditions of health. Due to the fact that the couple had lost another baby boy at the same age due to cardiopulmonary dysfunction (probably myocarditis) the physician admitted the baby to a hospital. At 15:30 PM the baby was found in reduced status of health and tachypnoeic. After 45 min and repeated reanimation intents the baby died of sudden death. An autopsy was performed on [redacted]. The physician only considered vaccination as a trigger. Results of histological and toxicological examinations included significant findings like heart cell necrosis, lymphocytic myocarditis, and haemorrhagic pulmonary oedema as well as acute blood congestion in spleen, liver, adrenal glands and kidneys. Indications of active ingredients were found (probable substances which were administered during emergency treatment at intensive care unit. Cause of death was cardiac failure left side and pulmonary oedema cardiac cause.

  *Company comment: This case describes a 5-month-old male subject who died of acute cardiac failure 8 hours after vaccination with 3rd dose of Infanrix hexa and 3rd dose of Prevenar. Family history included a subject's sibling who died suddenly of fulminant cardiomyopathy at the age of 5 months. An autopsy was performed. Results of histological and toxicological examinations included significant findings like heart cell necrosis, lymphocytic myocarditis, and haemorrhagic pulmonary oedema as well as acute blood congestion in spleen, liver, adrenal glands and kidneys. Cause of death was cardiac failure left side and pulmonary oedema cardiac cause. This case fulfils a '**confirmed**' level of diagnostic certainty of acute myocarditis criteria [Morgan, 2008]. Unlikely related to vaccination due to the presence of lymphocytic infiltrate which is characteristic for a viral etiology [*Barton, *2008].*

- [redacted] **Respiratory tract inflammation, Pneumonitis, Myocarditis, Bacterial tracheitis, Pyrexia**

  This case was reported by a [redacted] regulatory authority [redacted] and described the occurrence of severe infection of respiratory tract in a 12-week-old male subject who was vaccinated with the first dose of Synflorix and Infanrix hexa on [redacted]. Less than one week after these vaccinations, on an unknown date in [redacted], the subject experienced mild fever. Fever was resolved after one day. Approximately seven days after the vaccinations, on [redacted] at around 18:30, the subject died at home. Medical history included normal course of pregnancy and regular visits of a paediatrician for child health checks. An autopsy was performed. Macroscopic autopsy showed normal general and nutritional condition, no signs of malformations, bloody foam in respiratory tract, bloody wet lung, no signs of punctual hemorrhage at serous membranes, and no signs of mechanical external force. Microbiological examinations showed no bacteria in cerebrospinal fluid (CSF) and in blood from heart, *Staphylococcus aureus* and *Escherichia coli* in pulmonary swab, as well as *Staphylococcus aureus*, *Moraxella catarrhalis* and *Escherichia coli* in pharyngeal swab. Histology showed mucous-haemorrhagic inflammation of respiratory tract with mixed cell infiltration of mucous membrane of respiratory tract, in parts acute bloating of lung tissues next to areas with underventilation, activation of bronchus associated lymphatic tissue, acute blood congestion in lungs, focal inflammatory pulmonary infiltrations, in parts with multinuclear giant cells; a singular round-cell infiltration in heart muscle, so called tubular heart muscle change; acute blood congestion in the liver. Autopsy, as well as subsequent microbiological and histological examinations, showed severe infection of respiratory tract and to a lesser extent of lungs above all with bacteria of the species *Staphylococcus aureus*. Furthermore, histology showed a single inflammatory focus in the heart muscle. With reservation of outstanding results of chemical-toxicological examinations the findings were consistent with death within the scope of inflammation of respiratory tract with involvement of the lungs and accompanying myocarditis. No signs of external mechanical force have been found, but killing with low evidence, e. g. soft covering of mouth and nose, cannot be excluded.

  *Company comment: This case describes a 12-week-old male who died seven days post vaccination with 1st dose of Synflorix and Infanrix hexa. Autopsy revealed severe respiratory tract inflammation and myocarditis as death causes. Microbiological examinations showed a singular round-cell infiltration in heart muscle, so called tubular heart muscle change. This case fulfils a '**confirmed**' level of diagnostic certainty of acute myocarditis criteria [Morgan, 2008]. A causal role of the vaccinations is considered unlikely as there are other etiological factors that may have likely contributed to the occurrence of myocarditis (i.e. infection with Staphylococcus aureus).*

- [redacted]**Kawasaki's disease, Meningitis, Leukocytosis, Pericarditis, Mitral valve incompetence, Pyrexia, Fluid intake reduced, General physical health deterioration, Rash maculo-papular, Fungal skin infection, Cheilitis, Chapped lips, Palmar erythema, Lymphadenopa**

  This case was reported by a regulatory authority [redacted] and described the occurrence of atypical Kawasaki's disease in a nearly 12-month-old male who was vaccinated with 2nd doses of Infanrix hexa and Prevenar13 on [redacted]. Previous vaccination included 1st dose of Infanrix hexa and Prevenar13 given on [redacted], which was well tolerated. At an unspecified time after 2nd vaccination with Infanrix hexa and Prevenar 13, the subject experienced fever with a body temperature up to 38.2°C. On [redacted] the subject received 3rd dose of Infanrix hexa and 3rd dose of Prevenar13. On [redacted], 3 days after 3rd vaccination with Infanrix hexa and Prevenar13, the subject experienced atypical Kawasaki's disease. The subject developed fever with body temperatures up to 40°C. On [redacted], the subject developed exanthema on abdomen and back. Exanthema of mycotic cause was suspected. The subject was treated symptomatically with antipyretic (Antipyretics).On [redacted], the subject's fluid intake was reduced. His general condition was reduced. The subject was treated with cefpodoxime. Symptoms did not improve. On [redacted] the subject was hospitalised. Atypical Kawasaki syndrome, secondary meningitis and pericarditis were diagnosed. He showed maculo-papular exanthema at trunk, arms, legs and face. His lips and palms were reddened. Cervical lymph nodes were enlarged. His body temperature was up to 40.3°C. Initially, there were clearly increased parameters for an infection (signs of infection) as well as distinct exanthema. Culture of blood and liquor were uneventfully. Due to abnormal midstream urine, the subject was treated with cefuroxime sodium (Cefuroxim). Fever did not resolve. On [redacted], the subject still suffered from fever. He showed chapped lips, palmar erythema, leukocytosis and mild cervical lymphadenopathy. Kawasaki's disease was suspected. The subject was treated with normal immunoglobulin (Immunoglobulin) and aspirin (Acetylsalicylacid). Fever resolved and general condition improved. On [redacted], echocardiography showed pericarditis and mitral insufficiency. On [redacted], the subject was discharged from hospital after 12 days. At the time of reporting atypical Kawasaki disease was unresolved. The reporter reported that the events were life threatening.

  Company comment: Kawasaki's disease in 12-month-old male subject 3 days after 3rd dose of Infanrix hexa and 2nd dose of Prevenar. Echocardiography showed pericarditis and mitral insufficiency. The subject was hospitalized. A causal role of the vaccinations is considered unlikely as there are other factors that may have likely contributed to the occurrence of the pericarditis (Kawasaki's disease) and the event resolved after treatment with immunoglobulins and aspirin.

c. Summary analysis of the temporal relationship between drug administration and the occurrence of the events

Both Boostrix and Infanrix-hexa spontaneously reported cases show a temporal relationship between drug administration and the occurrence of either myocarditis and/or pericarditis. This is not entirely unexpected in view of the reporting bias: spontaneous reporting levels decrease with time since vaccination.

Regardless of diagnosis certainty level, the time-to-onset of the three myocarditis cases reported after vaccination with Boostrix ranged between the same day of vaccination and the 3rd day after vaccination. Two cases out of three occurred within 48 hours after vaccination (Table 3).

Regardless of diagnosis certainty level, the time-to-onset of the three myocarditis cases reported after vaccination with Infanrix-hexa ranged between the same day of vaccination to the 7th day after vaccination (Table 4).

d. Summary analysis of possible risk factors and confounding variables

In adults myocarditis most often results from common viral infections; less commonly, specific forms of myocarditis may result from other pathogens, toxic or hypersensitivity drug reactions, giant-cell myocarditis, or sarcoidosis (Table 2). In children, the most common cause is idiopathic [Durani, 2009]. The risk factor reported among 4 of the retrieved cases was underlying viral or bacterial infection: parvovirus infection and recurrent bronchitis ([redacted]), lymphocytic infiltrate on myocardial tissue biopsy ([redacted]), herpes simplex virus infection [redacted]) and *Staphylococcus aureus* infection ([redacted]). In one other case pericarditis developed as a complication of Kawasaki's disease ([redacted]). Underlying viral or bacterial infections cannot be completely excluded for the 2 other reported cases, even if microbiological tests turn out negative or remained unreported ([redacted] and [redacted]). For case [redacted] it would aid the medical assessment to obtain details of the type of infiltrate (e.g. lymphocytic or eosinophilic) found during anatomopathologic examination. In case [redacted] no myocardial tissue biopsy was performed and cardiac MRI did not confirm myocarditis.

Time since vaccination is a risk factor for post-vaccination myocarditis since hypersensitivity acute myocarditis is more likely to happen within one to two weeks after vaccination. It is confounded by the reporting bias: spontaneous reporting levels decrease with time since vaccination.

Spontaneous reporting in general is further confounded by country-specific reporting rates and focus towards specific adverse events by local health authorities. It should be noted that most cases were received from[redacted].

Question No. 4

Analysis of differences in rates for myocarditis from clinical trials, observational studies and the literature.

The Company's response

The precise epidemiology/incidence rate of myocarditis in the general (unvaccinated) population is not known, particularly because diagnosis is difficult with many cases unrecognized/unconfirmed as confirmatory tests present an inherent risk to the patient, and because most populations are covered by vaccination programs. Whilst it is considered a rare disease, it is an important cause of sudden death and is associated with viral infection, particularly coxsackie viruses. Evidence of myocarditis is often found on autopsy.

Myocarditis was not reported in any of the Company's clinical trials and observational studies. Cumulative subject exposure[3] in interventional GSK-sponsored clinical trials is

- 15,114 subjects for Boostrix (data lock point 2 August 2012)
- 3,052 subjects for Boostrix-Polio (data lock point 15 December 2012)
- 21,659 subjects for Infanrix hexa (data lock point 22 October 2012)

Most published incidence estimates available in **children/adolescents/young adults regardless of vaccination** consist of ratios (not incidence rates in person-years) of myocarditis cases (acute and other types) observed (most often retrospectively) in specific sub-populations (pediatric patients attending a cardiology service [Friedman, 1998], emergency departments [Freedman, 2007] or hospital [Klugman, 2010]). They vary widely due to use of different case definitions, methodologies and target populations. These ratios were published in the context of papers where the objective was to describe myocarditis from a clinical rather than epidemiological point of view. For this reason, and because these ratios are expressed in 'cases per person' and not in 'cases per person-years', these are not appropriate for an observed-to-expected analysis of myocarditis following vaccination.

Saji [2012] also published a clinical review of **Japanese pediatric myocarditis** cases in patients aged between one month and 17 years. Cases were retrospectively collected via a survey questionnaire sent to 627 hospitals and an 'annual incidence' rate was extrapolated. However no details regarding incidence calculations were provided (population size covered by participating hospitals not described). The incidence in the article's summary (0.26 cases/100,000) is inconsistent with the one presented in the conclusion (0.24 cases/100,000 population). No details are provided on how follow-up time was used in the incidence calculation or whether it was or not taken into account.

[3] Exposure figures covers both studies within the Boostrix, Boostrix-Polio and Infanrix hexa clinical development programmes (CDPs), as well as studies outside of these CDPs where the vaccines are used as comparators or being co-administered. Exposure in GSK-supported and observational studies is not covered.

Finally, it is unknown to what extend a Japanese incidence rate could be extrapolated to a Caucasian population. For these reasons the incidence provided by Saji [2012] is inappropriate for an observed-to-expected analysis of myocarditis following vaccination.

Another group of publications described incidence and/or incidence rates in **populations vaccinated against smallpox** which is a known confounding factor. Therefore the below rates cannot be used to estimate expected rates in the current population:

- Incidence of 'vaccinia myocarditis' among Finnish military vaccinees 18 to 38 years between December 1976 and end 1979: 1 per 10,000 vaccinations [Karjalainen, 1983]. An incidence rate in person-years was not reported.
- Retrospective review of confirmed[4] and probable[5] post-vaccination (smallpox) myocarditis[6] cases (time to onset within 30 days post-vaccination) reported among US military service members since the reintroduction of vaccinia vaccine: 16.1 per 100,000 within 30 days of vaccination, thus **193.2** per 100,000 person-years [Arness, 2004].
- Prospective surveillance of myocarditis and pericarditis among civilians vaccinated during the US smallpox vaccination program between January and October 2003 [Morgan, 2008]:
  - Suspected & probable myocarditis or pericarditis: 55 cases per 100,000
  - Probable myocarditis or pericarditis only: 13 cases per 100,000

  Given that cases were collected via active and passive surveillance with different follow-up periods for each approach, no person-time was reported.

Two papers reported incidence rates in military service members:

- A prospective surveillance over a 20 year period (1977–1996) of cute **myocarditis in young Finnish military men 17-29 years** of age was published by Karjalainen in 1999. Finnish conscripts were vaccinated against smallpox until the end of 1979. During the study period 672,672 conscripts served a total of 495,283 man-years. After exclusion of vaccinia myocarditis cases, the yearly myocarditis incidence rate ranged between 0.08 and 0.25 per 1000 person-years. The mean incidence rate was 0.17 per 1000 person-years (thus **17** per 100,000 person-years). Shortcomings of this rate in view of the present evaluation include:

[4] Patient with acute myocarditis with or without pericarditis with symptom onset 4 to 30 days after vaccinia exposure and absence of another causal infection, disease or toxic agent and, virus culture or detection of vaccinia DNA by PCR identification of vacinia virus infection from myocardial tissue or pericardial fluid

[5] Patient with acute myocarditis with or without pericarditis with symptom onset 4 to 30 days after vaccinia exposure and absence of another causal infection, disease or toxic agent

[6] Based on the following International Classification of Diseases, Ninth Revision, codes: 420.90, 420.99, unspecified and other acute pericarditis; 422.90, 422.91, acute unspecified and idiopathic myocarditis; and 429.0, unspecified acute myocarditis

- that it covers a military (non-civilian) population where respiratory tract infections are especially common
- Age strata covering the cases in the GSK safety database are not covered (infants and adolescents aged 15 and 16 years)

- A retrospective review of confirmed[4] and probable[5] myocarditis[6] cases was reported among **US military service members** by Halsell [2003] and later updated by Arness [2004]. In addition to the incidence rate among vaccinees (see above), they also reported a background rate of 2.16 per 100,000 active-duty service members over any 30-day observation window, thus **31** per 100,000 person-years. This rate covers the time period between 15 December 2002 and 30 September 2003 (9,5 months). The shortcoming related to a military population applies again here, in addition to the fact that it is a US population, while cases in the GSK safety database are essentially from Germany. Also no clear age range was provided, only that the mean age was 27.8 years and that cases were categorized in the following age groups: ≤22, 23–26, 27–29, ≥30 years, thus not covering case in the GSK safety database.

In summary, the company is not aware of an incidence rate in the age groups of cases reported for Boostrix and Infanrix hexa (see answer to Question No. 3). Regarding the rates reported by Karjalainen [1999] and Arness [2004], the covered age groups (young adults) are older compared to those reported following vaccination with Boostrix (15-17 years of age). Compared to the general population, these rates might be biased to an unknown extend by the fact that they cover military personnel only, as well as other unknown factors (gender, country, time at which the studies were performed).

Question No. 5

Canadian and international patient exposure data (cumulative total and breakdown by year) in both

- **patient years and**
- **total number of patients exposed.**

The Company's response

Information on the actual number of individuals exposed to GSK vaccines in the different countries is not available to the MAH. Therefore, the total patient exposure is approximated by the number of doses distributed which is the only approximation available with regard to patient exposure for GSK vaccines in a post-marketing setting.

As Boostrix and Boostrix-Polio are indicated as a single booster dose, it was assumed that as many subjects were exposed as doses distributed. As vaccination with Infanrix hexa can vary between 1 and 4 doses per subject in accordance with local recommendations and compliance with the vaccination schedule, a range of exposure was calculated for each of these extreme options.

The cumulative number of doses distributed, an estimation of the cumulative number of patients exposed and an estimation of cumulative exposure in patient-years by year are provided for Canada and the rest of the world in Table 5 and Table 6, respectively.

Method used to estimate exposure in patient-years:
Number of doses distributed each month were extracted from the sales database and multiplied by the time between the 15th of the month of delivery and the date of 12 March 2013 (date of extraction of sales information). Summation across each month provided the total number of patient-years.

Table 5 Yearly cumulative number of doses distributed and exposure estimation in patient-years up to March 2013 - Canada

Vaccine	Year	Doses distributed	Patients exposed	Patient-years
Boostrix	2007	[redacted]	128 860	709 883
	2008		421 609	2 095 529
	2009		767 306	3 421 862
	2010		1 211 789	4 631 690
	2011		1 745 892	5 527 551
	2012		2 275 798	5 883 229
	2013		2 308 946	5 888 315
Boostrix Polio	2010		498	1 156
	2011		497	1 166
	2012		42 792	17 271
	2013		52 792	18 805
Infanrix hexa	2008		2 105 to 8 421	8 923 to 35 690
	2009		31 505 to 126 021	118 835 to 475 341
	2010		64 508 to 258 031	208 107 to 832 426
	2011		96 723 to 386 891	261 976 to 1 047 902
	2012		134 463 to 537 851	287 331 to 1 149 322
	2013		134 435 to 537 741	287 326 to 1 149 305

Table 6 Yearly cumulative number of doses distributed and exposure estimation in patient-years up to March 2013 - Rest of the world

Vaccine	Years	Doses distributed	Patients exposed	Patient-years
Boostrix	1999	4 927	4 927	65 932
	2000	130 770	130 770	1 657 567
	2001	256 378	256 378	3 121 702
	2002	479 314	479 314	5 487 744
	2003	765 113	765 113	8 254 496
	2004	1 932 802	1 932 802	18 374 041
	2005	4 233 684	4 233 684	35 762 422
	2006	8 241 076	8 241 076	62 320 442
	2007	12 447 131	12 447 131	86 197 526
	2008	16 488 888	16 488 888	105 121 360
	2009	24 386 825	24 386 825	134 033 006
	2010	34 340 129	34 340 129	160 418 182
	2011	45 818 261	45 818 261	179 584 170
	2012	60 404 353	60 404 353	189 375 715
	2013	61 801 756	61 801 756	189 541 401
Boostrix Polio	2004	38 020	38 020	323 430
	2005	152 376	152 376	1 205 230
	2006	828 036	828 036	5 676 806
	2007	1 762 353	1 762 353	10 974 523
	2008	2 778 294	2 778 294	15 713 439
	2009	4 353 403	4 353 403	21 516 941
	2010	5 975 028	5 975 028	25 868 405
	2011	7 617 550	7 617 550	28 635 456
	2012	9 624 020	9 624 020	29 997 758
	2013	9 933 213	9 933 213	30 041 891
Infanrix hexa	2000	235 493	58 873 to 235 493	724 877 to 2 899 508
	2001	1 446 712	361 678 to 1 446 712	4 246 962 to 16 987 847
	2002	3 347 895	836 974 to 3 347 895	9 310 908 to 37 243 633
	2003	5 604 671	1 401 168 to 5 604 671	14 782 454 to 59 129 814
	2004	8 458 156	2 114 539 to 8 458 156	20 983 957 to 83 935 828
	2005	12 848 133	3 212 033 to 12 848 133	29 353 251 to 117 413 003
	2006	19 729 273	4 932 318 to 19 729 273	40 876 562 to 163 506 246
	2007	28 098 009	7 024 502 to 28 098 009	52 783 643 to 211 134 570
	2008	38 618 040	9 654 510 to 38 618 040	65 066 913 to 260 267 653
	2009	50 000 691	12 500 173 to 50 000 691	75 609 780 to 302 439 121
	2010	62 934 470	15 733 618 to 62 934 470	84 249 234 to 336 996 935
	2011	75 928 205	18 982 051 to 75 928 205	89 713 374 to 358 853 496
	2012	90 439 944	22 609 986 to 90 439 944	92 098 307 to 368 393 228
	2013	92 018 242	23 004 561 to 92 018 242	92 151 510 to 368 606 041

Question No. 6

Copies of all the Council for the International Organization of Medical Science (CIOMS) full reports for Myocarditis

The Company's response

Refer to APPENDIX 1.

Question No. 7

Discussion of any risk mitigating actions planned.

The Company's response

GSK does not consider Myocarditis a potential or identified risk for Boostrix, Boostrix-Polio and Infanrix hexa (refer to answer to Question No. 8). Therefore the Company does not plan any risk mitigation actions.

Question No. 8

A conclusion as to the safety of Boostrix, Boostrix Polio and Infanrix hexa with regards to the occurrence of myocarditis.

The Company's response

Myocarditis due to hypersensitivity after immunization is rare. However its wide clinical spectrum and reliance of diagnosis on myocardial histopathology limit the determination of the true incidence and outcome of this condition. The nature of the inflammatory infiltrate present in myocardial tissue biopsy is a key for differentiating aetiology. Release of pro-inflammatory mediators and eosinophilic chemotactic factors facilitates peripheral eosinophilia and recruitment of eosinophils to affected tissues and induces cell damage [Barton,2008].

No evidence for a causal association beyond temporal relation
The query described in answer to Question No. 2 retrieved 3 cases associated with Boostrix, no case associated with Boostrix-Polio and 4 cases associated with Infanrix hexa. All cases were temporally related to vaccination.

Three of the four cases associated with Infanrix hexa were unlikely related to vaccination; concurrent infections were the most probable cause of the events, while in one case ([redacted]) pericarditis (and not myocarditis) developed as a complication of Kawasaki's disease.

One of the Boostrix cases ([redacted]) occurred in a subject suffering from concurrent HSV infection and is therefore considered unlikely related to vaccination. The two other Boostrix cases ([redacted] and [redacted]) contained insufficient clinical evidence beyond a temporal relationship to confirm or exclude causality. For case [redacted] it would aid the medical assessment to obtain details of the type of infiltrate (e.g. lymphocytic or eosinophilic) found during anatomopathologic examination. In case [redacted] no myocardial tissue biopsy was performed and cardiac MRI did not confirm myocarditis.

No indication for a class effect related to diphtheria and tetanus toxoids-containing vaccines
An additional search performed in the GSK safety database (data not provided) showed that myocarditis is being sporadically reported with other vaccines (influenza, hepatitis, measles-mumps-rubella, varicella, rotavirus, pneumococcal, meningococcal, polio). It is concluded that there is no indication for a class effect specifically related to diphtheria and tetanus toxoids-containing vaccines.

Literature
The conclusion from the literature search is that, except for smallpox [Halsell, 2003; Mora, 2009], myocarditis is not considered causally related to vaccination and the rare cases reported after non-smallpox vaccines are usually benign [Thanjan, 2007; Barton, 2008].

Boostrix and Myocarditis: Under which background incidence rate magnitude can the observed number of myocarditis cases be considered as expected?

Background: In the GSK safety database, at the date of 17 March 2013, no case was retrieved after vaccination with Boostrix-Polio, and the GSK causality assessment for the 4 cases retrieved after vaccination with Infanrix hexa and one case retrieved after vaccination with Boostrix highlighted underlying conditions more likely to have contributed to the reported events.

Idiopathic spontaneous cases of myocarditis were only reported post Boostrix immunization for 64,110,702 doses sold up to mid-March 2013. Among Boostrix cases, and regardless of causality assessment, one was considered confirmed (time-to-onset: 0 Days), one probable (time-to-onset: 3 Days) and one suspected (time-to-onset: 1 Day). A literature review performed to identify the background incidence rate of myocarditis in the general population did not retrieve incidence rate estimates applicable to the entire Boostrix immunized population (see answer to Question No. 4). Karjalainen [1999] provided an estimate of 17 per 100,000 person-years, but only for males from Finland within a restricted age range [17, 29] years (Table 7). This lack of key information prevents a regular observed-to-expected analysis.

Table 7 Demographic characteristics of the Boostrix immunized population compared to the population from which the background incidence rate was estimated

	Population from which the background incidence rate was measured	Boostrix-Immunized Population
Gender repartition[a]		
% Males	100%	39%
Age distribution[a]		
[0, 16] years	0%	57%
[17,29] years	100%	18%
[30, 65] years	0%	22%
65+ years	0%	3%
Geographical distribution[b]		
Finland	100%	0.9%
Europe	100%	20.1%
Latin America	0%	6.6%
United States	0%	54.9%
Canada	0%	3.6%
Rest of the World	0%	13.8%

[a] For the Boostrix-Immunized population, gender and age distributions were estimated based on spontaneous cases (regardless of event) within the GSK safety database where Boostrix is a suspect drug.
[b] For the Boostrix-Immunized population, geographical distribution was estimated based on sales data.

Objective: Provide a range of values for the background incidence of myocarditis in a Boostrix immunized population for which the observed number of myocarditis can be considered as expected. Different magnitudes of underreporting were also taken into account.

Method: Different background incidence rates were simulated (in a range between 0.01 and 20 per 100,000 person-years) as well as different percentages of cases actually

spontaneously reported, labelled "Reported fraction" which is a measure of underreporting (in a range between 1% and 100%). For these different combinations of simulated background incidence rates and underreporting, an observed-to-expected analysis was performed in order to determine if the observed number of myocarditis cases[7] was:

- Significantly higher than expected (at a 95% confidence level)
- Higher than expected
- Lower than expected
- Significantly lower than expected (at a 95% confidence level)

And that for two risk periods: 7 days post immunization and 30 days post immunization.

For each simulated values of background incidence rate and underreporting the following reporting rates were calculated and compared with a Poisson exact confidence interval around the "observed reporting rate"):

$$[Observed\ Reporting\ Rate] = \frac{[Observed\ number\ of\ myocarditis\ cases]}{\frac{Number\ of\ distributed\ doses}{100000} * \frac{[Risk\ period\ (in\ days)]}{365.25}}]$$

$$Expected\ Reporting\ Rate\ =\ Background\ Incidence\ Rate\ *\ [Reported\ fraction]$$

For example, in the present situation of 3 observed cases, 64,110,702 doses distributed and

- considering a risk period of **7 days** an Observed Reporting Rate of 0.24 per 100,000 [95% Poisson Exact CI 0.05; 0.71] was obtained
- considering a risk period of **30 days** an Observed Reporting Rate of 0.06 per 100,000 [95% Poisson Exact CI 0.01; 0.17]

while the Expected Reporting Rate is 17 per 100 000 with a reported fraction of 100%.

Results & Discussion: Figure 1 summarises the different possible conclusions assuming different values of background incidence rates and underreporting when performing the observed-to-expected analysis using a risk period of 7 days. The vertical line represents the rate reported by Karjalainen [1999] which is only applicable to a subgroup of the Boostrix immunized population (17 per 100,000 person-years). Should one extrapolate this background incidence ratio to the entire Boostrix immunized population, then the conclusion would be that observing three cases of myocarditis is lower than what is expected, except if the reported fraction is estimated to be as low as 1% of the cases actually occurring within 7 days post Boostrix immunization.

[7] All three cases were taken into account as a worst-case scenario, regardless of diagnosis certainty.

However, if the background incidence rate from Finland within the specific age group of [17, 29] years cannot be extrapolated to the Boostrix immunized population, and in order to be more sensitive for detecting a potential excess of observed cases compared to what is expected, Figure 1 shows the impact of different background rates on the observed-to-expected analysis. For example, if it is argued that the most relevant background rate for the Boostrix immunized population is 1 per 100,000 person-years (instead of 17 per 100,000 persons-years), then the conclusion would be that observing three cases of myocarditis is lower than what is expected, even if the reported fraction is estimated to be as low as 25% of the cases actually occurring within 7 days post Boostrix immunization. If there is strong evidence that the fraction reported within the Boostrix immunized population is lower than 5%, then observing 3 spontaneous reports of myocarditis would be significantly higher than what is expected (with a hypothetical background rate of 1/1,000,000 person-years and a hypothetical fraction reported lower than 5%).

Similarly, Figure 2 summarises the different possible conclusions provided different values of background incidence rates and fraction reported when performing the observed-to-expected analysis using a risk period of 30 days. When using a risk period of 30 days, observing 3 cases of myocarditis is even less unexpected overall. However, the reported fraction may potentially be lower on a long risk period than on a shorter one.

Conclusion: We extensively investigated what could be the conclusion of an observed-to-expected analysis under different values of background incidence rates and underreporting to palliate the gap in the literature. Even if the background incidence rate relevant for Boostrix immunized population was lower than the one from Finland for [17, 29] year males by a factor 10, observing three cases of myocarditis would still be lower than expected (at least for reported fractions above 15%). With the current information available, there is no reason to suspect that the background incidence rate and/or reported fraction applicable to the Boostrix immunized population could be in a range such that observing three myocarditits spontaneous cases within 7 days post Boostrix immunization for 64,110,702 doses sold would be higher than expected.

Figure 1 **Heat map of the observed-to-expected analysis conclusion in the parameter plane defined by the background incidence rate and the underreporting (two unknown parameters)**
7-day risk period post Boostrix immunization

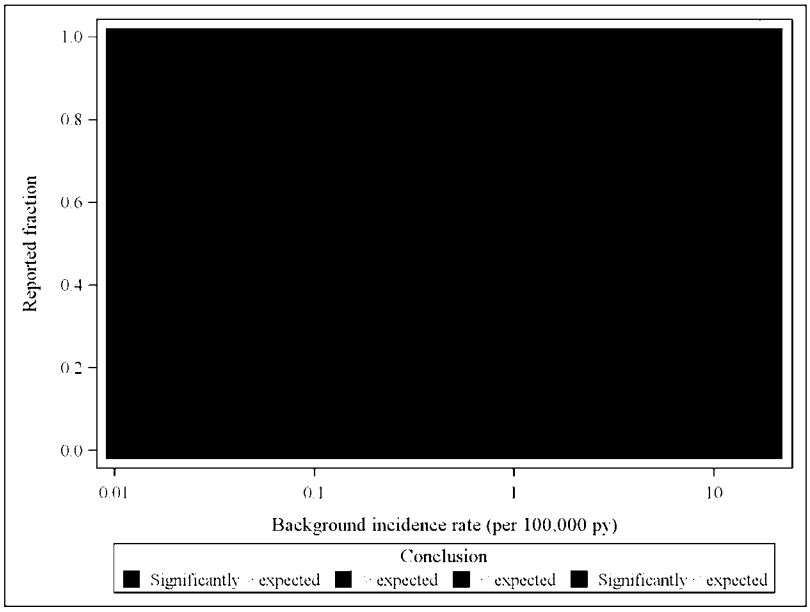
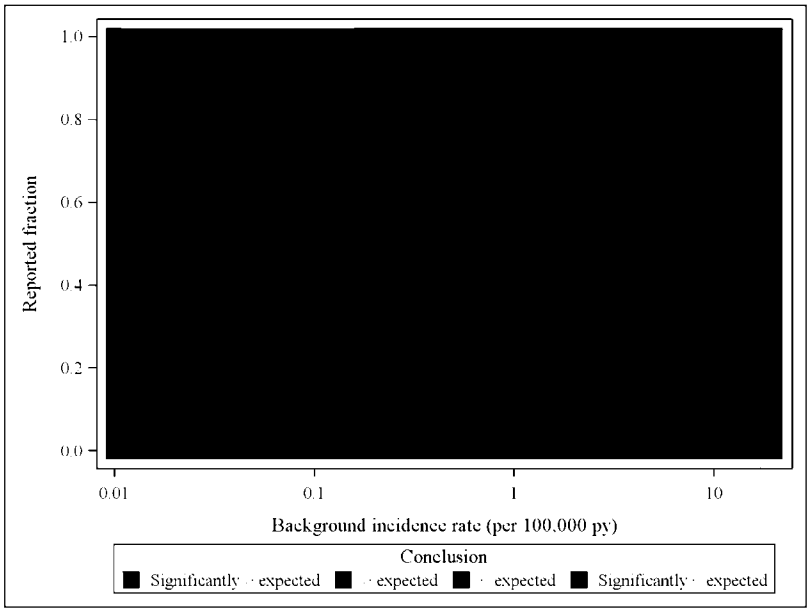


Figure 2 **Heat map of the observed-to-expected analysis conclusion in the parameter plane defined by the background incidence rate and the underreporting (two unknown parameters)**
30-day risk period post Boostrix immunization



General conclusion

In view of the above, including the limitations of this evaluation (spontaneous post-marketing data and unknown background incidence rate for myocarditis) GSK considers that there is insufficient evidence for a causal association between vaccination with Boostix, Boostrix-Polio or Infanrix hexa and myocarditis. The company does not consider myocarditis a potential risk.

GSK employs a routine, pro-active pharmacovigilance process for identifying safety signals. As part of this process, and like other severe adverse events, cases of myocarditis are being monitored on an ongoing basis.

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APPENDIX 1 CIOMS FORMS FOR MYOCARDITIS CASES RELATED TO BOOSTRIX AND INFANRIX HEXA

APPENDIX 7B.8b : Myocarditis CIOMS

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 2)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
PRIVACY	[redacted]	[redacted]		M	[redacted]

7. & 13. DESCRIBE EVENT(S)

Sudden death, Pyrexia, Headache, Cardiac arrest, Myocarditis, Skin lesion, Hypersensitivity,

This case was reported by a regulatory authority ([redacted]) and described the occurrence of sudden death in a 15-year-old male subject who was vaccinated with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (Boostrix, GlaxoSmithKline) for prophylaxis.

On [redacted] the subject received unspecified dose of Boostrix (unknown).

On [redacted], 24 hours after vaccination with Boostrix, the subject experienced fever and headache, lasting 2 days. On [redacted] the subject was feeling better. On [redacted] around 11:30am the subject was found dead on his bed.

The subject died on [redacted] from sudden. An autopsy was performed and showed cervical adenopathy, lung congestion and

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- [X] PATIENT DIED AS OUTCOME OF EVENT
- [ ] RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING
- [ ] CONGENITAL ANOMALY
- [ ] CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- [ ] OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) Boostrix Injection AC37B031CC (Tetanus vaccine + Diphtheria toxoid Acellular pertussis vax) GlaxoSmithKline

20. DID EVENT ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] N/A

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION
Unknown	Unknown

17. INDICATION(S) FOR USE: PROPHYLAXIS

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] N/A

18. THERAPY DATES (From / To)	19. THERAPY DURATION
[redacted]	1 Days

14. IDENTIFIED DRUG(S)

20. DID EVENT ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [ ] N/A

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [ ] N/A

18. THERAPY DATES (From / To)	19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

23. OTHER RELEVANT HISTORY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)

GlaxoSmithKline

Rue De L'Institut 89,
Rixensart, B-1330, Belgium

[redacted]

24c. DATE RECEIVED	DATE OF REPORT
21SEP2011	27SEP2011

24d. REPORT SOURCE [X] HEALTH PROFESSIONAL [ ] STUDY [ ] LITERATURE

25a. REPORT TYPE [ ] INITIAL [X] FOLLOW-UP

[redacted]	DESK COPY	(Page 2 of 2)

7. & 13. DESCRIBE EVENT(S)

splenomegaly. The pathology did not find any evident cause to explain the death. The pathologist was more oriented towards an infectious cause because the teen presented splenomegaly, cervical adenopathy and pulmonary congestion. Culture results were negative for Strep A. Microscopy results were pending.

Follow-up received 02 June 2009 from Quality Assurance. The Boostrix vaccine lot AC37B031CC was produced in compliance with the Good Manufacturing Practices. No deviation that could have impacted the quality of the product was highlighted during the investigation. No incident during distribution and no cold chain deviation that could have been linked to the adverse event were recorded.

On 12 May 2010 this case was identified as duplicate of [redacted]. The following information was added from duplicate case which was reported by a physician.

The subject received the vaccine on [redacted]. He presented with headache and fever for 2-3 days and felt better in the evening of [redacted]. In the morning of [redacted] the subject was found in cardiac arrest. The final autopsy report identified severe active myocarditis with acute changes and chronic lesions. The precise etiology could not be determined. Viral cultures and other cultures were negative and the toxicology was negative for alcohol, drugs and medication. The subject's medical history was negative. The physician reported that the subject had received all required vaccines since 1993.

It could not be excluded that the acute myocarditis was due to a hypersensitivity reaction. It was suspected that the lesions were due to hypersensitivity since they were 2-5 days old which was around the time of the vaccination. The cause was not viral since all cultures came back negative.

The physician considered the acute myocarditis was possibly related to vaccination with Boostrix. The subject died on [redacted] from acute myocarditis. An autopsy was performed.

Case [redacted] was voided and all future documentation will be placed in this case.

Follow-up received from a regulatory authority ([redacted]) on 21 September 2011: This case was reviewed by the advisory committee on causality assessment who considered the event to be sudden unexpected death, and the relationship between vaccination with Boostrix and the event to be unclassifiable.

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 2)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
PRIVACY	[redacted]	[redacted]		M	[redacted]

7. & 13. DESCRIBE EVENT(S)

Myocarditis;

This case was reported by a physician via a sales representative and described the occurrence of myocarditis in a 17-year-old male subject who was vaccinated with diphtheria-tetanus-pertussis vaccine (Boostrix) for prophylaxis.

The subject's medical history included pollinosis. There were no concurrent drugs. The subject received several former vaccinations with vaccines from other manufacturers.

On [redacted] the subject received the first dose of diphtheria-tetanus-pertussis vaccine, intramuscularly, deltoid as a booster. Approximately three days post vaccination, in the morning of the [redacted], the subject woke up with fever and chest pressure. During the day the symptoms improved and the subject was riding bike. At about 17:00 the subject developed chest pain and was hospitalised. On admission the subject had fever up to 38,4 degC. The lung showed vesicular breath sound, sonorous percussion sound

(See attached page)

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- ☐ PATIENT DIED AS OUTCOME OF EVENT
- ☒ RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☐ CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- ☐ OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) Boostrix Injection 37754B9 (Tetanus vaccine + Diphtheria toxoid + Acellular pertussis vax) GlaxoSmithKline

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ N/A

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION
.5 ml	Intramuscular

17. INDICATION(S) FOR USE: PROPHYLAXIS

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ N/A

18. THERAPY DATES (From / To)	19. THERAPY DURATION
[redacted]	1 Days

14. IDENTIFIED DRUG(S)

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ N/A

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ N/A

18. THERAPY DATES (From / To)	19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

23. OTHER RELEVANT HISTORY

(See attached page)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)

GlaxoSmithKline

Rue De L'Institut 89,
Rixensart, B-1330, Belgium

[redacted]

24c. DATE RECEIVED	DATE OF REPORT
27SEP2004	29SEP2004

24d. REPORT SOURCE ☒ HEALTH PROFESSIONAL ☐ STUDY ☐ LITERATURE

25a. REPORT TYPE ☐ INITIAL ☒ FOLLOW-UP

[redacted]	DESK COPY	(Page 2 of 2)

7. & 13. DESCRIBE EVENT(S)

and no rattling. There were no pathologic heart sounds. Neurology was without findings. Laboratory tests showed increased creatine kinase, troponin T and C-reactive protein. An electrocardiogram (ECG) showed increased ST take-off in II, III aVF and V4-V6. An echocardiogram showed mitral insufficiency with decreased function of the left ventricle.

An X-ray of the thorax on [redacted] was without pathologic findings.
A magnetic resonance tomogram (MRT) on [redacted] showed good function of the left ventricle, an indication for anterior hyperkinesias, no indication for myocardial edema, a mild pericardial effusion without haemodynamic effect and a mild pleural effusion at the right side. There were no clear signs for myocarditis, but in case of a skeletal muscle damage by tetanus toxoid a damage of myocardium was considered to be possible. No scars or fibroses were visible.
Drug-induced myocarditis was diagnosed. The subject was treated with metoprolol succinate (Beloc-Zok mite) and ramipril (Delix). The laboratory values and ECG-findings normalised.

On [redacted] the subject was discharged from hospital. The clinical symptoms had resolved on [redacted].
The reporting physician considered that the events were possibly related to vaccination with diphtheria-tetanus-pertussis vaccine due to the time frames.

Examinations:
Electrocardiogram (ECG) on admission
Results: normofrequent sinus rhythm, vertical heart, increased ST take-off in II, III aVF, V4-V6, no dysthythmia
Control on discharge: only mildly increased ST take-off

X-ray of the thorax on [redacted]
results: no pathologic findings.

Echocardiogram (ECG) on [redacted]
Results: normal size of left ventricle with mildly decreased function and regional kinetic disorder; mitral insufficiency.

Magnetic resonance tomogram (MRT) on [redacted]
Results: Good function of left ventricle, indication for anterior hyperkinesias, no indication for myocardial edema. Mild pericardial effusion without haemodynamic effect. Mild pleural effusion at right side. No clear signs for myocarditis. In case of a skeletal muscle damage a damage of myocardium was possible. No scars or fibroses visible.

LABORATORY TEST NAME	TEST DATE	TEST RESULT	LOW NORMAL	HIGH NORMAL
Blood pressure	[redacted]	130/80mmHg		
Body temperature		38.4degC		
C-reactive protein		63,1		
C-reactive protein		27		
Creatine kinase		492		
Creatine kinase		92		
Heart rate		76/min		
Troponin T		1,35		
Troponin T		0,74		

MEDICAL CONDITION	START DATE	END DATE	CONTINUING
POLLINOSIS	Unknown	Unknown	Yes

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 3)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
Unknown	[redacted]	[redacted]		M	[redacted]

7. & 13. DESCRIBE EVENT(S)

Myopericarditis, Myocarditis, Pericarditis, Pleurisy, Painful respiration, Pyrexia, Pericardial effusion, Pleural effusion, Fatigue, Cough,

This case was reported by a [redacted] regulatory authority [redacted] and described the occurrence of perimyocarditis in 16-year-old male subject who was vaccinated with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed (Boostrix, GlaxoSmithKline) for prophylaxis.

Co-suspect vaccinations included diphtheria + poliomyelitis vaccine + tetanus vaccine (non-GSK) (Revaxis, Sanofi Pasteur MSD).

Concurrent medical conditions included Herpes simplex virus (HSV) infection.

On [redacted] the subject received an unspecified dose of Boostrix (0.5 ml, intramuscular, unknown) and an unspecified dose of Revaxis

(See attached page)

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- ☐ PATIENT DIED AS OUTCOME OF EVENT
- ☒ RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☐ CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- ☐ OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) Boostrix Injection unknown (Tetanus vaccine + Diphtheria toxoid + Acellular pertussis vax) GlaxoSmithKline

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ N/A

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION
.5 ml	Intramuscular

17. INDICATION(S) FOR USE PROPHYLAXIS

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ N/A

18. THERAPY DATES (From / To)	19. THERAPY DURATION
[redacted]	1 Days

14. IDENTIFIED DRUG(S) Revaxis Injection unknown (Diphth+polio+teta Non GSK) Sanofi Pasteur MSD

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ N/A

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION
.5 ml	Intramuscular

17. INDICATION(S) FOR USE PROPHYLAXIS

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ N/A

18. THERAPY DATES (From / To)	19. THERAPY DURATION
10Jul2009-10Jul2009	1 Days

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

23. OTHER RELEVANT HISTORY

(See attached page)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)

GlaxoSmithKline

Rue De L'Institut 89,
Rixensart, B-1330, Belgium

[redacted]

24c. DATE RECEIVED	DATE OF REPORT
09OCT2009	19OCT2009

24d. REPORT SOURCE ☐ HEALTH PROFESSIONAL ☐ STUDY ☐ LITERATURE

25a. REPORT TYPE ☒ INITIAL ☐ FOLLOW-UP

[redacted]	DESK COPY	(Page 2 of 3)

7. & 13. DESCRIBE EVENT(S)

(0.5 ml, intramuscular, unknown).

Approximately one day post vaccination with Boostrix and Revaxis, on [redacted], the subject experienced perimyocarditis (myocarditis and pericarditis) and pleuritis.

In the evening of [redacted] the subject experienced persistent pain in thorax upon breathing left parasternal with protective shallow breathing and fever of 38.7 degC.

On the next day, on [redacted], the subject was hospitalised for persistent thoracic pain for nine days.

On admission to hospital the subject showed fatigue and was only coughing slightly and cautiously. The subject showed no palpable lymph nodes. The oral cavity was normal. The spine was not excitable by percussion. The medial part of the sternum was sensitive to pressure. Lungs: Percussion sound of lungs sonorous, lower limit of lungs normal and well adjustable by breathing, vesicular respiration, no pleural friction sound. Heart: regularly, heart rate 104 /min, heart sounds clear, blood pressure 140/90 mmHg. Abdomen: palpatory and auscultatory normal.

Transthoracic echocardiogram showed mild pericardial effusion dorsal and minor pleural effusion left. Electrocardiogram (ECG) showed elevated ST segment on admission, followed by negative T waves since [redacted]. Serology showed Herpes simplex virus 1 (HSV-1) and Herpes simplex virus 2 (HSV-2) infection with increased IgG levels. C-reactive protein (CRP) was increased.

The hospital physician(s) considered that the cause of the events was unknown.

The reporting physician considered that the events were temporally related to vaccination with Boostrix and Revaxis, but considered that a causal relationship of the event to vaccination with Boostrix and Revaxis was most questionable.

The reporting physician also considered that the causal relationship of the events to Herpes simplex virus (HSV) infection stayed unclear. The presence of IgG antibodies speaks for a former infection with HSV, because seroconversion post infection in average needs about eight weeks. Furthermore myocarditis was a very atypical event associated with HSV infection.

Epstein-Barr virus (EBV) infection was mainly excluded because of antibody titre and missing typical symptoms like lymph node enlargement or splenomegaly.

The subject received no antiviral medication because the events were already very much improved.

On [redacted] the subject was discharged from hospital.

At the time of writing the reports, on [redacted], the events were unresolved, but distinctly improved.

No further information will be available.

Lymphoid leukocyte percentage, determined on [redacted]: 2%.

Serology:
Antibodies against Borrelia burgdorferi; no signs of chronic infection.
Epstein-Barr virus (EBV) IgG: 1:80 (less than 1:10).
Herpes simplex virus 1 (HSV-1) IgG: 1416 U/ml (less than 25 U/ml).
Herpes simplex virus 2 (HSV-2) IgG: 323 U/ml (less than 80 U/ml).
Coxsackie virus IgG: 84 U/l (less than 80 U/l).

Electrocardiogram (ECG), performed on [redacted]:
Sinus rhythm, heart rate 105 /min, vertical type, incomplete right bundle-branch block, elevated ST segment consisting of R wave and elevation in II, III, aVF, V2 - V8.
Electrocardiogram (ECG), performed on [redacted]:
Elevated ST segment less pronounced.
Electrocardiogram (ECG), performed on [redacted]:
Elevated ST segment further regressive. Newly found distinct terminal negative T waves in V3 - V6, I, II, aVL, aVF.
Electrocardiogram (ECG), performed on [redacted]:
ST segment isoelectric, negative T waves only flat pronounced and on monitor in parts unambiguously positive T waves.
Long-term electrocardiogram, performed from [redacted] to [redacted]:
Most of the time normal heart rate with physiological bradycardia around 55 - 60 /min at night: Once during course on physical exertion sinus tachycardia with 130 /min.

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Transthoracic echocardiogram, performed on [redacted]:
Heart cavity normal sized, heart muscle normal contractility, heart valves normal.
Minimal pericardial effusion dorsal. Minor pleural effusion left.
Transthoracic echocardiogram, performed on [redacted]:
Still minor pericardial effusion and minor pleural effusion.

LABORATORY TEST NAME	TEST DATE	TEST RESULT	LOW NORMAL	HIGH NORMAL
Albumin	[redacted]	71.3%		
Alpha 1 globulin		3.7%		
Alpha 2 globulin		8.3%		
Band neutrophil percentage		7%		
Basophil percentage		2%		
Beta globulin		8.0%		
Blood pressure		140/90mmHg		
Body temperature		38.7degC		
C-reactive protein		7.49mg/dl		
C-reactive protein		1.64mg/dl		
C-reactive protein		8.93mg/dl		
Creatine kinase		661U/l		
Creatine kinase		95U/l		
Creatine kinase MB		21U/l		
Creatine kinase MB		61U/l		
Eosinophil percentage		7%		
Gamma globulin		8.7%		
Heart rate		104/min		
Heart rate		105/min		
Lymphocyte percentage		6.2%		
Lymphocyte percentage		40.4%		
Lymphocyte percentage		32%		
Monocyte percentage		9%		
Myoglobin blood		153ng/ml		
Myoglobin blood		70ng/ml		
Protein total		6.8g/dl		
Segmented neutrophil percentage		41%		
Troponin I		9.59ug/l		
Troponin I		9.14ug/l		
Troponin I		144.42ug/l		
White blood cell count		5900/ul		
White blood cell count		15400/ul		

MEDICAL CONDITION	START DATE	END DATE	CONTINUING
HERPES SIMPLEX INFECTION	Unknown	Unknown	Unknown

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 3)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
PRIVACY	[redacted]	[redacted]		M	[redacted]

7. & 13. DESCRIBE EVENT(S)

Myocarditis;.
Pneumonia;.
Pallor, General physical health deterioration,

A physician reported the occurrence of myocarditis in a 16-month-old male who was vaccinated with diphtheria-tetanus-pertussis(a)-poliomyelitis-hepatitis B/haemophilus influenzae b vaccine (Infanrix hexa) for prophylaxis. As follow-up information, the hospital report was sent.

Former vaccinations with diphtheria-tetanus-pertussis(a)-poliomyelitis-hepatitis B/haemophilus influenzae b vaccine were well tolerated. No concurrent medications were reported.
The subject's parents had allergies. The subject's further family anamnesis was uneventful.
Birth anamnesis revealed that the subject was born after placental insufficiency via cesarian section in the 37th week of gestation.
Birth weight was 2370 g and APGAR was 9/9. The subject had a

(See attached page)

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- ☐ PATIENT DIED AS OUTCOME OF EVENT
- ☒ RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☐ CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- ☐ OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) Infanrix hexa Injection 21H0121 (Hepatitis B vaccine + Polio.vaccine inactivated + Tetanus vaccine + Diphtheria toxoid + Haemophilus influenzae ty + Acellular pertussis vax) GlaxoSmithKline

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ N/A

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION
.5 ml	Intramuscular

17. INDICATION(S) FOR USE: PROPHYLAXIS

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ N/A

18. THERAPY DATES (From / To)	19. THERAPY DURATION
[redacted]	1 Days

14. IDENTIFIED DRUG(S)

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ N/A

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ N/A

18. THERAPY DATES (From / To)	19. THERAPY DURATION

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

Infanrix hexa (GlaxoSmithKline) Unknown
(Hepatitis B vaccine + Polio.vaccine inactivated + Tetanus vaccine + Diphtheria toxoid + Haemophilus influenzae ty + Acellular pertussis vax)

23. OTHER RELEVANT HISTORY

(See attached page)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)

GlaxoSmithKline

Rue De L'Institut 89,
Rixensart, B-1330, Belgium

[redacted]

24c. DATE RECEIVED	DATE OF REPORT
10SEP2003	19SEP2003

24d. REPORT SOURCE ☒ HEALTH PROFESSIONAL ☐ STUDY ☐ LITERATURE

25a. REPORT TYPE ☐ INITIAL ☒ FOLLOW-UP

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7. & 13. DESCRIBE EVENT(S)

pneumonia when he was six weeks old (in [redacted]) and further pneumonias in [redacted], [redacted] and [redacted]. The subject had otitis media in [redacted] and tonsillitis in [redacted]. Five weeks prior to hospitalisation, on an unknown date in [redacted], the subject had a parvovirus infection.
Current medical conditions included recurrent obstructive chronic bronchitis.

The subject was under treatment of the reporting physician since [redacted]. The reporting physician administered the third and fourth Infanrix hexa doses. The reporting physician did not know whether the first two vaccinations were done with Infanrix hexa. The third vaccination with diphtheria-tetanus-pertussis(a)-poliomyelitis-hepatitis B/haemophilus influenzae b vaccine was administered with delay due to frequent bronchitis. The subject was healthy at the time of the fourth vaccination and there was no evidence for an infection.

On [redacted], the subject received the fourth dose of diphtheria-tetanus-pertussis(a)-poliomyelitis-hepatitis B/haemophilus influenzae b vaccine, lot number 21H0121, intramuscularly in an unknown deltoid. Two days post vaccination on [redacted] the subject started to drink not well. There was no fever and no cough. Some days prior to hospitalisation, the subject developed tachypnea and he was pale. The subject was brought to the hospital due to his reduced general condition.

The subject was hospitalised on [redacted] as pneumonia was suspected. The subject received antibiotic treatment. In hospital, the subject developed metabolic acidosis. Echocardiogram showed dilatative cardiomyopathy. Myocarditis with global heart failure was suspected. Auscultation showed low-frequent proto-mesosystoles with puncto maximum over the fourth intercostal area, left parasternal. Electrocardiogram showed sinus rhythm with a frequency of 170/min. There was low voltage. There were no clear signs for hypertrophy. Biventricular excitation disturbances were found. Echocardiography revealed an increased left atrium, dilated right and left ventricle with clearly restricted systolic function, mild mitral valve insufficiency, bilateral pleural effusion and mild pericardial effusion. According to the reporting physician, myocarditis started on 25 July 2003, two days post vaccination. X-ray of the thorax revealed enlarged left side of the heart, a vessels pattern in the lung and pleural effusion.

Laboratory examinations showed the following values: leukocytes 13.4/nl, hemoglobin 9.0 g/dl, electrolytes were normal, C-reactive protein 6.0 mg/dl (maximal 16.2 mg/dl), creatinine and urea were normal, lactate dehydrogenase 528 U/l (maximal value 1.762 U/l), glutamic pyruvic transaminase (GPT) maximal 838 U/l, glutamic oxaloacetic transaminase (GOT) maximal 1023 U/l, creatine kinase 206 U/l, creatine kinase MB 33 U/l, Quick's value 34%, partial thromboplastin time 41 seconds and antithrombin III 62%. Blood gas analysis showed pH 7.25, base excess - 13 and bicarbonate 14 mmol/l.
Serological tests for cardiotropic viruses showed positive immunoglobulin G (IgG) and negative IgM antibodies to parvovirus B19; the other values were normal. Irregular anti-Lua antibodies were found.

Increasing hemodynamic disturbance and tachypnea/dyspnea led to intubation and artificial respiration. The subject also received intensive diuretic therapy, adrenaline (Suprarenin) and milrinone until [redacted]. On [redacted], right pleural effusion was emptied (100 ml clear pleural secretion). The subject developed pneumonia with atelectasis of the right upper lung lobe. Haemophilus influenzae was detected in tracheal secretion, and Enterobacter cloacae was detected in throat swab. The subject was treated with imipenem, vancomycin and physiotherapeutic therapy. The subject's condition improved and laboratory infectious parameters normalised. Laboratory signs of heart failure normalised and liver and blood clotting values normalised.
The subject was extubated on [redacted]. The subject was clinical cardial compensated under anticongestive medication and was discharged from hospital after 26 days, on 22 August 2003. In the hospital report, the vaccination was not mentioned; it was mentioned that parvovirus infection was the suspected cause for myocarditis. The reporting physician also considered that myocarditis was unrelated to the vaccination. The outcome of myocarditis was reported as improved.

LABORATORY TEST NAME	TEST DATE	TEST RESULT	LOW NORMAL	HIGH NORMAL
Activated partial thromboplast in time abnormal	2003	41s		
Antithrombin III	2003	62%		
Base excess	2003	-13		
Bicarbonate	2003	14mmol/l		
Blood creatine phosphokinase M B	2003	33U/l		
Blood electrolytes NOS	2003	normal		
Blood pH NOS	2003	7.25		
C-reactive protein	2003	16.2mg/dl		
C-reactive protein	2003	16.2mg/dl		
C-reactive protein	2003	0.6mg/dl		

Creatine kinase	2003	206U/l
Creatinine	2003	normal
Glutamic-oxaloacetic transfera se	2003	1023U/l
Glutamic-pyruvate transaminase	2003	838U/l
Hemoglobin	2003	9.0g/dl
Lactate dehydrogenase	2003	1762U/l
Lactate dehydrogenase	2003	528U/l
Leukocyte count NOS	2003	13.4/nl
Quick's test	2003	34%
Urea	2003	normal

MEDICAL CONDITION	START DATE	END DATE	CONTINUING
CESAREAN SECTION	[redacted]	Unknown	No
PNEUMONIA	[redacted]	Unknown	No
PNEUMONIA	[redacted]	Unknown	No
PNEUMONIA	[redacted]	Unknown	No
OTITIS MEDIA	[redacted]	Unknown	No
TONSILLITIS	[redacted]	Unknown	No
PARVOVIRUS INFECTION	[redacted]	Unknown	Unknown
OBSTRUCTIVE CHRONIC BRONCHITIS	Unknown	Unknown	Yes
PLACENTAL INSUFFICIENCY	Unknown	Unknown	No

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 3)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
Unknown	[redacted]	[redacted]		M	[redacted]

7. & 13. DESCRIBE EVENT(S)

Cardiac failure acute, Pulmonary oedema, Sudden death, Cardiopulmonary failure, Respiration abnormal, Tachypnoea, Myocarditis, Myocardial infarction, Haemostasis,

This case was reported by a physician and described the occurrence of acute cardiac failure in a 5-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis. Co-suspect vaccination included pneumococcal vaccines (non-gsk) (Prevenar, Wyeth).

On [redacted] the subject received 3rd dose of Infanrix hexa and 3rd dose of Prevenar (unknown route and application site). According to subject's mother, the subject developed breathing not normal since the day of vaccination on [redacted]. At examination during doctor visit saturation and pulse were normal. At the time of reporting the outcome of the event was unspecified.

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- [X] PATIENT DIED AS OUTCOME OF EVENT
- [X] RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [X] LIFE THREATENING
- [ ] CONGENITAL ANOMALY
- [ ] CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- [ ] OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) Infanrix hexa Injection A21CA482A (Hepatitis B vaccine + Polio.vaccine inactivated + Tetanus vaccine + Diphtheria toxoid + Haemophilus influenzae ty + Acellular pertussis vax) GlaxoSmithKline

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION	17. INDICATION(S) FOR USE	18. THERAPY DATES (From / To)	19. THERAPY DURATION
Unknown	Intramuscular	PROPHYLAXIS	30Apr2009-30Apr2009	1 Days

20. DID EVENT ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] N/A

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] N/A

14. IDENTIFIED DRUG(S) Prevenar Injection 36470 (Pneumococcal vac NonGSK) Wyeth Labs

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION	17. INDICATION(S) FOR USE	18. THERAPY DATES (From / To)	19. THERAPY DURATION
Unknown	Intramuscular	PROPHYLAXIS	[redacted]	1 Days

20. DID EVENT ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] N/A

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] N/A

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

23. OTHER RELEVANT HISTORY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)

GlaxoSmithKline

Rue De L'Institut 89,
Rixensart, B-1330, Belgium

[redacted]

24c. DATE RECEIVED	DATE OF REPORT
09AUG2010	10AUG2010

24d. REPORT SOURCE [X] HEALTH PROFESSIONAL [ ] STUDY [ ] LITERATURE

25a. REPORT TYPE [ ] INITIAL [X] FOLLOW-UP

7. & 13. DESCRIBE EVENT(S)

Follow-up information was received on 14 May 2009 by the physician.
Previous vaccinations with Infanrix hexa and Prevenar were well tolerated.
Subject's sibling also died suddenly at the age of 5 months without receiving prior vaccinations.

On [redacted] the subject received 3rd dose of Infanrix hexa (intramuscular, unknown application site left sided) and 3rd dose of Prevenar (intramuscular, right upper thigh).

On [redacted], less than one day after vaccination with Infanrix hexa and Prevenar, the subject died. Reanimation was ineffective.

The physician considered death was possibly related to vaccination with Infanrix hexa and Prevenar.
The subject died on [redacted] from death NOS. An autopsy was performed on 7 May 2009.

Follow-up information was received on 3 June 2009 by the physician.
A targeted follow-up questionnaire was provided but not filled in.
According to the physician it was not a sudden infant death. The subject died in hospital.
Autopsy results were not available for the reporter.

Follow-up information was received on 10 June 2009 by the physician via telephone call.
Subject's brother showed same symptoms of abnormal breathing on [redacted] after unspecified vaccination on [redacted]. The sibling died from cardiomegaly on [redacted] in hospital. The physician did not see a relation to vaccination. Subject's parents consulted genetic advice, but a cause was not found.

The subject was vaccinated at nine o'clock in the morning at a wide-awake general condition. Three hours after vaccination subject's mother had a doctor call and came for a doctor visit. There, the subject suffered from breathing not normal (tachypnea).
Otherwise the subject was bright and awake.
The subject was hospitalised for security due to anamnesis. At hospital subject's condition was normal except tachypnea.
Approximately 40 minutes later tachypnea worsened significantly, the subject experienced cardiopulmonal failure and died of an unknown cause.
The physician only considered vaccination as a trigger at an unknown genetic or familiar predisposition.

Follow-up information was received on 22 April 2010 from [redacted] regulatory authority [redacted].
Following information was provided:
Case narrative including clinical course, therapeutic measures, outcome and additional relevant information:
A 5-month-old male patient was vaccinated with Prevenar, batch-no.: 36470 and with Infanrix hexa, batch-no.: A21CA482 for Prophylactic vaccination. Past medical history were not provided. 8 hours after vaccination the patient presented with Sudden infant death. An autopsy was performed. Further information is requested.
Phone information of the pediatrician on 12.05. 2009:
The baby was vaccinated in the morning in good status of health with Infanrix hexa and Prevenar.
At about 12:oo am the parents presented again in the practice claming that the baby was tachypnoic. The pediatrician found the baby in good staus of health and sent them home.
at 15:00 p.m the parent presented again in the practice and the baby was found a little bit tachypnoic but in good conditions of health.
Due to the fact that the couple had lost another baby boy at the same age due to cardiopolmonary disfuction (probably myocarditis) the physician admitted the baby to a hospital. At 15:30 p.m the baby was found in reduced status of health and tachpnoic.
After 45 min and repeated reanimation intents the baby died.
Intensified diagnostics (post-mortem diagnostics in the hospital) as well as pathological diagnostics have be initiated.

Additional information was received regarding the events, patient's demographics, dose details, medical history and outcome.
Information regarding Prevenar (pneumococcal 7-valent conjugate vaccine (diphtheria crm197 protein) syringe pre-filled) was received from a healthcare professional regarding a 5-month-old male patient who experienced tachypnoea and who died of sudden death. The patient received the third dose on [redacted].
MEDICAL HISTORY:
Past vaccinations included the first two doses of Prevenar (pneumococcal 7-valent conjugate vaccine (diphtheria crm197 protein) syringe pre-filled) and Infanrix hexa (diphtheria vaccine/tetanus vaccine/acellular pertussis vaccine/polio virus inactivated/haemophilus influenzae b/hepatitis b vaccine). One of the patient's siblings died of fulminant cardiomyopathy at the same age. The sibling has received the last

vaccination 2.5 months prior to date of death.
PRODUCT DETAILS:
Indication for Prevenar was immunisation. Product was administered in right thigh at 9.20 am on [redacted]. Dose regimen was 1 dose 1 time per day (intramuscular).
Additional suspect medication included Infanrix hexa (diphtheria vaccine/tetanus vaccine/acellular pertussis vaccine/polio virus inactivated/haemophilus influenzae b/hepatitis b vaccine) which was administered in left thigh on the same time.
CONCOMITANT THERAPY:
Concomitant medications were not reported.
EVENT DETAILS:
After vaccination the parents went twice to the doctor with the patient on the same morning. The patient experienced mild tachypnoea (tachypnoea). The patient was clinically without severe findings. The second visit to the doctor was approximately three hours after the vaccination and during the visit the doctor decided to hospitalize the patient due to the death of the patient's sibling. Therefore the patient's parents took the patient to hospital for monitoring. The way to hospital was without any complications but on arrival at hospital the patient's condition impaired and the patient received permanent drop infusion for example. 40 minutes after the arrival at hospital the patient's condition got really worse so that reanimation was performed but without success. The patient died of sudden death on [redacted]. An autopsy was performed but at the time of report the result was unknown.
The reporting physician's assessment of relatedness between the adverse events and Prevenar and Infanrix hexa was possible related.
The cause of death was reported as sudden death.
No additional information was available at the time of this report.

Follow-up information was received on 28 July 2009 by the prosecutors' office:
The cause of death and manner of death were unknown at the date of the autopsy result.
Further results of histological and toxicological examinations are requested.

Follow- up information was received from prosecution on 20 April 2010:
The results of histological and toxicological examinations were not yet available at the date of this report.

Follow-up information was received on 9 August 2010 from regulatory authority.
Results of histological and toxicological examinations included significant findings like heart cell necrosis, lymphocytic myocarditis, and haemorrhagic pulmonary edema as well as acute blood congestion in spleen, liver, adrenal glands and kidneys. Indications of active ingredients were found (probable substances which were administered during emergency treatment at intensive care unit. Cause of death was cardiac failure left side and pulmonary edema cardiac cause.

No further information will be available.

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 2)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
Unknown	[redacted]	[redacted]		M	[redacted]

7. & 13. DESCRIBE EVENT(S)

Respiratory tract inflammation, Pneumonitis, Myocarditis, Bacterial tracheitis,.
Pyrexia,

This case was reported by a [redacted] regulatory authority [redacted] and described the occurrence of severe infection of respiratory tract in a 12-week-old male subject who was vaccinated with 10 valent pneumococcal conjugate vaccine (Synflorix, GlaxoSmithKline) and combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis.
Initially suspected sudden infant death syndrome (SIDS) was not confirmed.

Up to now the subject has been healthy.

On [redacted] the subject received the first dose of Synflorix (0.5 ml, unknown, right thigh) and the first dose of Infanrix hexa

(See attached page)

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- [X] PATIENT DIED AS OUTCOME OF EVENT
- [ ] RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING
- [ ] CONGENITAL ANOMALY
- [ ] CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- [ ] OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) Synflorix Injection ASPNA007AE (Pneumoc.polysac S.Type 1 + Pneumoc.polysac S.Type 4 + Pneumoc.polysac S.Type 5 + Pneumoc.polysac S.Type 6B + Pneumoc.polysac S.Type 7F + Pneumoc.polysac S.Type 9V + Pneumoc.polysac S.Type 14 +

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION	20. DID EVENT ABATE AFTER STOPPING DRUG?
.5 ml	Unknown	[ ] YES [ ] NO [X] N/A

17. INDICATION(S) FOR USE	21. DID EVENT REAPPEAR AFTER REINTRODUCTION?
PROPHYLAXIS	

18. THERAPY DATES (From / To)	19. THERAPY DURATION	
17Aug2009-17Aug2009	1 Days	[ ] YES [ ] NO [X] N/A

14. IDENTIFIED DRUG(S) Infanrix hexa Injection A21CA596A (Hepatitis B vaccine + Polio.vaccine inactivated + Tetanus vaccine + Diphtheria toxoid + Haemophilus influenzae ty + Acellular pertussis vax) GlaxoSmithKline

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION	20. DID EVENT ABATE AFTER STOPPING DRUG?
.5 ml	Unknown	[ ] YES [ ] NO [X] N/A

17. INDICATION(S) FOR USE	21. DID EVENT REAPPEAR AFTER REINTRODUCTION?
PROPHYLAXIS	

18. THERAPY DATES (From / To)	19. THERAPY DURATION	
[redacted]	1 Days	[ ] YES [ ] NO [X] N/A

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

23. OTHER RELEVANT HISTORY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)

GlaxoSmithKline

Rue De L'Institut 89,
Rixensart, B-1330, Belgium

[redacted]

24c. DATE RECEIVED	DATE OF REPORT
15JAN2010	22JAN2010

24d. REPORT SOURCE

[ ] HEALTH PROFESSIONAL [ ] STUDY [ ] LITERATURE

25a. REPORT TYPE

[ ] INITIAL [X] FOLLOW-UP

[redacted]	DESK COPY	(Page 2 of 2)

7. & 13. DESCRIBE EVENT(S)

(0.5 ml, unknown, left thigh), contralaterally.

Less than one week post vaccination with Synflorix and Infanrix hexa, on an unknown date in [redacted], the subject experienced fever. Fever was resolved after one day.

Approximately seven days post vaccination with Synflorix and Infanrix hexa, on [redacted] at around 18:00, the subject died from possible sudden infant death syndrome (SIDS).

An autopsy has been applied for. At the time of reporting, on [redacted], autopsy was performed.

Follow-up information including autopsy report was received on 14 December 2009 from the [redacted] regulatory authority [redacted].

Medical history included normal course of pregnancy and regular visits of a paediatrician for child health checks.

On [redacted] the subject was vaccinated with Synflorix and Infanrix hexa.

On the next day, on [redacted], the subject experienced mild fever.

The subject died on [redacted] at around 18:30 at home. The nearly 3-month-old male subject was found dead on [redacted] at around 19:00 by the subject's mother.

An autopsy was performed on [redacted] at 08:30. The autopsy report was dated [redacted]

Macroscopically autopsy showed normal general and nutritional condition, no signs of malformations, bloody foam in respiratory tract, bloody wet lung, no signs of punctual hemorrhage at serous membranes, and no signs of mechanical external force.
Microbiological examinations showed no bacteria in cerebrospinal fluid (CSF) and in blood from heart, Staphylococcus aureus and Escherichia coli in pulmonary swab, as well as Staphylococcus aureus, Moraxella catarrhalis and Escherichia coli in pharyngeal swab.
Histology showed mucous-hemorrhagic inflammation of respiratory tract with mixed cell infiltration of mucous membrane of respiratory tract, in parts acute bloating of lung tissues next to areas with underventilation, activation of bronchus associated lymphatic tissue, acute blood congestion in lungs, focal inflammatory pulmonary infiltrations, in parts with multinuclear giant cells; a singular round-cell infiltration in heart muscle, so called tubular heart muscle change; acute blood congestion in the liver.

Autopsy, as well as subsequent microbiological and histological examinations, showed severe infection of respiratory tract and to a lesser extent of lungs above all with bacteria of the species Staphylococcus aureus. Furthermore, histology showed a single inflammatory focus in the heart muscle. With reservation of outstanding results of chemical-toxicological examinations the findings were consistent with death within the scope of inflammation of respiratory tract with involvement of the lungs and accompanying myocarditis. No signs of external mechanical force have been found, but killing with low evidence, e. g. soft covering of mouth and nose, cannot be excluded.
The subject's body was released for funeral.

Follow-up information was received on 15 January 2009 from the [redacted] regulatory authority [redacted].

The case has been reassessed. Initially suspected sudden infant death syndrome (SIDS) was excluded by autopsy and therefore has been deleted as adverse event.

No further information will be available.

LABORATORY TEST NAME	TEST DATE	TEST RESULT	LOW NORMAL	HIGH NORMAL
Head circumference	[redacted]	41cm		

INTERNATIONAL EVENT REPORT

DESK COPY (Page 1 of 3)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
Unknown	[redacted]	[redacted]		M	[redacted]

7. & 13. DESCRIBE EVENT(S)

Kawasaki's disease, Meningitis, Leukocytosis, Pericarditis, Mitral valve incompetence, Pyrexia, Fluid intake reduced, General physical health deterioration, Rash maculo-papular, Fungal skin infection, Cheilitis, Chapped lips, Palmar erythema, Lymphadenopathy, Infection,

This case was reported by a regulatory authority ([redacted]) and described the occurrence of atypical kawasaki disease in an nearly 12-month-old male subject who was vaccinated with combined diphtheria, tetanus-acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenzae type b vaccine (Infanrix hexa, GlaxoSmithKline) for prophylaxis.
Co-suspect vaccination included pneumococcal vaccines (non-gsk) (Prevenar 13, Pfizer).

Previous vaccination included 1st dose of Infanrix hexa and Prevenar 13 (each unknown route and application site) given on [redacted], which was well tolerated.

(See attached page)

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- ☐ PATIENT DIED AS OUTCOME OF EVENT
- ☒ RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☒ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☐ CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- ☐ OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) 1) Infanrix hexa Injection A21CB004A (Hepatitis B vaccine + Polio.vaccine inactivated + Tetanus vaccine + Diphtheria toxoid + Haemophilus influenzae ty + Acellular pertussis vax) GlaxoSmithKline

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION	17. INDICATION(S) FOR USE	18. THERAPY DATES (From / To)	19. THERAPY DURATION
Unknown	Unknown	PROPHYLAXIS	[redacted]	1 Days

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ N/A

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ N/A

14. IDENTIFIED DRUG(S) 2) Prevenar 13 Injection PAA012842 (Pneumococcal vac NonGSK) PFIZER

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION	17. INDICATION(S) FOR USE	18. THERAPY DATES (From / To)	19. THERAPY DURATION
Unknown	Unknown	PROPHYLAXIS	06May2011-06May2011	1 Days

20. DID EVENT ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ N/A

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ N/A

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

23. OTHER RELEVANT HISTORY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)

GlaxoSmithKline

Rue De L'Institut 89,
Rixensart, B-1330, Belgium

[redacted]

24c. DATE RECEIVED 03JUN2011

DATE OF REPORT 10JUN2011

24d. REPORT SOURCE ☒ HEALTH PROFESSIONAL ☐ STUDY ☐ LITERATURE

25a. REPORT TYPE ☒ INITIAL ☐ FOLLOW-UP

INTERNATIONAL EVENT REPORT

DESK COPY (Page 2 of 3)

I. EVENT INFORMATION

1. PATIENT INITIALS	1a. COUNTRY	2. DATE OF BIRTH	2a. AGE	3. SEX	4. - 6. EVENT ONSET
Unknown	[redacted]	[redacted]		M	[redacted]

7. & 13. DESCRIBE EVENT(S)

On [redacted] the subject received 2nd dose of Infanrix hexa and 2nd dose of Prevenar 13 (each unknown route and application site).

At an unspecified after 2nd vaccination with Infanrix hexa and Prevenar 13, the subject experienced fever with a body temperature up to 38.2 degC.

On [redacted] the subject received 3rd dose of Infanrix hexa and 3rd dose of Prevenar 13 (each unknown route and application site).

On [redacted] 3 days after 3rd vaccination with Infanrix hexa and Prevenar 13, the subject experienced atypical Kawasaki disease. The subject developed fever with body temperatures up to 40 degC.

On [redacted], the subject developed exanthema on abdomen and back. Exanthema of mycotic cause was suspected. The subject was treated symptomatically with antipyretic (Antipyretics).

8. - 12. CHECK ALL APPROPRIATE TO EVENT

- ☐ PATIENT DIED AS OUTCOME OF EVENT
- ☐ RESULTED IN OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☐ CLINICALLY SIGNIFICANT / REQUIRED INTERVENTION
- ☐ OTHER

II. DRUG INFORMATION

14. IDENTIFIED DRUG(S) 3) Infanrix hexa Injection (Hepatitis B vaccine + Polio.vaccine inactivated + Tetanus vaccine + Diphtheria toxoid + Haemophilus influenzae ty + Acellular pertussis vax) GlaxoSmithKline

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION	20. DID EVENT ABATE AFTER STOPPING DRUG?
Unknown	Unknown	☐ YES ☐ NO ☒ N/A
17. INDICATION(S) FOR USE PROPHYLAXIS		**21. DID EVENT REAPPEAR AFTER REINTRODUCTION?**
18. THERAPY DATES (From / To) [redacted]	**19. THERAPY DURATION** 1 Days	☒ YES ☐ NO ☐ N/A

14. IDENTIFIED DRUG(S) 4) Prevenar 13 Injection (Pneumococcal vac NonGSK) PFIZER

15. DAILY/CUMULATIVE DOSE	16. ROUTE OF ADMINISTRATION	20. DID EVENT ABATE AFTER STOPPING DRUG?
Unknown	Unknown	☐ YES ☐ NO ☒ N/A
17. INDICATION(S) FOR USE PROPHYLAXIS		**21. DID EVENT REAPPEAR AFTER REINTRODUCTION?**
18. THERAPY DATES (From / To) [redacted]	**19. THERAPY DURATION** 1 Days	☒ YES ☐ NO ☐ N/A

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (Exclude those used to treat event)

23. OTHER RELEVANT HISTORY

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (Include Zip Code)

[redacted]

24c. DATE RECEIVED	DATE OF REPORT
03JUN2011	10JUN2011

24d. REPORT SOURCE

☐ HEALTH PROFESSIONAL ☐ STUDY ☐ LITERATURE

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOW-UP

[redacted]	DESK COPY	(Page 3 of 3)

7. & 13. DESCRIBE EVENT(S)

On [redacted], the subject's fluid intake was reduced. His general condition was reduced. The subject was treated with cefpodoxime. Symptoms did not improve.

On [redacted] the subject was hospitalised. Atypical Kawasaki syndrome, secondary meningitis and pericarditis were diagnosed. He showed maculo-papular exanthema at trunk, arms, legs and face. His lips and palms were reddened. Cervical lymph nodes were enlarged. His body temperature was up to 40.3 degC.
Initially, there were clearly increased parameters for an infection (signs of infection) as well as distinct exanthema. Culture of blood and liquor were uneventfully. Due to abnormal midstream urine, the subject was treated with cefuroxime sodium (Cefuroxim). Fever did not resolve.

On [redacted], the subject still suffered from fever. He showed chapped lips, palmar erythema, leukocytosis and mild cervical lymphadenopathy. Kawasaki's disease was suspected. The subject was treated with normal immunoglobulin (Immunoglobulin) and aspirin (Acetylsalicylacid). Fever resolved and general condition improved.

On [redacted], echocardiography showed pericarditis and mitral insufficiency.

On [redacted], the subject was discharged from hospital after 12 days.

At the time of reporting atypical Kawasaki disease was unresolved.

The reporter reported that the events were life threatening.

No further information will be available.

Examination:
Analysis of cerebrospinal fluid on [redacted]:
Leukocytes: 17/mcl
Glucose, protein and lactate: normal

Throat swab on [redacted]: no growth

Analysis of midstream urine in [redacted]: abnormal
Midstream urine culture on [redacted]: no growth

LABORATORY TEST NAME	TEST DATE	TEST RESULT	LOW NORMAL	HIGH NORMAL
Blood culture	[redacted]	no growth		
Body temperature		38.2degC		
Body temperature		40degC		
Body temperature		40.3degC		
C-reactive protein		24.84mg/dl		
C-reactive protein		8.04mg/dl		
CSF culture		no growth		
Echocardiogram		mitral insuffici		
Echocardiogram		pericarditis		
Leukocyte count NOS		23000/mcl		
Platelet count		598000/mcl		
Stool culture		normal		

APPENDIX 7B.9 : Cyanosis

Vaccines Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Infanrix hexa: Cyanosis

Date of review	15 October 2013
Vaccine terms included	Infanrix hexa (combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine) GSK drug code: IGA182
Adverse events (MedDRA preferred terms) included	Cyanosis, Cyanosis neonatal, Cyanosis central
Authors	[redacted] Safety Scientist) (Safety Physician)

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LIST OF ABBREVIATIONS

MedDRA	Medical Dictionary for Regulatory Activities
PSUR	Periodic Safety Update Report
PT	Preferred term
RSI	Reference Safety Information

1. BACKGROUND

In the context of periodic aggregate safety reports, the Company first described events of cyanosis in PSUR (periodic safety update report) No 12 (covering the period between 23 October 2006 and 22 October 2007). Since then cyanosis has been routinely described in periodic Infanrix hexa PSURs.

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b. The primary vaccination schedule consists of three or two doses during the first 6 months of age. After a vaccination with 2 doses (e.g. 3, 5 months) a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age. After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

Cyanosis is a bluish discoloration of the skin resulting from an inadequate amount of oxygen in the blood. Cyanosis is not listed in the reference safety information (RSI). However events likely to cause or be related to cyanosis are listed, such as convulsions with or without fever, allergic reactions including anaphylactic and anaphylactoid reactions, collapse or shock-like state (hypotonic-hyporesponsive episode), apnoea and syncope.

This is a cumulative evaluation of data from spontaneous reporting sources on cyanosis following administration of Infanrix hexa.

2. POST-MARKETING EXPOSURE TO VACCINE

Infanrix hexa was first approved in European Union on 23 October 2000 (centralized procedure) and is currently licensed in 95 countries (extracted from PSUR No 17, data lock point 22 October 2012). Since launch, more than 100 million doses of Infanrix hexa were distributed worldwide. As vaccination with Infanrix hexa varies between one and four doses per subject, post-marketing exposure to Infanrix hexa since launch until the data lock point of this evaluation (2 October 2013) is estimated as being between 25 and 100 million subjects.

3. SAFETY DATA REVIEWED

This evaluation presents relevant information on reports of cyanosis from the GSK worldwide safety database.

3.1. Database Search Strategy

The GSK worldwide safety database was searched on 3 October 2013 using the following criteria:

- **Data lock point**: since marketing launch until 2 October 2013
- **Report types**: All spontaneous reports

- **Suspect drug**: Infanrix hexa
- **MedDRA preferred terms (PTs)**: Cyanosis, Cyanosis neonatal, Cyanosis central

Limitations to quantitative analysis of spontaneous reports
Post-marketing surveillance for suspected adverse reactions is required to characterise the full safety profile of vaccines. Individual case safety reports are the primary source of information to detect potential risks in regular clinical practice. However such reports are anecdotal in nature and do not represent a random sample; they are not suitable as a basis for statistical inference, but statistical methods can provide real value in identifying outstanding reporting patterns for further investigation (signals) and in flagging reporting artefacts that may otherwise be misleading. Indeed invalid information may be generated because of several factors including: biased reporting, under-reporting, secular trends, media effects, missing or limited information, absence of case validation, absence of adequate comparator group.

3.2. Summary of Overall Dataset

A total of 404 cases were retrieved from the GSK worldwide safety database (APPENDIX 1), including 408 cyanosis events since cyanosis was reported twice in 4 cases ([redacted], [redacted], [redacted] and [redacted]) following 2 different doses of Infanrix hexa. Of these 404 cases:

- 241 (59.6%) had a healthcare professional as a report source.
- The majority were received from Germany (31.9%), Italy (28.7%) and The Netherlands (13.1%).

Most (401) were coded using the PT 'Cyanosis', 3 with the PT 'Cyanosis central' and none with the PT 'Cyanosis neonatal'. Further characteristics are summarised in Table 1. The median age (3 months) of subjects for which cyanosis was reported was expected given the indicated population. Cyanosis was reported slightly more frequently for girls than for boys. The median time-to-onset was 4 hours and the case outcome was 'resolved' in most cases. Cases in which cyanosis was reported were mainly serious.

Table 1 Summary of characteristics of cyanosis cases

Patient Age	Median		3 months	
	Range		1 month to 4 years	
	Unknown	n (%)	1	(0.2%)
Gender	Male	n (%)	172	(42.6%)
	Female	n (%)	221	(54.7%)
	Unknown	n (%)	11	(2.7%)
Time to onset since last dose	Median		4 hours	
	Range		same day to 3 years	
	Unknown	n (%)	26	(6.4%)
Outcome	Fatal	n (%)	12	(3.0%)
	Improved	n (%)	10	(2.5%)
	Resolved	n (%)	308	(76.2%)
	Resolved with Sequelae	n (%)	2	(0.5%)
	Unknown (at the time of reporting)	n (%)	51	(12.6%)
	Unresolved	n (%)	20	(5.0%)
	Worse	n (%)	1	(0.2%)
Dose number*	1	n (%)	130	(31.9%)
	2	n (%)	67	(16.4%)
	3	n (%)	44	(10.8%)
	4	n (%)	25	(6.1%)
	Unknown	n (%)	142	(34.8%)
Cases classified as serious		n (%)	381	(94.3%)

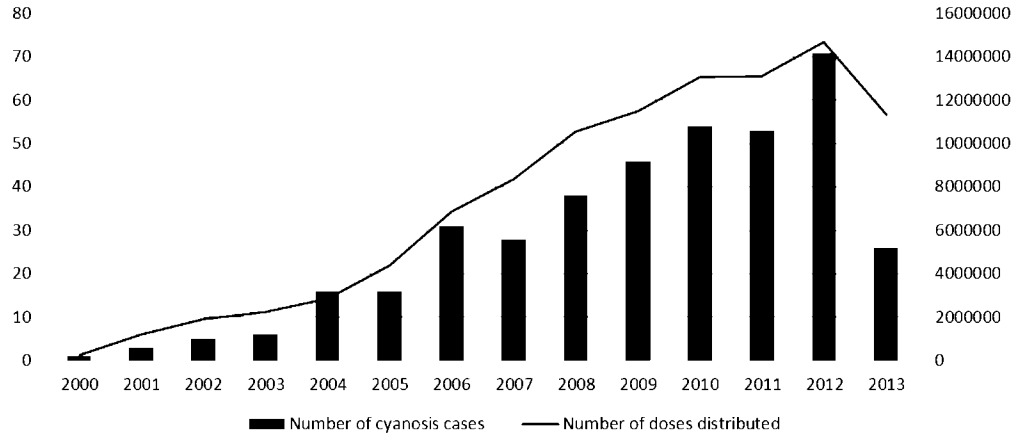
* In 4 cases cyanosis was reported twice, following 2 different doses; therefore the total number of doses is 408

3.3. Reporting trends over time

The blue line and the right vertical axis in Figure 1 show the evolution of the worldwide distribution of Infanrix hexa doses per calendar year, while the red bars and the left vertical axis represent the distribution of the 394 cyanosis events retrieved by the above search per calendar year[1], and for which a cyanosis onset date was reported. Overall, the increased trend in yearly case reporting followed the increase of sales over time. Note that the data for 2013 only covers months January to October and is therefore incomplete compared to the previous years.

Figure 2 shows the yearly reporting frequency for cyanosis over time[1] expressed in number of cases per 100 000 doses distributed. The reporting frequency varied between 0.2 and 0.6 cases per 100 000 doses distributed. Higher fluctuations were observed during the first years following marketing due to lower sales volumes at that time. During the past 14 years the reporting frequency did not tend to increase or decrease.

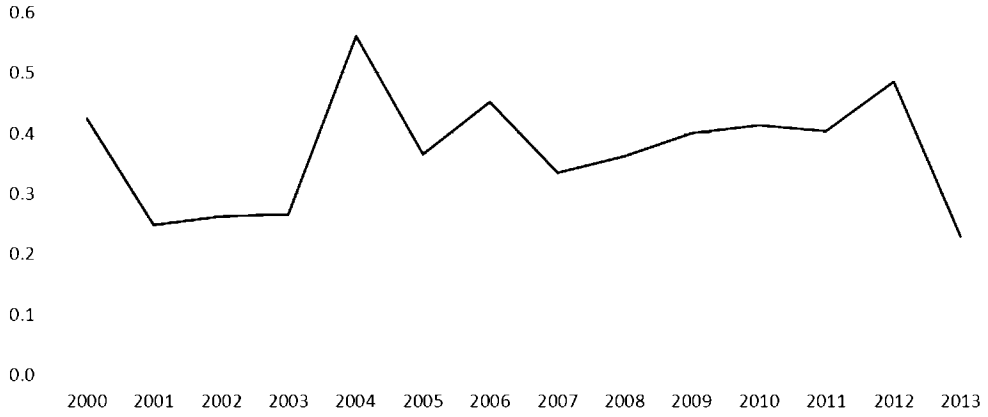
Figure 1 Yearly sales and number of spontaneous cyanosis cases received



*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

[1] The reporting date used was the cyanosis onset date, not the case receipt date because for spontaneous cases there might be a long delay between event onset and reporting to GSK. Out of the 408 cyanosis events, onset date was missing for 14 of them.

Figure 2 Yearly and cumulative reporting frequency in number of cases per 100 000 doses distributed

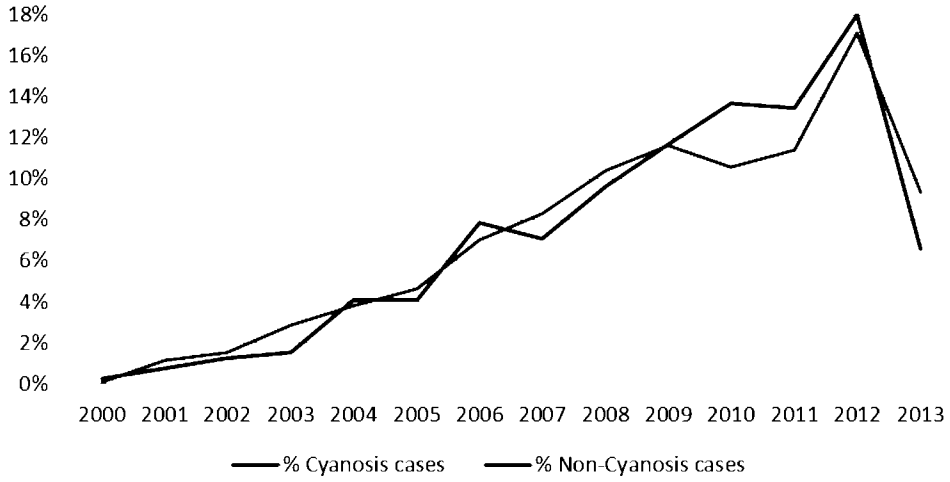


*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

The comparison of cyanosis reporting with sales data has limitations since the time between dose distribution and actual vaccine administration is unknown. Also, the efficiency of the spontaneous reporting system varies in the different countries where Infanrix hexa is distributed. In order to correct for these limitations, the yearly[1] proportion of cyanosis cases among all cyanosis cases was plotted in Figure 3 (red line) and compared to the yearly[2] proportion of non-cyanosis cases among all non-cyanosis cases (green line). This approach allows visualizing whether, at some point in time, more cyanosis cases were received compared to other cases received for Infanrix hexa, while taking into account changes in reporting trends (e.g. following marketing in a high reporting country). The fact that the proportion of cyanosis cases crosses several times the proportion of non-cyanosis cases in Figure 3 suggests that there was no disproportionate reporting of cyanosis since the past 14 years; and that the changes in reporting trends observed in Figure 1 and Figure 2 were random fluctuations.

[2] For non-cyanosis cases, the case onset date, which is the date of occurrence of the first event of the case, was used as the reporting date.

Figure 3 **Proportion of cyanosis cases *versus* non-cyanosis cases reported for Infanrix hexa over time**



*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

3.4. Other events reported in cyanosis cases

Table 2 lists events reported in the 386 (95.5%) of the 404 cyanosis cases retrieved with the query described in Section 3.1 that are more likely to cause cyanosis than vaccination. For each system organ class (SOC), the events are sorted by decreasing number of cases. Some of these are listed in the Infanrix hexa reference safety information (RSI), others are unlikely to be related to vaccination. Note that one case often includes more than one event; therefore the total number of events is greater than the total number of cases (404).

In addition to these 386 cases, two cases had pre-existing conditions likely to have caused cyanosis. Patent foramen ovale was reported for the subject in case [redacted], and brain malformation where cyanosis occurred during sleep was reported for the subject in case [redacted], suggesting a respiratory centre abnormality or a neck hypotonia causing tracheal obstruction.

Among the remaining 16 cases (4%, [redacted]), cyanosis was not reported with medical events likely to have caused it. In most of these cases cyanosis occurred and resolved (spontaneously or following treatment) within minutes or hours. In cases [redacted] and [redacted] cyanosis was reported after both dose 1 and dose 2, and considered unrelated or unlikely related to vaccination by respective reporters. Subjects were often hospitalised or brought to emergency rooms as a precautionary measure for medical observation and/or treatment; long term hospitalisations were not reported. In case [redacted] the events of cyanosis of lower limbs and stiffness on lower limbs were considered by the reporting paediatrician as a normal reaction to painful stimulus and not as a serious reaction.

Table 2 Events co-reported in cyanosis cases more likely to have caused cyanosis than vaccination

Event SOC	Event PT	Number Of Cases	Listed?
Blood and lymphatic system disorders	*Anaemia*	5	No
	Disseminated intravascular coagulation	2	No
	Anaemia neonatal	1	No
Cardiac disorders	*Bradycardia*	15	No
	Tachycardia	13	No
	Cardiac arrest	5	No
	Cardiac failure	2	No
	Cardio-respiratory arrest	2	No
	Cardiomegaly	2	No
	Cardiovascular disorder	2	No
	Arrhythmia	1	No
	Atrial septal defect acquired	1	No
	Bundle branch block right	1	No
	Cardiopulmonary failure	1	No
	Cardiovascular insufficiency	1	No
	Congestive cardiomyopathy	1	No
	Left ventricular dysfunction	1	No
	Myocarditis	1	No

	Pulmonary valve stenosis	1	No
	Supravalvular aortic stenosis	1	No
	Systolic dysfunction	1	No
	Ventricular asystole	1	No
	Ventricular dysfunction	1	No
Congenital, familial and genetic disorders	***Hypertrophic cardiomyopathy***	1	No
General disorders and administration site conditions	***Pyrexia***	125	Yes
	Crying	106	Yes
	General physical health deterioration	7	No
	Sudden infant death syndrome	5	No
	Multi-organ failure	3	No
	Systemic inflammatory response syndrome	2	No
	Death	1	No
	Sudden death	1	No
	Terminal state	1	No
Hepatobiliary disorders	***Acute hepatic failure***	1	No
Immune system disorders	***Anaphylactic reaction***	3	Yes
	Anaphylactic shock	3	Yes
	Hypersensitivity	3	Yes
	Allergy to vaccine	1	Yes
	Anaphylactoid reaction	1	Yes
Infections and infestations	***Pertussis***	11	No
	Upper respiratory tract infection	6	Yes
	Pneumonia	5	No
	Meningitis	4	Yes
	Respiratory tract infection	4	Yes
	Bronchitis	3	Yes
	Infection	3	No
	Sepsis	3	No
	Bronchopneumonia	2	No
	Septic shock	2	No
	Atypical pneumonia	1	No
	Bacterial infection	1	No
	Meningococcal sepsis	1	No
Injury, poisoning and procedural complications	***Carbon monoxide poisoning***	1	No
Investigations	***Oxygen saturation decreased***	14	No
	Cardiac murmur	2	No
	Heart sounds abnormal	2	No
Metabolism and nutrition disorders	***Dehydration***	4	No
	Acidosis	2	No
	Hyponatraemia	2	No
	Metabolic acidosis	1	No
Nervous system disorders	***Hypotonia***	137	Yes
	Loss of consciousness	79	No
	Convulsion	56	Yes
	Hypotonic-hyporesponsive episode	49	Yes
	Febrile convulsion	47	Yes
	Depressed level of consciousness	29	No
	Grand mal convulsion	20	Yes
	Hypertonia	20	No
	Unresponsive to stimuli	19	No

	Syncope	15	No
	Epilepsy	13	Yes
	Presyncope	7	No
	Clonus	6	No
	Myoclonus	6	No
	Partial seizures	5	Yes
	Atonic seizures	4	Yes
	Tonic convulsion	4	Yes
	Altered state of consciousness	3	No
	Encephalitis	3	Yes
	Stupor	3	Yes
	Brain injury	2	Yes
	Brain oedema	2	No
	Cerebral atrophy	2	No
	Clonic convulsion	2	Yes
	Coma	2	No
	Lethargy	2	No
	Postictal state	2	No
	Brain stem thrombosis	1	No
	Cerebral disorder	1	No
	Complex partial seizures	1	No
	Encephalopathy	1	Yes
	Hyporesponsive to stimuli	1	No
	Hypoxic-ischaemic encephalopathy	1	No
	Meningism	1	No
	Partial seizures with secondary generalisation	1	Yes
Respiratory, thoracic and mediastinal disorders	***Apnoea***	56	Yes
	Dyspnoea	28	No
	Respiratory arrest	23	Yes
	Apparent life threatening event	18	No
	Cough	16	Yes
	Respiratory disorder	11	No
	Respiration abnormal	10	No
	Choking	7	No
	Tachypnoea	6	No
	Aspiration	5	No
	Pharyngeal erythema	5	No
	Apnoeic attack	4	Yes
	Asphyxia	3	No
	Cyanosis central	3	No
	Pneumonia aspiration	3	No
	Productive cough	3	Yes
	Rales	3	No
	Respiratory failure	3	No
	Bradypnoea	2	No
	Bronchospasm	2	No
	Laryngospasm	2	No
	Acute respiratory failure	1	No
	Anoxia	1	No
	Asthma	1	No
	Hypopnoea	1	No
	Hypoventilation	1	Yes
	Obstructive airways disorder	1	No
	Pharyngeal disorder	1	No

	Pneumothorax	1	No
	Respiratory distress	1	No
	Rhonchi	1	No
	Stridor	1	No
	Wheezing	1	No
Vascular disorders	***Pallor***	135	No
	Circulatory collapse	14	Yes
	Peripheral coldness	10	Yes
	Hypotension	5	Yes
	Shock	3	Yes
	Peripheral vascular disorder	2	No
	Poor peripheral circulation	1	Yes
	Vasospasm	1	No

4. DISCUSSION AND CONCLUSION

Cyanosis is a bluish discoloration of the skin resulting from an inadequate amount of oxygen in the blood. Cyanosis is not listed in the reference safety information (RSI); however events likely to cause or be related to cyanosis are listed, such as convulsions with or without fever, allergic reactions including anaphylactic and anaphylactoid reactions, collapse or shock-like state (hypotonic-hyporesponsive episode), apnoea and syncope (Section 1). Therefore it is expected that these events, as well as other signs and symptoms of these events are often co-reported with cyanosis (Table 2).

Cyanosis is a sign or symptom indicative of a variety of events. In itself cyanosis is unspecific and uninformative. In the present cumulative review, which covered the past 14 years, the spontaneous reporting trend of cyanosis did not indicate any safety signal (Section 3.3). Also, the events co-reported with cyanosis (Section 3.4) did not reveal any new information regarding the known safety profile of Infanrix hexa.

The fact that cyanosis was mainly reported in serious cases (94.3%, see Table 1) reflects that many co-reported events are considered important medical events (IMEs) by EMA and are thus considered serious by GSK. Also, hospitalisation was reported in 270 (66.8%) of cases. Since cyanosis can be a sign or symptom of a serious condition, subjects are often hospitalised for a short period of time as a precautionary measure for observation.

In cases where cyanosis was reported alone (Section 3.4), the short time-to-onset and short duration both suggest that cyanosis is more likely a physiological reaction to fear or pain resulting from the injection technique (needle) rather than from the vaccine itself. In case [redacted] this aetiology was supported by the reporter.

GSK's routine process for medical review and safety signal detection and evaluation performed on the 404 cases including the PT cyanosis did not reveal any new risks regarding the known Infanrix hexa safety profile.

Data currently available to GSK, including the limitations of this evaluation (see Section 3.1), suggest there is no increased risk of cyanosis following vaccination with Infanrix hexa. Since the PT Cyanosis is in itself unspecific and uninformative, GSK will no longer routinely describe cyanosis in future Infanrix hexa aggregate safety reports.

GSK will continue to employ a routine, pro-active process for identifying safety signals with three main components:

1. Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
2. Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
3. Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

5. REFERENCES

Smirnov NV. Estimate of deviation between empirical distribution functions in two independent samples. *Bulletin Moscow Univ* 1939; 2(2): 3–16.

Van Holle L, Zeinoun Z, Bauchau V *et al.* Using time-to-onset for detecting safety signals in spontaneous reports of adverse events following immunization: a proof of concept study. *Pharmacoepidemiol Drug Saf.* 2012; 21: 603-610.

APPENDIX 1 LINE LISTING OF CYANOSIS CASES (N=404)

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	2 Months Female		Infanrix hexa	1		4 Days	Convulsion, Vomiting, Diarrhoea, Crying, Cyanosis, Hypotonia	Serious	Resolved
	4 Months Male		Infanrix hexa			Same day	Cyanosis, Mobility decreased, Oedema peripheral, Injection site erythema, Injection site reaction, Crying, Rash macular	Not serious	Resolved
	2 Months Male		Infanrix hexa		Paracetamol	1 Weeks	Pertussis, Pneumonia, Cough, Apnoea, Cyanosis, Vomiting, Rales	Serious	Improved
	5 Months Male		Infanrix hexa			2 Days	Febrile convulsion, Ear infection, Hyperpyrexia, Pyrexia, Hyperaemia, Hyperhidrosis, Tremor, Crying, Cyanosis, Loss of consciousness, White blood cell count increased, Neutrophil count increased	Serious	Resolved
	Unknown		Infanrix hexa	1		Unknown	Muscle rigidity, Cyanosis, Lethargy	Serious	Resolved
	2 Months Female		Infanrix hexa			Same day	Cyanosis, Irritability, Hypertonia, Crying	Serious	Resolved
	2 Months Male		Infanrix hexa	1		4 Hours	Hypotonic-hyporesponsive episode, Hypotonia, Cyanosis, Moaning, Asthenia, Pallor, Eye movement disorder, Agitation	Serious	Resolved
	4 Months Male	Mechanical urticaria	Infanrix hexa	1	DTPa-IPV (Non-GSK), Haemophilus influenzae type b vaccine (Non-GSK)	Unknown	Hypersensitivity, Erythema, Swelling, Cyanosis, Injection site pain	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Male		Infanrix hexa	2	Infanrix hexa, DTPa-IPV (Non-GSK)	15 Hours	Apnoea, Salivary hypersecretion, Cyanosis, Staring, Pallor, Malaise	Serious	Resolved
	2 Months Female		Infanrix hexa	1		8 Hours	Loss of consciousness, Cyanosis, Pallor, Vomiting	Serious	Resolved
	2 Years Female		Infanrix hexa			0 Days	Cyanosis, Slow response to stimuli, Pallor	Serious	Resolved
	16 Months Female		Infanrix hexa, Priorix	4		1 Days	Febrile convulsion, Pyrexia, Loss of consciousness, Eye disorder, Cyanosis, Hypotonia	Serious	Resolved
	1 Years Male		Infanrix hexa			0 Days	Convulsion, Cyanosis, Slow response to stimuli, Injection site reaction	Serious	Resolved
	2 Months Female		Infanrix hexa				Retching, Pallor, Cyanosis	Not serious	Resolved
	3 Months Female		Infanrix hexa	1 and 2		10 Days	Cyanosis, Bradycardia, Cough, Malaise, Pertussis	Serious	Unresolved
	11 Months Female		Infanrix hexa		MMR vaccine (Non-GSK)	0 Days	Cyanosis, Dyspnoea	Serious	Resolved
	5 Months Male		Infanrix hexa			Same day	Cyanosis, Diarrhoea, Pyrexia, Pallor	Not serious	Unknown
	4 Months Female		Infanrix hexa			0 Days	Cyanosis, Crying, Rash maculo-papular, Vasodilatation	Not serious	Resolved
	3 Months Male		Infanrix hexa	1		60 Seconds	Anaphylactoid reaction, Cyanosis, Pallor, Hypothermia	Serious	Resolved
	5 Months Male	Apnoea	Infanrix hexa	2		Minutes	Anaphylactic reaction, Pallor, Unresponsive to stimuli, Respiratory disorder, Cyanosis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	1 Years Male	Enteritis, Milk allergy, Abdominal pain, Gastroenteritis viral, Dehydration, Atopy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		Same day	Febrile convulsion, Cyanosis, Local swelling, Injection site erythema, Pain, Pallor, Pyrexia	Serious	Resolved
	3 Months Female		Infanrix hexa			7 Hours	Cyanosis, Dyspnoea, Musculoskeletal stiffness, Pain, Depressed level of consciousness	Serious	Resolved
	10 Months Female		Infanrix hexa, Hepatitis B vaccine (Non-GSK)	1	Polio Sabin (Oral), Vitamin K, Infanrix HepB, Haemophilus influenzae type b vaccine (Non-GSK)	24 Hours	Convulsion, Musculoskeletal stiffness, Cyanosis, Eye movement disorder, Dyskinesia, Lymphadenopathy, Injection site erythema	Serious	Resolved
	3 Months Male		Infanrix hexa			5 Hours	Hypotonia, Pallor, Cyanosis, Slow response to stimuli	Serious	Resolved
	11 Weeks Female	Premature baby	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Apnoea, Cyanosis, Bradycardia, Pyrexia	Serious	Resolved
	4 Months Male		Infanrix hexa	3	Pneumococcal vaccines (Non-GSK)	1 Days	Pyelonephritis, Cyanosis, Pyrexia, Escherichia infection	Serious	Resolved
	3 Months Male		Infanrix hexa			0 Days	Cyanosis, Peripheral coldness, Food aversion, Crying	Serious	Resolved
	7 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Slow response to stimuli, Cyanosis, Pallor, Restlessness, Stupor, Platelet count decreased, White blood cell count increased	Serious	Resolved
	5 Months Male		Infanrix hexa			0 Days	Cyanosis, Asthma, Bronchospasm, Vomiting, Tachypnoea, Pharyngeal erythema, Pyrexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	11 Months Male	Convulsion	Infanrix hexa	3		0 Days	Febrile convulsion, Cyanosis, Loss of consciousness, Convulsion, Musculoskeletal stiffness, Posture abnormal, Crying, Injection site erythema, Pyrexia	Serious	Resolved
[redacted]	30 Months Male		Infanrix hexa			Unknown	Cyanosis, Rash	Not serious	Resolved
[redacted]	3 Months Female	Muscle hypertrophy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			7 Hours	Circulatory collapse, Depressed level of consciousness, Cyanosis, Dyskinesia, Pallor, Social avoidant behaviour, Pyrexia, Vomiting	Serious	Resolved
[redacted]	2 Months Male		Infanrix hexa			0 Days	Cyanosis, Urticaria	Not serious	Resolved
[redacted]	4 Months Female		Infanrix hexa	2	Pneumococcal vaccines (Non-GSK)	9 Hours	Circulatory collapse, Depressed level of consciousness, Cyanosis, Hypotonia, Pallor, Respiratory disorder, Chest discomfort	Serious	Resolved
[redacted]	11 Months Male		Infanrix hexa			0 Days	Loss of consciousness, Cyanosis, Salivary hypersecretion, Pyrexia	Serious	Resolved
[redacted]	60 Days Female		Infanrix hexa		Synflorix	4 Hours	Circulatory collapse, Cyanosis, Depressed level of consciousness, Foaming at mouth, Hypotonia, Pallor, Pyrexia, Increased appetite, Choking	Serious	Resolved
[redacted]	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			2 Days	Apparent life threatening event, Respiratory arrest, Depressed level of consciousness, Circulatory collapse, Cyanosis, Peripheral coldness, Oligodipsia, Tachycardia, Pallor, Hypotonia, Pyrexia	Serious	Unknown
[redacted]	2 Months Male		Infanrix hexa			1 Hours	Apnoea, Cyanosis, Erythema, Crying	Serious	Resolved
[redacted]	2 Months Female		Infanrix hexa	1		Hours	Convulsion, Cyanosis, Pyrexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Male	Premature baby, Enterocolitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			2 Hours	Apnoea, Cyanosis, Malaise, Hypotonia, Pyrexia	Serious	Resolved
	2 Months Male		Infanrix hexa	1		3 Hours	Hypotonic-hyporesponsive episode, Slow response to stimuli, Cyanosis, Hypotonia, Fatigue, Pallor, Crying	Serious	Resolved
	4 Months Male		Infanrix hexa			0 Days	Cyanosis, Pallor	Serious	Resolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		Immediate	Syncope, Cyanosis, Loss of consciousness, Hypotonia	Serious	Resolved
	3 Months Male	Breast feeding	Infanrix hexa			0 Days	Cyanosis, Lethargy, Eye movement disorder, Pallor, Tremor, Vomiting projectile	Serious	Resolved
	2 Months Male	Caesarean section, Apgar score	Infanrix hexa, N. Meningitidis Group C polysaccharide			1 Hours	Hypotonia, Unresponsive to stimuli, Cyanosis, Gastrooesophageal reflux disease, Staring, Eyelid disorder, Pallor, Hypersomnia, Crying, Vomiting	Serious	Resolved
	3 Months Female		Infanrix hexa			30 Minutes	Cyanosis, Hypotonia	Serious	Resolved
	2 Months Female		Infanrix hexa			0 Days	Apnoea, Cyanosis, Hypotonia, Vomiting	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			2 Days	Convulsion, Encephalitis, Cyanosis, Eye movement disorder	Serious	Unresolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Staring, Pallor, Ill-defined disorder, Decreased appetite, Restlessness	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	27 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			1 Days	Petit mal epilepsy, Cyanosis, Hypotonia, Pallor	Serious	Resolved
[redacted]	15 Weeks Male	Apnoea, Premature baby, Bradycardia	Infanrix hexa	1		9 Hours	Apnoea, Respiratory rate decreased, Cyanosis, Ill-defined disorder	Serious	Resolved
[redacted]	2 Months Male	Gestational diabetes	Infanrix hexa		Pneumococcal vaccines (Non-GSK)	2 Days	Pertussis, Cyanosis, Productive cough	Serious	Resolved
[redacted]	2 Months Female		Infanrix hexa			5 Hours	Cyanosis, Hypertonia, Ear infection, Conjunctival hyperaemia, Ear pain	Serious	Resolved
[redacted]	6 Months Male		Infanrix hexa	2		6 Hours	Cyanosis, Decreased activity, Hypotonic-hyporesponsive episode, Tachycardia, Pyrexia	Serious	Resolved
[redacted]	3 Months Female		Infanrix hexa, N. Meningitidis Group C polysaccharide		Pneumococcal vaccines (Non-GSK)	0 Days	Cyanosis, Hypotonia, Crying	Serious	Resolved
[redacted]	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Carbon monoxide poisoning, Syncope, Cyanosis, Hypotonic-hyporesponsive episode, Pallor	Serious	Resolved
[redacted]	5 Months Male		Infanrix hexa			1 Days	Cyanosis, Hypertonia, Tremor, Physical examination abnormal, Pyrexia	Not serious	Resolved
[redacted]	5 Months Male		Infanrix hexa			0 Days	Febrile convulsion, Tremor, Cyanosis, Loss of consciousness, Somnolence	Serious	Resolved
[redacted]	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Months	Cyanosis, Irritability, Crying	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			6 Hours	Hypotonic-hyporesponsive episode, Cyanosis, Apnoea, Hypotonia, Crying, Decreased activity, Staring, Cardiac murmur	Serious	Resolved
	2 Months Male		Infanrix hexa			0 Days	Cyanosis, Hypertonia	Serious	Resolved
	63 Days Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			5 Hours	Apparent life threatening event, Cyanosis, Hypotonic-hyporesponsive episode, Pallor, Asthenia, Feeling abnormal	Serious	Resolved
	11 Months Female	Pharyngitis, Ear infection	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		7 Hours	Febrile convulsion, Cyanosis, Apnoea, Loss of consciousness, Hypertonia, Pallor, Crying, Drooling, Eating disorder	Serious	Resolved
	1 Months		Infanrix hexa			50 Minutes	Cyanosis, Apnoea, Muscle spasms	Serious	Unknown
	10 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		3 Hours	Convulsion, Depressed level of consciousness, Cyanosis, Microcytosis, Iron deficiency, Breath holding, Pallor, Hypotonia	Serious	Unknown
	2 Months Male	Premature baby, Respiratory distress, Viral infection, Hyponatraemia, Convulsion	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			1 Days	Cyanosis, Hypotonia, Pallor, Decreased appetite	Serious	Improved
	12 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		9 Hours	Febrile convulsion, Loss of consciousness, Apnoea, Cyanosis, Upper respiratory tract infection, Hypotonia, Skin warm, Pallor, Crying	Serious	Resolved
	59 Days Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		6 Hours	Apnoea, Loss of consciousness, Cyanosis, Pallor, Hypotonia, Chills, Crying, Pyrexia	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months		Infanrix hexa	2		5 Hours	Cyanosis, Purpura, Anxiety, Rash macular, Crying	Serious	Resolved
	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		0 Days	Depressed level of consciousness, Cyanosis, Skin warm, Hypotonia, Somnolence, Pyrexia	Serious	Resolved
	3 Months Male	Gastrooesophageal reflux disease	Infanrix hexa, Infanrix-polio-HIB, Pneumococcal vaccines (Non-GSK)	1	Omeprazole	2 Days	Respiratory arrest, Eye disorder, Loss of consciousness, Presyncope, Vomiting, Hypertonia, Crying, Pyrexia, Injection site induration, Injection site erythema, Decreased appetite, Cyanosis, Laryngospasm, Respiratory disorder	Serious	Unknown
	11 Months Female	Gastrooesophageal reflux disease	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Aluminium hydroxide + magnesium trisilicate	0 Days	Convulsion, Pharyngitis, Loss of consciousness, Cyanosis, Gastrooesophageal reflux disease, Pallor, Hypotonia, Hyperhidrosis, Staring, Pyrexia	Serious	Resolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Apnoea, Cyanosis, Rash, Crying, Drooling	Serious	Resolved
	4 Months Female	Regurgitation	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		11 Hours	Presyncope, Cyanosis, Hypotonia, Staring, Crying, Lividity, Pallor	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Hyporesponsive to stimuli, Hypotonia, Pallor	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	7 Weeks Male	Premature baby, Apparent life threatening event, Gastrooesophageal reflux disease, Cardiac murmur	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Omeprazole	0 Days	Loss of consciousness, Apnoea, Pallor, Hypotonia, Vomiting, Pyrexia, Bradycardia, Cyanosis	Serious	Resolved
	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	6 Hours	Loss of consciousness, Cyanosis, Pallor, Cold sweat, Crying, Somnolence, Hypotonia	Serious	Resolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		5 Hours	Loss of consciousness, Apnoea, Cyanosis central, Drooling, Pallor, Hypotonia, Injection site reaction, Pain, Diarrhoea, Crying, Pyrexia	Serious	Resolved
	2 Months Male		Infanrix hexa	1		4 Hours	Thrombocytosis, Apnoea, Protein deficiency anaemia, Cyanosis, Anaemia, Nasopharyngitis, Crying	Serious	Unknown
	1 Years Male		Infanrix hexa		Priorix	1 Days	Cyanosis, Pain in extremity, Vaccination site induration, Injection site oedema, Pyrexia	Not serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Cyanosis, Hypotonia, Crying, Pyrexia	Serious	Resolved
	4 Months Male		Infanrix hexa	2		0 Days	Cyanosis, Crying, Erythema	Serious	Resolved
	5 Months Male		Infanrix hexa	2			Cyanosis, Slow response to stimuli, Hypotonia, Pallor	Serious	Resolved
	6 Months Female		Infanrix hexa	3		0 Days	Cyanosis, Somnolence, Fatigue, Pallor, Pyrexia	Not serious	Resolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Slow response to stimuli, Cyanosis, Hypotonia, Staring, Pallor, Diarrhoea	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Male	Mastitis, Surgery, Injection site abscess, Infantile colic	Infanrix hexa		Bacillus Calmette-Guerin Vaccine (Non-GSK)	0 Days	Convulsion, Cyanosis, Respiratory arrest, Loss of consciousness, Eye movement disorder, Protrusion tongue, Hypertonia, Muscle spasms, Crying, Pyrexia, Injection site oedema, Erythema, Injection site urticaria	Serious	Unknown
	6 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Hypertonia, Pyrexia	Serious	Resolved
	11 Weeks Male	Premature baby, Respiratory distress, Apnoea, Jaundice	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			24 Hours	Apparent life threatening event, Apnoea, Cyanosis, Slow response to stimuli, Brain oedema, Irritability, Decreased appetite, Crying, Hypotonia, Blood sodium decreased	Serious	Resolved
	5 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Vasospasm, Hypotonia, Slow response to stimuli	Serious	Resolved
	5 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		10 Minutes	Cyanosis	Not serious	Resolved
	11 Weeks Male	Premature baby, Low birth weight baby, Acute respiratory distress syndrome, Patent ductus arteriosus	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		8 Hours	Cyanosis, Apnoea, Bradycardia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	11 Weeks Male	Premature baby, Low birth weight baby, Respiratory distress, Patent ductus arteriosus	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Abidec, Ferrous sulfate	8 Hours	Cyanosis, Apnoea, Bradycardia	Serious	Resolved
	4 Months Female		Infanrix hexa			0 Days	Syncope, Cyanosis, Hypotonia	Serious	Improved
	1 Years Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		1 Days	Circulatory collapse, Loss of consciousness, Respiration abnormal, Pallor, Hypotonia, Cyanosis, Crying, Injection site pain, Pyrexia	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		3 Hours	Depressed level of consciousness, Peripheral coldness, Hypotonia, Pallor, Respiratory disorder, Cyanosis central, Chills, Pyrexia, Crying	Serious	Resolved
	4 Months Male		Infanrix hexa	2		0 Days	Cyanosis, Hypotonic-hyporesponsive episode, Pallor, Pyrexia	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Cyanosis, Hypotonic-hyporesponsive episode, Pallor	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		6 Hours	Loss of consciousness, Hypotonia, Vomiting, Pallor, Cyanosis, Drooling	Serious	Resolved
	8 Weeks Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		8 Hours	Yellow skin, Circulatory collapse, Depressed level of consciousness, Hypotonic-hyporesponsive episode, Cyanosis, Pallor, Hypotonia, Somnolence, Pyrexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	4 Months Female		Infanrix hexa			0 Days	Syncope, Cyanosis, Hyperhidrosis	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		Immediate	Cyanosis, Apnoea, Erythema, Hypotonia, Crying, Eye disorder, Breath holding	Serious	Resolved
	8 Months Female	Hydronephrosis	Infanrix hexa	2	Bacillus Calmette-Guerin Vaccine (Non-GSK), Infanrix hexa, Vigantol	Hours	Cyanosis, Convulsion, Loss of consciousness, Somnolence	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Hypotonia, Poor sucking reflex, Crying	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		2 Hours	Cyanosis, Vomiting, Hypotonia	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		5 Hours	Respiration abnormal, Gaze palsy, Loss of consciousness, Pallor, Cyanosis, Hypotonia	Serious	Resolved
	11 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	0 Days	Febrile convulsion, Loss of consciousness, Grand mal convulsion, Cyanosis, Tremor, Staring, Vomiting, Pyrexia	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Cyanosis, Pallor, Hypotonia, Diarrhoea, Vomiting, Injection site reaction	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	13 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			Immediate	Hypotonic-hyporesponsive episode, Cyanosis, Unresponsive to stimuli, Hypotonia, Areflexia	Serious	Resolved
	10 Weeks Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			5 Hours	Cyanosis, Apnoea, Apparent life threatening event, Somnolence, Hypotonic-hyporesponsive episode, Hypothermia, Vomiting, Skin discolouration, Hypotonia	Serious	Resolved
	2 Months Female		Infanrix hexa			Unknown	Apnoea, Cyanosis, Cough	Serious	Resolved
	5 Months Female	Areflexia, Cyanosis, Apnoea, Hospitalisation	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		24 Hours	Loss of consciousness, Cyanosis, Epilepsy, Hypotonia, Asthenia, Areflexia, Pyrexia	Serious	Resolved
	1 Months Male		Infanrix hexa			4 Hours	Leukocytosis, Cyanosis, Injection site reaction, Restlessness, Crying	Serious	Resolved
	2 Months Female	Premature baby	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Caffeine	4 Hours	Depressed level of consciousness, Respiration abnormal, Pallor, Cyanosis, Hypotonia, Oligodipsia, Pyrexia	Serious	Resolved
	2 Months Male		Infanrix hexa	1		10 Hours	Status epilepticus, Grand mal convulsion, Loss of consciousness, Cyanosis, Muscle spasms, Somnolence, Pyrexia	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Crying	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Cyanosis, Slow response to stimuli, Pallor, Hypotonia, Rotavirus infection	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	8 Weeks Male	Ill-defined disorder	Infanrix hexa			Unknown	Cyanosis, Loss of consciousness, Hypotonia, Pallor	Serious	Resolved
	5 Months Female		Infanrix hexa	2		0 Days	Cyanosis, Pallor, Hypotonia	Serious	Resolved
	8 Weeks Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		2 Hours	Crying, Cyanosis, Respiration abnormal, Pyrexia, Hypotonia, Depressed level of consciousness	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			6 Hours	Loss of consciousness, Gaze palsy, Pallor, Cyanosis, Hypotonia, Vomiting	Serious	Resolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			1 Days	Cyanosis, Pyrexia	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)		Desloratadine	4 Hours	Cyanosis, Dyspnoea, Pyrexia	Serious	Resolved
	2 Months Female	Ill-defined disorder	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		3 Minutes	Apparent life threatening event, Apnoea, Cyanosis, Respiration abnormal, Pallor, Crying, Pyrexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	2 Months Female		Infanrix hexa			0 Days	Cyanosis, Slow response to stimuli, Body temperature decreased, Presyncope, Lip swelling, Skin discolouration, Rash macular, Ill-defined disorder, Ear swelling, Asthenia, Pallor, Weight decreased, Swelling face, Local swelling, Erythema, Lip oedema, Hyperaemia, Pain in extremity, Feeling cold, Pulse pressure increased, Injection site swelling, Somnolence, Decreased appetite, Vomiting, Urticaria, Irritability, Crying, Injection site erythema	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Bradycardia, Hypotonia, Oxygen saturation decreased, Pallor, Vomiting, Dyspnoea	Serious	Resolved
	6 Months Male	Gastric volvulus, Gastrooesophageal reflux disease, Eating disorder, Crying, Vomiting	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Ranitidine hydrochloride, Domperidone, Infanrix hexa	1 Days	Unresponsive to stimuli, Cyanosis, Hypotonia, Skin ulcer, Crying	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		6 Hours	Respiratory disorder, Pallor, Cyanosis	Not serious	Resolved
	11 Months Male	Pyrexia, Crying, Malaise	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		30 Minutes	Febrile convulsion, Respiratory disorder, Apnoea, Loss of consciousness, Pallor, Cyanosis, Drooling, Staring, Convulsion, Rash, Depressed level of consciousness, Pyrexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	2 Months Female		Infanrix hexa			1 Hours	Apnoea, Cyanosis, Tremor, Hypotonic-hyporesponsive episode, Hypotonia, Pyrexia, Crying, Food aversion	Serious	Resolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			Hours	Hypotonic-hyporesponsive episode, Pyrexia, Malaise, Cyanosis, General physical health deterioration, Decreased eye contact, Agitation	Serious	Resolved
	4 Months Male		Infanrix hexa	3		Immediate	Hypotonic-hyporesponsive episode, Cyanosis, Pallor, Bradykinesia	Serious	Resolved
	6 Months Male	Haemangioma, Mental impairment	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Epilepsy, Grand mal convulsion, Loss of consciousness, Gaze palsy, Cyanosis, Pyrexia, Salivary hypersecretion, Somnolence, Hyperaemia, Escherichia urinary tract infection, Electroencephalogram abnormal, Drooling, Tremor, Muscle spasms, Partial seizures, Infantile spasms, Hydrocele, Phimosis, Epidermal naevus, Cough, Bronchitis	Serious	Unknown
	6 Weeks Male		Infanrix hexa, Rotavirus vaccine			2 Hours	Febrile convulsion, Pyrexia, Cyanosis, Somnolence, Chills, Decreased appetite	Serious	Resolved
	3 Months Male	Regurgitation, Gastrooesophageal reflux disease, Milk allergy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		3 Minutes	Convulsion, Cyanosis central, Apnoea, Loss of consciousness, Staring, Oligodipsia, Pallor, Vomiting, Pyrexia, Crying	Serious	Unknown
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		5 Hours	Apnoea, Loss of consciousness, Respiratory disorder, Cyanosis, Staring, Regurgitation, Crying, Vomiting	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	12 Months Female	Gastroenteritis, Allergic bronchitis	Infanrix hexa, Infanrix-polio-HIB	3		8 Months	Pertussis, Cough, Salivary hypersecretion, Vomiting, Cyanosis, Rhinitis, Vaccination failure, Inappropriate schedule of drug administration	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Discomfort, Emotional distress, Erythema, Screaming	Serious	Resolved
	11 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Hypertonia, Vomiting, Pyrexia	Not serious	Resolved
	3 Months Male	Convulsion	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		10 Minutes	Convulsion, Cyanosis, Grand mal convulsion, Sensory loss, Drooling, Hypotonia, Trismus, Tachypnoea, Tachycardia	Serious	Improved
	4 Months Male	Jaundice	Infanrix hexa, Rotavirus vaccine, Pneumococcal vaccines (Non-GSK)			13 Hours	Epilepsy, Convulsion, Cyanosis, Musculoskeletal stiffness	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Hypotonic-hyporesponsive episode, Cyanosis	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			Hours	Cyanosis, Crying, Tachycardia, Livedo reticularis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Syncope, Loss of consciousness, Cyanosis, Pallor, Hypotonia, Vomiting, Pyrexia	Serious	Resolved
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		6 Hours	Cyanosis, Hypotonic-hyporesponsive episode, Pallor, Vomiting, Pyrexia	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Hypotonia, Pallor	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		3 Minutes	Meningitis viral, Convulsion, Yellow skin, Cyanosis, Dehydration, Diarrhoea, Somnolence, Crying, Vomiting	Serious	Fatal
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Urticaria	Not serious	Resolved
	3 Months Male		Infanrix hexa			0 Days	Cyanosis, Oculogyric crisis, Myoclonus, Pyrexia	Serious	Resolved
	18 Months Male	Nasopharyngitis, Cough, H1N1 influenza, Eczema	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		4 Hours	Febrile convulsion, Loss of consciousness, Pallor, Tremor, Hypotonia, Peripheral coldness, Respiratory disorder, Cyanosis, Chills, Postictal state, Pyrexia	Serious	Resolved
	4 Months Unknown		Infanrix hexa, Rotavirus vaccine			0 Days	Hypotonic-hyporesponsive episode, Cyanosis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	8 Weeks Female	Premature baby, Nasopharyngitis, Small for dates baby	Infanrix hexa, Pneumococcal vaccines (Non-GSK)		Paracetamol	0 Days	Cyanosis, Acidosis, Apnoeic attack, Injection site inflammation, Oxygen saturation decreased, Bradycardia, Injection site pain, Injection site swelling, Injection site erythema, Bacterial infection, Injection site irritation	Serious	Resolved
	13 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		0 Days	Cyanosis, Pallor, Rhinorrhoea, Stupor, Decreased appetite, Pyrexia	Not serious	Improved
	4 Months Male	Premature baby, Mechanical ventilation, Patent ductus arteriosus, Bronchopulmonary dysplasia	Infanrix hexa		Respiratory syncytial virus vaccine, Palivizumab, Frusemide, Iron polymaltose, Multivitamins, Nutritional supplement, Emollient, Ibuprofen, Indomethacin, Cortisone	0 Days	Anaphylactic reaction, Circulatory collapse, Slow response to stimuli, Cyanosis, Hypotonia, Hypothermia, Pallor, Bradycardia, Oxygen saturation decreased, Pyrexia	Serious	Resolved
	2 Months Male		Infanrix hexa, Rotavirus vaccine, Pneumococcal vaccines (Non-GSK)	1	Rotavirus vaccine, Pneumococcal vaccines (Non-GSK)	0 Days	Hypotonic-hyporesponsive episode, Loss of consciousness, Depressed level of consciousness, Unresponsive to stimuli, Cyanosis, Cough, Ill-defined disorder, Fatigue, Adverse event, Vomiting, Eyelid disorder, Crying, Somnolence	Serious	Resolved
	2 Months Female		Infanrix hexa	1		Immediate	Presyncope, Bradycardia, Hypotonia, Injection site pain, Loss of consciousness, Cyanosis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	2 Months Female		Infanrix hexa	1		3 Hours	Hypotonic-hyporesponsive episode, Cyanosis, Somnolence, Crying, Restlessness, Pyrexia, Hypotonia, Anxiety, Lividity	Serious	Resolved
	5 Months Male	Premature baby, Apnoea, Respiratory distress, Patent ductus arteriosus, Intraventricular haemorrhage, Anaemia neonatal, Pyloric stenosis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Apnoea, Cyanosis, Hypertonia, Pyrexia	Serious	Resolved
	14 Months Female	Vaccination complication, Asthma	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		48 Hours	Respiratory failure, Cyanosis, Bronchospasm, Respiratory disorder	Serious	Unknown
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		1 Hours	Erythema, Crying, Cyanosis, Hyperaesthesia	Not serious	Resolved
	2 Months Female		Infanrix hexa			0 Days	Cyanosis, Pallor, Hypotonia	Serious	Resolved
	5 Months Male	Pharyngitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Antibiotics	0 Days	Cyanosis, Pallor, Hypotonic-hyporesponsive episode, Crying	Serious	Resolved
	13 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		Hours	Loss of consciousness, Depressed level of consciousness, Convulsion, Gaze palsy, Respiration abnormal, Pallor, Hypotonia, Drooling, Cyanosis, Pyrexia, Vomiting	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	1 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		4 Hours	Cyanosis, Hypotonic-hyporesponsive episode, Dyspnoea, Foaming at mouth	Serious	Unknown
	12 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			22 Hours	Circulatory collapse, Cyanosis, Pallor	Serious	Resolved
	2 Months Male		Infanrix hexa	1		Minutes	Cyanosis, Apnoea, Hypotonic-hyporesponsive episode	Serious	Resolved
	15 Months Female		Infanrix hexa, Meningococcal polysaccharide vaccine group C (Non-GSK)			0 Days	Cyanosis, Loss of consciousness, Apnoea, Hypotonia, Crying	Serious	Resolved
	2 Months Female		Infanrix hexa		Pneumococcal vaccines (Non-GSK)	Hours	Hypertonia, Loss of consciousness, Cyanosis, Clonus, Eye disorder, Apathy, Convulsion	Serious	Resolved
	13 Months Male		Infanrix hexa, Meningococcal polysaccharide vaccine group C (Non-GSK)			0 Days	Febrile convulsion, Cyanosis, Loss of consciousness, Clonus, Salivary hypersecretion, Hypertonia	Serious	Resolved
	2 Months Female	Gastrooesophageal reflux disease	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			7 Hours	Malaise, Hypotonia, Cyanosis	Serious	Resolved
	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Convulsion, Slow response to stimuli, Cyanosis, Grand mal convulsion, Hypotonia, Pallor, Tremor, Staring, Salivary hypersecretion, Hypertonia, Tachycardia, Oxygen saturation decreased	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		36 Hours	Loss of consciousness, Apnoea, Depressed level of consciousness, Gaze palsy, Pallor, Cyanosis, Hypotonia, Peripheral coldness, Pyrexia	Serious	Resolved
	11 Months Female	Mental retardation, Dysmorphism	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		0 Days	Cyanosis, Dyspnoea, Hypertonia	Serious	Resolved
	3 Months Female	Postmature baby, Neonatal asphyxia, Low birth weight baby, Resuscitation	Synflorix, Infanrix hexa			0 Days	Loss of consciousness, Convulsion, Cyanosis, Somnolence, Body temperature increased, Crying	Serious	Resolved
	10 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Loss of consciousness, Hypotonia	Serious	Resolved
	1 Months Unknown		Infanrix hexa			0 Days	Hypotonic-hyporesponsive episode, Pallor, Lividity, Cyanosis	Serious	Resolved
	5 Months Female	Premature baby	Infanrix hexa, Rotavirus vaccine	2		2 Hours	Cyanosis, Fatigue, Cold sweat, Pyrexia, Irritability	Serious	Resolved
	6 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		Hours	Cyanosis, Unresponsive to stimuli, Dyspnoea, Glossoptosis, Staring	Serious	Resolved
	6 Months Male		Infanrix hexa		Pneumococcal vaccines (Non-GSK)	1 Days	Cyanosis, Pyrexia	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			12 Hours	Erythrosis, Pallor, Cyanosis, Hypotonia, Eye disorder, Crying	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	5 Months Unknown		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Hypotonic-hyporesponsive episode, Crying	Serious	Resolved
	2 Months Female	Vomiting, Gastrooesophageal reflux disease, Hiatus hernia	Infanrix hexa, Synflorix	1		10 Hours	Stridor, Febrile convulsion, Cyanosis, Myoclonus, Pyrexia, Dysphagia, Choking	Serious	Unknown
	3 Months Male		Infanrix hexa, Synflorix	2 and 3	Paracetamol	Hours	Cyanosis, Skin discolouration, Erythema, Gastrointestinal disorder, Injection site inflammation, Pyrexia	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Injection site urticaria, Crying, Irritability	Serious	Resolved
	9 Months Female		Infanrix hexa	3		77 Days	Pertussis, Cyanosis, Cough, Pyrexia, Vaccination failure	Serious	Improved
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			5 Hours	Febrile convulsion, Cyanosis, Lividity, Pyrexia	Serious	Resolved
	2 Months Male	Milk allergy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Escherichia infection, Oxygen saturation decreased, C-reactive protein increased, Weight decreased, Decreased appetite, Hypotonic-hyporesponsive episode, Somnolence	Serious	Resolved
	3 Months Male	Premature baby, Regurgitation	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Sleep apnoea syndrome, Loss of consciousness, Cyanosis, Neutropenia, Salivary hypersecretion, Hyperpyrexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Anaemia neonatal, Cyanosis, Dyspnoea, Pallor, Hyperhidrosis, Crying	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			1 Days	Epilepsy, Loss of consciousness, Grand mal convulsion, Convulsion, Cyanosis	Serious	Unresolved
	3 Months Male	Breast feeding, Skin candida	Infanrix hexa	1	Miconazole	0 Days	Loss of consciousness, Cyanosis, Irritability, Crying, Vomiting	Serious	Improved
	4 Months Unknown	Paresis	Infanrix hexa, Rotavirus vaccine, Pneumococcal vaccines (Non-GSK)			12 Hours	Apnoea, Cyanosis, Loss of consciousness, Hypotonic-hyporesponsive episode, Hypotonia, Pallor	Serious	Resolved
	4 Months Female	Premature baby, Neonatal respiratory distress syndrome, Low birth weight baby, Congenital hypothyroidism, Bronchopulmonary dysplasia	Infanrix hexa, Pneumococcal vaccines (Non-GSK)		Palivizumab, Iron salt, Vitamin	10 Minutes	Cardiac arrest, Cardiopulmonary failure, Loss of consciousness, Shock, Slow response to stimuli, Cyanosis, Hypotonia, Mydriasis, Clonus, Anuria	Serious	Fatal
	2 Months Male		Infanrix hexa, Rotavirus vaccine, Pneumococcal vaccines (Non-GSK)		Vigantol	9 Hours	Convulsion, Cyanosis, Staring	Serious	Resolved
	5 Months Male		Infanrix hexa, Synflorix			6 Days	Convulsion, Cyanosis, Eye movement disorder, Myoclonus	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Female	Breast feeding, Delivery, Normal newborn	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa, Nutritional supplement	0 Days	Loss of consciousness, Slow response to stimuli, Cyanosis, Hypotonia, Pallor	Serious	Resolved
	2 Months Female		Infanrix hexa	1		0 Days	Loss of consciousness, Cyanosis, Hypotonia	Serious	Resolved
	2 Months Male		Infanrix hexa	1	Thuja	Hours	Febrile convulsion, Cyanosis, Hypotonia	Serious	Resolved
	3 Months Male		Infanrix hexa, Synflorix, Rotavirus vaccine		Vigantol	1 Days	Waterhouse-Friderichsen syndrome, Multi-organ failure, Septic shock, Disseminated intravascular coagulation, Altered state of consciousness, Meningitis, Shock, Cardiac failure, Meningococcal sepsis, Petechiae, Cough, Body temperature increased, Nasopharyngitis, Dyspnoea, Cyanosis, Arrhythmia, Bradycardia, Tachycardia, Hypotension, Faeces discoloured, Terminal state, Somnolence	Serious	Fatal
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		Immediate	Syncope, Hypotonia, Pallor, Pyrexia, Fall, Cyanosis, Crying	Serious	Resolved
	8 Weeks Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)			2 Days	Hypotonic-hyporesponsive episode, Pallor, Hypotonia, Cyanosis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	5 Months Female	Viral upper respiratory tract infection, Conjunctivitis, Exanthema subitum, Familial risk factor	Infanrix hexa, Pneumococcal vaccines (Non-GSK)		Vigantol	1 Days	Febrile convulsion, Respiratory arrest, Loss of consciousness, Cyanosis, Eye movement disorder, Dyskinesia, Chills, Somnolence, Crying, Pyrexia	Serious	Resolved
	7 Months Male		Infanrix hexa	3		40 Minutes	Anaphylactic reaction, Incorrect route of drug administration, Cyanosis, Emotional distress, Tachypnoea, Wheezing, Dyspnoea	Serious	Resolved
	2 Months Female		Infanrix hexa, Meningococcal polysaccharide vaccine group C (Non-GSK), Pneumococcal vaccines (Non-GSK)			Minutes	Cyanosis, Hypotonia, Pallor	Serious	Resolved
	3 Months Male		Infanrix hexa	2		0 Days	Grand mal convulsion, Cyanosis, Vomiting, Pyrexia, Irritability, Restlessness, Crying	Serious	Unknown
	13 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		Hours	Loss of consciousness, Febrile convulsion, Cyanosis, Hypochromic anaemia, Lymphadenitis, Injection site pain, Hyperpyrexia, Injection site induration, Tachypnoea, Injection site oedema, Chills, Liver disorder, Blood immunoglobulin M decreased, Pyrexia	Serious	Resolved
	4 Months Male	Tracheomalacia, Respiratory distress	Infanrix hexa, Synflorix	3		7 Hours	Obstructive airways disorder, Cyanosis, Dyspnoea, Pallor, Loss of consciousness, Somnolence, Hypotonia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Male	Nervousness, Constipation	Infanrix hexa	1		0 Days	Hypotonia, Pallor, Cyanosis, Crying	Serious	Resolved
	3 Months Unknown		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		2 Days	Cyanosis, Generalised oedema, Urticaria	Serious	Resolved
	18 Months Male		Infanrix hexa		Hepatitis A vaccine (Non-GSK)	0 Days	Injection site erythema, Extensive swelling of vaccinated limb, Cyanosis, Crying, Fall, Dyspnoea, Initial insomnia, Emotional distress	Serious	Resolved
	5 Months Male		Rotavirus vaccine, Infanrix hexa			0 Days	Cyanosis, Convulsion, Loss of consciousness, Pyrexia, Tremor	Serious	Unknown
	12 Weeks Male		Infanrix hexa, Synflorix	2		2 Hours	Presyncope, Injection site pain, Skin discolouration, Crying, Local swelling, Erythema, Cyanosis, Syncope, Pallor, Hypotonia, Somnolence	Serious	Resolved
	2 Months Male		Infanrix hexa, Synflorix	1		0 Weeks	Cyanosis, Breath holding, Allergy to vaccine	Serious	Unknown
	3 Months Male		Infanrix hexa			0 Days	Cyanosis, Irritability, Crying, Pallor	Serious	Resolved
	4 Months Male		Infanrix hexa, Synflorix	2		0 Days	Cyanosis, Injection site swelling, Injection site inflammation, Pyrexia, Crying, Hypotonia, Injection site pain	Serious	Resolved
	3 Months Female		Infanrix hexa	2	Pneumococcal vaccines (Non-GSK)	0 Days	Hypotonic-hyporesponsive episode, Cyanosis, Somnolence, Hypersensitivity	Serious	Resolved
	3 Months Male		Infanrix hexa	1		Hours	Loss of consciousness, Cyanosis, Leukocytosis, Thrombocytosis, Irritability, Crying, Vomiting, Hypotonia, Pallor	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		4 Hours	Hypotonic-hyporesponsive episode, Apathy, Cyanosis, Pallor, Vomiting	Serious	Resolved
	5 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Urticaria, Cyanosis, Musculoskeletal stiffness, Skin discolouration, Nodule	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Loss of consciousness, Shock, Pallor, Cold sweat, Dyspnoea	Serious	Resolved
	3 Months Male		Infanrix hexa, Synflorix			10 Hours	Crying, Cyanosis, Pyrexia	Serious	Resolved
	4 Months Female		Infanrix hexa			1 Days	Cyanosis, Hypotonia, Pyrexia	Serious	Resolved
	11 Months Female	Premature baby, Ventricular septal defect repair	Infanrix hexa	4		1 Minutes	Gaze palsy, Cyanosis, Breath holding, Crying, Ill-defined disorder, Pallor	Serious	Resolved
	4 Months Male		Infanrix hexa, Synflorix	3		2 Hours	Hypotonic-hyporesponsive episode, Respiratory arrest, Cyanosis, Depressed level of consciousness, Ill-defined disorder, Crying, Pallor	Serious	Resolved
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Dyspnoea	Not serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	12 Weeks Male	Congenital anomaly, Cytogenetic abnormality, Cleft palate, Congenital tracheomalacia, Developmental delay	Infanrix hexa, Synflorix			36 Hours	Apparent life threatening event, Cyanosis, Unresponsive to stimuli, Ill-defined disorder	Serious	Resolved
	1 Months Female	Abdominal pain, Urine output decreased, Appetite disorder, Dyspnoea, Irritability, Crying, Lethargy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Simethicone, Paracetamol	0 Days	Pneumonia, Hypophagia, Crying, Dyspnoea, Irritability, Cyanosis, Respiratory arrest, Apnoea, Convulsion, Eye movement disorder, Hypotonia, Dehydration, Meningitis, Aspiration, Failure to thrive, Hypothermia, Sudden infant death syndrome	Serious	Fatal
	3 Months Male		Infanrix hexa	2	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	5 Minutes	Injection site warmth, Crying, Erythema, Cyanosis, Skin warm	Serious	Resolved
	17 Months Male	Urinary tract infection, Pallor, Hypotonia	Infanrix hexa			Hours	Cyanosis, Pyrexia, Vomiting, Pallor, Muscle rigidity, Staring, Hypotonia, Somnolence, Fontanelle bulging, Fontanelle depressed	Serious	Unknown
	3 Months Female		Infanrix hexa, Synflorix	2		6 Hours	Cyanosis, Crying, Injection site inflammation, Skin discolouration, Restlessness, Hypophagia, Local swelling	Not serious	Resolved
	5 Months Male		Infanrix hexa			0 Days	Cyanosis, Hypotonia, Tachycardia	Serious	Resolved
	3 Months Female		Infanrix hexa		Pneumococcal vaccines (Non-GSK)	0 Days	Cyanosis, Asthenia, Pyrexia, Somnolence, Decreased appetite	Serious	Resolved

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[redacted]	2 Months Female		Infanrix hexa	2	EMLA	0 Weeks	Petechiae, Oedema peripheral, Cyanosis, Papule, Hypersensitivity	Serious	Resolved
	5 Months Female	Sudden infant death syndrome, Atrial septal defect	Synflorix, Infanrix hexa		Vigantol	5 Minutes	Rash, Injection site induration, Bradycardia, Extensive swelling of vaccinated limb, Injection site erythema, Respiratory arrest, Urticaria, Injection site extravasation, Oxygen saturation decreased, Cyanosis, Pallor, Apparent life threatening event, Injection site haemorrhage	Serious	Unknown
	8 Weeks Female	Milk allergy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Malaise, Cyanosis, Hypotonia, Pyrexia, Asthenia, Apparent life threatening event, Incorrect route of drug administration	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Pyrexia, Crying, Cyanosis, Muscle rigidity	Not serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Loss of consciousness, Cyanosis, Pallor	Serious	Unknown
	12 Months Male		Infanrix hexa	3		Hours	Partial seizures with secondary generalisation, Loss of consciousness, Gaze palsy, Grand mal convulsion, Irritability, Change of bowel habit, Hypotonia, Psychomotor hyperactivity, Vomiting, Cyanosis, Staring, Sinus tachycardia, Trismus, Clonus	Serious	Unknown
	6 Months Male		Infanrix hexa	1	DTPa-HepB-IPV-HIB (Non-GSK)	6 Hours	Epilepsy, Convulsion, Depressed level of consciousness, Cyanosis, Staring, Muscle rigidity	Serious	Unknown

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[redacted]	13 Weeks Male		Infanrix hexa			Immediate	Syncope, Screaming, Cyanosis, Erythema, Dyskinesia, Hunger, Pallor, Hypotonia	Not serious	Resolved
	8 Weeks Male	Nasopharyngitis, Pyrexia	Infanrix hexa, Synflorix	1		4 Hours	Meningitis, Meningism, Screaming, Cyanosis, Fontanelle bulging, Pyrexia, Gaze palsy, Depressed level of consciousness, Upper respiratory tract infection	Serious	Resolved
	4 Months Male		Synflorix, Infanrix hexa			6 Hours	Loss of consciousness, Grand mal convulsion, Tonic clonic movements, Dyspnoea, Cyanosis, Pyrexia	Serious	Unknown
	3 Months Male		Infanrix hexa	1		0 Days	Urinary tract infection, Loss of consciousness, Hypotonia, Cyanosis	Serious	Unknown
	8 Weeks Female		Infanrix hexa, Synflorix			1 Days	Apnoeic attack, Respiratory arrest, Cyanosis, Foaming at mouth, Dyskinesia, Nasopharyngitis, Salivary hypersecretion, Respiratory tract infection	Serious	Resolved
	2 Months Male	Necrotising enterocolitis neonatal, Premature baby, Neonatal respiratory distress syndrome, Respiratory distress, Hospitalisation, Rectal haemorrhage, Breast feeding, Pneumothorax, Gastrooesophageal reflux disease	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Ferrous fumarate, Multivitamins, Phytomenadione, Antibiotics	0 Days	Cardio-respiratory arrest, Tonic convulsion, Malaise, Agitation, Crying, Laryngospasm, Asphyxia, Cyanosis	Serious	Resolved

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[redacted]	3 Months Male		Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)			10 Minutes	Anaphylactic shock, Pallor, Cyanosis, Apathy, Hypotonia, Slow response to stimuli, Somnolence, Hypotension, Syncope	Serious	Resolved
	2 Months Male	Caesarean section	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			2 Days	Partial seizures, Immobile, Staring, Cyanosis, Pallor, Somnolence	Serious	Resolved with Sequelae
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			Minutes	Loss of consciousness, Hypotonic-hyporesponsive episode, Cyanosis, Crying, Pallor, Hypotonia	Serious	Resolved
	11 Months Female		Infanrix hexa, Synflorix	4		Hours	Depressed level of consciousness, Injection site inflammation, Presyncope, Cyanosis, Pyrexia, Injection site swelling, Injection site warmth, Injection site erythema, Injection site discolouration, Tremor	Serious	Resolved
	3 Months Unknown		Infanrix hexa		Rotavirus vaccine	5 Minutes	Crying, Cyanosis, Hypotonia	Serious	Resolved
	5 Months Female	Cough, Rhinitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Gaze palsy, Musculoskeletal stiffness, Cyanosis, Hypotonia, Drooling	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Hypotonia, Cyanosis	Serious	Resolved
	5 Months Female		Infanrix hexa	1		0 Days	Cyanosis, Pyrexia, Livedo reticularis	Serious	Resolved

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[redacted]	18 Weeks Female		Infanrix hexa, Synflorix	3		6 Hours	Hypotonic-hyporesponsive episode, Depressed level of consciousness, Hypotonia, Pallor, Cyanosis, Crying, Syncope	Serious	Resolved
	9 Months Female		Infanrix hexa			Hours	Convulsion, Vaccination complication, Pyrexia, Vomiting, Cyanosis	Serious	Unknown
	3 Months Male		Infanrix hexa, Synflorix	2		8 Hours	Presyncope, Hypotonic-hyporesponsive episode, Mental impairment, Hypotonia, Eye movement disorder, Cyanosis, Pallor, Vomiting, Crying	Serious	Resolved
	11 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		3 Hours	Febrile convulsion, Hypertonia, Clonus, Gaze palsy, Cyanosis, Pyrexia	Serious	Resolved
	12 Weeks Male	Jaundice neonatal	Synflorix, Infanrix hexa	2		0 Days	Sudden death, Dysphagia, Oligodipsia, Cyanosis, Choking, Crying	Serious	Fatal
	15 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Febrile convulsion, Loss of consciousness, Gaze palsy, Cyanosis, Pyrexia, Tremor	Serious	Resolved
	4 Months Male	Coarctation of the aorta, Atrioventricular septal defect, Premature baby	Infanrix hexa, Pneumococcal vaccines (Non-GSK)		Surgery	0 Days	Encephalitis, Oculogyric crisis, Cyanosis, Dyspnoea, Irritability, Hypertonia, Pyrexia	Serious	Resolved
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, DTPa-Polio-HIB (Non-GSK), Pneumococcal vaccines (Non-GSK)	27 Days	Sudden infant death syndrome, Coma, Cyanosis, Respiratory arrest, Cardiac arrest, Asphyxia	Serious	Fatal

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix-polio-HIB, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1 Days	Hypotonic-hyporesponsive episode, Cyanosis, Loss of consciousness, Fatigue, Hypersomnia, Oxygen saturation decreased, Epilepsy	Serious	Unresolved
	2 Months Female	Jaundice neonatal	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Apparent life threatening event, Unresponsive to stimuli, Hypotonia, Cyanosis, Pallor, Pyrexia	Serious	Resolved
	15 Months Male	Influenza B virus test positive, Norovirus test positive	Infanrix hexa			3 Days	Myocarditis, Diarrhoea, Vomiting, Gastroenteritis, General physical health deterioration, Hypotonia, Tachycardia, Pallor, Tachypnoea, Rales, Hepatomegaly, Hypotension, Cyanosis, Hepatic pain, Cardiomegaly, Ventricular dysfunction, Systolic dysfunction, Incorrect route of drug administration	Serious	Unknown
	6 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Anaphylactic shock, Loss of consciousness, Cardio-respiratory arrest, Cyanosis, Hypotonia, Hypertonia	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Cyanosis, Pallor	Serious	Resolved
	5 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Febrile convulsion, Hyperpyrexia, Altered state of consciousness, Staring, Hypotonia, Cyanosis, Pallor, Dyspnoea, Tremor	Serious	Improved
	2 Months Male		Infanrix hexa	1		Immediate	Anaphylactic shock, Apnoea, Cyanosis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	6 Months Male		Infanrix hexa	3		1 Days	Gaze palsy, Cyanosis, Drooling, Hypotonia	Serious	Resolved
	2 Months Male		Infanrix hexa, Synflorix	1		Hours	Pertussis, Cough, Crying, Cyanosis, Body temperature increased	Serious	Unresolved
	18 Months Unknown		Infanrix hexa			8 Hours	Hypotonic-hyporesponsive episode, Loss of consciousness, Convulsion, Extensive swelling of vaccinated limb, Injection site oedema, Hypotonia, Asthenia, Pallor, Cyanosis, Somnolence, Eye movement disorder	Serious	Unknown
	12 Months Male	Conjunctivitis, Infection	Infanrix hexa, Synflorix	4		5 Hours	Febrile convulsion, Respiratory disorder, Respiratory arrest, Cyanosis, Eye movement disorder, Unresponsive to stimuli, Mental impairment	Serious	Resolved
	2 Months Male		Infanrix hexa		Meningococcal polysaccharide vaccine group C (Non-GSK)	8 Hours	Hypotonic-hyporesponsive episode, Pallor, Cyanosis, Peripheral coldness	Serious	Resolved
	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			6 Hours	Hypotonic-hyporesponsive episode, Cyanosis, Pallor	Serious	Resolved
	2 Months Male		Infanrix hexa, Synflorix	1		0 Days	Hypotonic-hyporesponsive episode, Choking, Gaze palsy, Cyanosis, Pyrexia, Somnolence, Decreased activity	Serious	Resolved
	11 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Loss of consciousness, Vomiting, Pallor, Cyanosis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	10 Weeks Male		Infanrix hexa	1	Sodium Fluoride	5 Hours	Respiratory arrest, Cyanosis	Serious	Resolved
	7 Months Male		Infanrix hexa	3		53 Days	Loss of consciousness, Cyanosis	Serious	Unknown
	16 Weeks Male	Conjunctivitis, Dacryostenosis acquired	Infanrix hexa	1		6 Hours	Hypotonic-hyporesponsive episode, Cyanosis, Loss of consciousness, Circulatory collapse, Pallor, Unresponsive to stimuli, Convulsion, Tremor, Vomiting, Aspiration, Pyrexia	Serious	Resolved
	4 Months Male	Cardiopulmonary failure, Cephalhaematoma, Hyperbilirubinaemia, Polycythaemia neonatorum	Infanrix hexa	1		6 Days	Convulsion, Respiration abnormal, Cyanosis	Serious	Resolved
	18 Months Male	Otitis media	Infanrix hexa	4		Same day	Pyrexia, Febrile convulsion, Loss of consciousness, Cyanosis	Serious	Resolved
	3 Months Male		Infanrix hexa	1		90 Minutes	Breath holding, Crying, Cyanosis, Restlessness, Pallor, Pyrexia, Injection site induration	Serious	Unknown
	7 Months Male		Infanrix hexa	3		Same day	Febrile convulsion, Pyrexia, Respiratory tract infection, Gastroenteritis, Diarrhoea, Crying, Cyanosis, Dehydration	Serious	Resolved
	4 Months Female		Infanrix hexa	1	Ergocalciferol		Grand mal convulsion, Convulsion, Cyanosis	Serious	Improved
	16 Months Female	Rhinitis	Infanrix hexa	4	Infanrix hexa	2 Days	Febrile convulsion, Grand mal convulsion, Staring, Cyanosis, Somnolence, Aphthous stomatitis, Ear infection, Body temperature increased	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Male	Respiratory disorder, Patent ductus arteriosus, Microcephaly, Premature baby, Urinary tract disorder, Vomiting, Apgar score low	Infanrix hexa	1	D-fluoretten	4 Days	Sudden infant death syndrome, Cyanosis	Serious	Fatal
	4 Months Female		Infanrix hexa	2			Respiratory arrest, Cyanosis	Serious	Resolved
	3 Months Male	Premature baby	Infanrix hexa	2	Pneumococcal vaccines (Non-GSK)	8 Hours	Febrile convulsion, Pyrexia, Apnoea, Cyanosis, Somnolence	Serious	Resolved
	2 Months Female		Infanrix hexa	1	Sodium Fluoride	Immediate	Breath holding, Muscle spasms, Crying, Apnoea, Cyanosis, Incorrect route of drug administration	Serious	Resolved
	12 Months Female		Infanrix hexa	4	Infanrix hexa	2 Hours	Febrile convulsion, Eye movement disorder, Pyrexia, Cyanosis, Pharyngitis	Serious	Unknown
	3 Months Female		Infanrix hexa		Pneumococcal vaccines (Non-GSK)	Same day	Convulsion, Pyrexia, Respiratory arrest, Bradycardia, Oxygen saturation decreased, Cyanosis, Apnoea	Serious	Unknown
	15 Months Male	Hypoglycaemia, Pharyngitis	Infanrix hexa	4	D-fluoretten	Hours	Febrile convulsion, Loss of consciousness, Eye movement disorder, Cyanosis, Body temperature increased, Fatigue, Asthenia, Crying, Hypotension, Respiration abnormal, Vomiting	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	2 Months Male	Upper respiratory tract infection, Conjunctivitis infective	Infanrix hexa	1		4 Hours	Hypotonic-hyporesponsive episode, Hypotonia, Pallor, Somnolence, Injection site reaction, Injection site erythema, Injection site induration, Pain, Gastroenteritis, Ill-defined disorder, Diarrhoea, Soft tissue infection, Peripheral coldness, Rash macular,	Serious	Unknown
	4 Months Male		Infanrix hexa, Infanrix-polio-HIB	1	Infanrix-polio-HIB	Immediate	Cyanosis	Serious	Resolved
	5 Months Female	Atrial septal defect, Coarctation of the aorta	Infanrix hexa	2	Infanrix hexa	Same day	Hypotonic-hyporesponsive episode, Opisthotonus, Moaning, Cyanosis, Staring, Respiratory disorder	Serious	Resolved
	3 Months Male		Infanrix hexa	1		Same day	Cyanosis, Cold sweat, Respiration abnormal	Serious	Resolved
	6 Months Female		Infanrix hexa	2		2 Hours	Local swelling, Cyanosis, Crying	Not serious	Resolved
	3 Months Male		Infanrix hexa	2	Paracetamol	1 Days	Convulsion, Cyanosis, Depressed level of consciousness, Musculoskeletal stiffness, Pyrexia, Injection site erythema	Serious	Resolved
	4 Months Male		Infanrix hexa			1 Days	Convulsion, Cyanosis	Serious	Resolved
	3 Months Male	Rhinitis	Infanrix hexa	1		1 Days	Convulsion, Infantile spasms, Eye movement disorder, Hypertonia, Cyanosis	Serious	Unknown
	6 Months Male		Infanrix hexa	3		0 Days	Grand mal convulsion, Apnoea, Depressed level of consciousness, Hypotonia, Cyanosis	Serious	Resolved
	3 Months Female		Infanrix hexa	1		0 Days	Hypotonic-hyporesponsive episode, Cyanosis, Pyrexia	Not serious	Resolved
	5 Months Male	Atrial septal defect	Infanrix hexa	2	Infanrix hexa	5 Days	Cyanosis	Serious	Unresolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Female		Infanrix hexa			0 Days	Cyanosis, Crying	Serious	Resolved
	4 Months Female	Premature baby, Small for dates baby, Hospitalisation	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		4 Days	Resuscitation, Systemic inflammatory response syndrome, Sepsis, Staphylococcal infection, Respiratory syncytial virus infection, Rotavirus infection, Disseminated intravascular coagulation, Thrombocytopenia, Anaemia, Pneumonia aspiration, Respiratory distress, Multi-organ failure, Renal failure acute, Acute hepatic failure, Hypertension, Cerebral hygroma, Atrial septal defect acquired, Cyanosis, Hypotonia, Haematochezia	Serious	Unresolved
	3 Months Female		Infanrix hexa	1	Infanrix hexa	6 Hours	Cyanosis, Depressed level of consciousness, Foaming at mouth, Hypotonia, Pallor, Vomiting, Pyrexia	Serious	Resolved
	3 Months Female		Infanrix hexa	1	D-fluoretten	4 Hours	Dyspnoea, Cyanosis, Lividity, Crying, Restlessness, Epistaxis, General physical health deterioration, Aspartate aminotransferase increased, Product quality issue	Serious	Unknown
	3 Months Male		Infanrix hexa	1		0 Days	Tachycardia, Livedo reticularis, Cyanosis, Erythema, Agitation	Serious	Resolved
	6 Months Female	Atrial septal defect	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		1 Days	Cyanosis, Pyrexia	Serious	Resolved
	3 Months Male		Infanrix hexa	1		5 Days	Cyanosis	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		Unknown	Apathy, Apnoea, Crying, Cyanosis, Pyrexia, Asthenia	Serious	Unknown
	2 Months Female		Infanrix hexa	1 and 2	Pneumococcal vaccines (Non-GSK)	0 Hours	Cyanosis	Not serious	Resolved
	3 Months Male	Premature baby, Trisomy 21, Foot deformity, Atrial septal defect, Arteriovenous malformation, Congenital cerebrovascular anomaly, Gene mutation, Brain stem infarction, Brain stem thrombosis, Microcephaly	Infanrix hexa	1	Hepatitis B vaccine, Infanrix-polio-HIB	2 Days	Convulsion, Encephalitis, Disorientation, Stupor, Coma, Pneumonia aspiration, Brain stem thrombosis, Supravalvular aortic stenosis, Pulmonary valve stenosis, Hyponatraemia, Oral candidiasis, Anaemia, Grand mal convulsion, Cyanosis, Petechiae, Lymphoedema,	Serious	Unknown
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		10 Hours	Grand mal convulsion, Cyanosis	Serious	Resolved
	4 Months Female		Infanrix hexa	1		12 Hours	Grand mal convulsion, Convulsion, Febrile convulsion, Eye movement disorder, Pallor, Cyanosis	Serious	Unknown
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		5 Hours	Atonic seizures, Respiratory arrest, Loss of consciousness, Cyanosis, Hypotonia, Hypopnoea, Pallor	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	3 Months Male	Congenital central nervous system anomaly, Dysplasia	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Hours	Cyanosis	Serious	Unresolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Febrile convulsion, Cyanosis, Hypotonia, Crying, Pallor, Depressed level of consciousness, Pyrexia, Fatigue	Serious	Resolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		6 Hours	Cyanosis, Skin discolouration, Pallor, Hypotonia	Serious	Resolved
	Infant Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Cyanosis	Serious	Resolved
	5 Months Male	Convulsion neonatal, Pneumonia, Bacterial sepsis, Premature rupture of membranes, Breast feeding, Hospitalisation	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2 and 3	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Vigantol, Phenytoin, Pyridoxine hydrochloride	7 Months	Epilepsy, Febrile convulsion, Electroencephalogram abnormal, Pharyngeal disorder, Upper respiratory tract infection, Crying, Syncope, Cyanosis, Respiratory arrest, Pyrexia, Vomiting	Serious	Unresolved
	4 Months Male		Infanrix hexa			0 Years	Cyanosis	Serious	Unknown
	3 Months Male	Familial risk factor	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	D-fluoretten, Paracetamol	1 Days	Convulsion, Epilepsy, Status epilepticus, Cyanosis, Hypotonia, Cardiac murmur	Serious	Improved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	5 Months Male	Premature baby, Bronchopneumonia, Rhinitis, Family stress, Social problem	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2 Days	Apparent life threatening event, Aspiration, Resuscitation, Blood pH decreased, Pupil fixed, Ventricular asystole, Hyperthermia therapy, Pneumonia aspiration, Brain injury, Candida infection, Cyanosis	Serious	Unresolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	6 Hours	Hypotonic-hyporesponsive episode, Pallor, Depressed level of consciousness, Apathy, Cyanosis	Serious	Resolved
	3 Months Female	Viral test positive, Gastrooesophageal reflux disease, Dyspnoea, Apnoea, Hospitalisation, Umbilical cord around neck, Abnormal faeces	Infanrix hexa	1	D-fluoretten	9 Hours	Respiratory arrest, Resuscitation, Hypotonic-hyporesponsive episode, Body temperature increased, Crying, Syncope, Cyanosis, Apathy, Skin discolouration, Hypotonia, Leukocytosis, Oxygen saturation decreased	Serious	Resolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2			Epilepsy, Partial seizures, Petit mal epilepsy, Muscle spasms, Clonus, Cyanosis, Eye movement disorder, Depressed level of consciousness, Somnolence, Muscle hypertrophy, Hypotonia, Developmental delay, Restlessness, Crying, Diarrhoea	Serious	Resolved with Sequelae
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		14 Hours	Crying, Cyanosis	Serious	Resolved
	19 Months Female	Premature baby, Sleep apnoea syndrome, Bradycardia, Allergy to vaccine	Infanrix hexa			Unknown	Febrile convulsion, Apnoea, Cyanosis, Pyrexia, Pallor, Cardiovascular insufficiency	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	5 Months Female	Breast feeding	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Convulsion, Febrile convulsion, Cyanosis, Crying, Peripheral coldness, Vomiting, Pallor, Yellow skin, Cardiovascular disorder, Electroencephalogram abnormal, Peripheral vascular disorder	Serious	Resolved
	4 Months Female	Physical assault	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		0 Days	Skull fracture, Subdural haematoma, Brain oedema, Subarachnoid haemorrhage, Haematoma, Crying, Vomiting, Apathy, Cyanosis, Dyspnoea	Serious	Fatal
	3 Months Male		Infanrix hexa	2	Pneumococcal vaccines (Non-GSK)	12 Hours	Cyanosis, Apathy, Communication disorder, Pallor	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		12 Hours	Apparent life threatening event, Cyanosis, Pallor, Apathy, Fatigue, Somnolence, Pyrexia	Serious	Resolved
	8 Weeks Unknown		Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	2	Infanrix hexa	3 Days	Cyanosis, Dyspnoea	Serious	Unknown
	4 Months Male	Vaccination complication	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1 Days	Hypotonic-hyporesponsive episode, Cyanosis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	Child Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		27 Days	Waterhouse-Friderichsen syndrome, Pyrexia, Vomiting, Diarrhoea, Loss of consciousness, Cyanosis, Circulatory collapse, Convulsion, Petechiae, Musculoskeletal stiffness	Serious	Fatal
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		7 Hours	Dyspnoea, Cyanosis	Serious	Resolved
	Infant Male	Rhinitis	Infanrix hexa	3		0 Days	Tonsillitis, Pyrexia, Cerebral disorder, Muscle twitching, Nervousness, Crying, Restlessness, Hyperacusis, Eye disorder, Peripheral coldness, Somnolence, Musculoskeletal stiffness, Poor quality sleep, Dysphagia, Choking, Pallor, Insomnia, Diarrhoea, Balanitis, Cough, Cyanosis, Nasopharyngitis, Body temperature decreased	Serious	Unresolved
	2 Months Female	Familial risk factor, Bottle feeding	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Apparent life threatening event, Apnoea, Pallor, Cyanosis, Pyrexia	Serious	Resolved
	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa, Ergocalciferol	1 Days	Screaming, Tremor, Vomiting, Pallor, Cyanosis, Hypotonia, Staring, Fatigue, Hyperglycaemia, Blood lactic acid increased, Feeding disorder neonatal	Serious	Resolved
	3 Months Male	Premature baby	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa, Ferro	2 Minutes	Apnoea, Bradycardia, Cyanosis, Foaming at mouth, Bradypnoea	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	12 Weeks Male	Abdominal pain, Abdominal pain upper, Respiratory tract infection, Familial risk factor, Macrocephaly, Delivery	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Simethicone, D-fluoretten	8 Hours	Respiratory arrest, Circulatory collapse, Resuscitation, Apnoea, Apparent life threatening event, Crying, Abdominal distension, Frequent bowel movements, Pallor, Cyanosis, Pulse absent, Apathy, Dyspnoea	Serious	Resolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Sodium Fluoride	0 Days	Apnoea, Apparent life threatening event, Crying, Agitation, Cyanosis, Vaccination complication	Serious	Resolved
	5 Months Female	Gastroenteritis rotavirus, Diabetic relative, Familial risk factor, Hypoglycaemia neonatal, Diarrhoea	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		0 Days	Convulsion, Pyrexia, Meningitis, Electroencephalogram abnormal, Febrile convulsion, Grand mal convulsion, Staring, Cyanosis, Epilepsy	Serious	Resolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		6 Hours	Cyanosis	Serious	Resolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		1 Days	Convulsion, Cyanosis, Apnoea, Musculoskeletal stiffness, Gaze palsy	Serious	Resolved
	2 Years Male	Fall, Haematoma	Infanrix hexa	4		1 Days	Febrile convulsion, Pyrexia, Convulsion, Loss of consciousness, Depressed level of consciousness, Musculoskeletal stiffness, Gaze palsy, Cyanosis, Disorientation, Viral infection, Injection site erythema, Injection site swelling	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	3 Months Female	Gene mutation, Varicella, Influenza, Pyrexia	Infanrix hexa	1		1 Days	Opsoclonus myoclonus, Myoclonus, Complex partial seizures, Apathy, Staring, Hypotonia, Monoparesis, Developmental delay, Psychomotor hyperactivity, Hypothyroidism, Cyanosis, Convulsion	Serious	Unresolved
	13 Months Female	Vaccination complication	Synflorix, Infanrix hexa	4	Pneumococcal vaccines (Non-GSK)	0 Days	Urticaria, Cyanosis	Serious	Unknown
	9 Weeks Male		Synflorix, Infanrix hexa	1		5 Minutes	Hypotonia, Pallor, Oxygen saturation decreased, Cyanosis, Apnoeic attack	Serious	Resolved
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		7 Hours	Syncope, Hypotonic-hyporesponsive episode, Hypotonia, Pallor, Cyanosis, Faecal incontinence, Urinary incontinence, Diarrhoea, Abdominal pain, Apathy, Loss of consciousness	Serious	Resolved
	12 Weeks Male		Infanrix hexa	1		5 Hours	Cyanosis	Serious	Resolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		3 Days	Cardiac arrest, Sudden infant death syndrome, Sepsis, Viral infection, Resuscitation, Pyrexia, Loss of consciousness, Cyanosis	Serious	Fatal
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Rotavirus vaccine	0 Days	Apparent life threatening event, Cyanosis, Hypotonia, Gaze palsy, Fatigue, Somnolence, Sleep apnoea syndrome, Gastroenteritis rotavirus, Apnoea, Apathy	Serious	Unknown
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa	4 Hours	Apnoea, Convulsion, Cyanosis, Crying, Hypotonia, Blood lactic acid increased	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	5 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Ergocalciferol	0 Days	Convulsion, Febrile convulsion, Atonic seizures, Grand mal convulsion, Pyrexia, Diarrhoea, Gaze palsy, Cyanosis, Disturbance in attention, Staring, Pharyngeal erythema, Rhinitis, Leukocytosis, Gastroenteritis, Gastroenteritis norovirus	Serious	Unresolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		1 Days	Convulsion, Gaze palsy, Musculoskeletal stiffness, Cyanosis	Serious	Resolved
	3 Months Male	Jaundice neonatal, Atrial septal defect, Ventricular septal defect	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Circulatory collapse, Pallor, Cyanosis, Hypotonia, Body temperature increased	Serious	Resolved
	14 Months Male		Priorix Tetra, Infanrix hexa			5 Days	Febrile convulsion, Unresponsive to stimuli, Cyanosis, Eye movement disorder, Posture abnormal, Dyskinesia, Pyrexia, Infection, Pharyngeal erythema	Serious	Resolved
	4 Months Male	Mitral valve incompetence, Tricuspid valve incompetence	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		1 Days	Convulsion, Cyanosis, Gastrooesophageal reflux disease, Rash, Staring, Abnormal faeces, Body temperature increased, Ill-defined disorder, Depressed level of consciousness, Fatigue	Serious	Resolved
	13 Months Female	Familial risk factor	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		10 Hours	Febrile convulsion, Poor quality sleep, Chills, Eye movement disorder, Pallor, Cyanosis, Ill-defined disorder, Postictal state, Pharyngeal erythema, Pyrexia	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	9 Weeks Female	Patent ductus arteriosus, Premature baby	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	D-fluoretten	8 Hours	Tonic convulsion, Cyanosis, Hypotonic-hyporesponsive episode, Convulsion, Gastrooesophageal reflux disease, Hypotonia, Aspiration, Respiratory arrest, Opisthotonus, Oral discharge, Pallor, Tachycardia, Heart sounds abnormal, Abdominal distension	Serious	Resolved
	3 Months Male	Atrial septal defect	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Hours	Circulatory collapse, Apnoea, Loss of consciousness, Pallor, Bradycardia, Salivary hypersecretion, Cyanosis, Epilepsy, Partial seizures, Foaming at mouth, Hypotonia, Cardiac arrest, Vomiting, Dyskinesia, Eye movement disorder, Productive cough, Unresponsi	Serious	Resolved
	4 Months Male	Premature baby, Pneumonia bacterial, Conjunctivitis infective	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	1		3 Days	Meningitis pneumococcal, Grand mal convulsion, Epilepsy, Hydrocephalus, Subdural hygroma, Subdural empyema, Anaemia, Generalised oedema, Ileus paralytic, Conjunctivitis, Septic shock, Atypical pneumonia, Neurosurgery, Pyrexia, Abdominal distension, Ill-defined disorder, Restlessness, Hyperaesthesia, Oligodipsia, Eye movement disorder, Hypertonia, Tachycardia, Oxygen saturation decreased, Ascites, Respiratory arrest, Drug ineffective, Cyanosis, Splenomegaly	Serious	Unresolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	12 Weeks Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		7 Hours	Circulatory collapse, Respiratory arrest, Cyanosis, Hypotonic-hyporesponsive episode, Screaming, Agitation, Hypotonia, Peripheral coldness, Ill-defined disorder, Fatigue, Pyrexia	Serious	Resolved
	6 Months Female	Premature baby, Neonatal respiratory distress syndrome, Neonatal respiratory failure, Apnoea neonatal, Bradycardia neonatal, Hyperbilirubinaemia neonatal, Regurgitation	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Intubation, Mechanical ventilation	0 Days	Apnoea, Cyanosis, Febrile convulsion, Gaze palsy, Altered state of consciousness, Convulsion, Body temperature increased, Breath holding, Moaning, Erythema, Swelling, Hypokinesia, Pain, Pyrexia, Dyspnoea, Infection	Serious	Unknown
	8 Weeks Male	Premature baby, Bradycardia neonatal, Apnoea neonatal, Infection	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Caffeine, Ferrous glycine sulphate, D-fluoretten	6 Hours	Apnoea, Cyanosis, Oxygen saturation decreased	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		6 Hours	Apnoeic attack, Cyanosis, Upper respiratory tract infection, Body temperature increased	Serious	Resolved
	6 Months Male		Infanrix hexa, Rotavirus vaccine	3		0 Days	Cardiovascular disorder, Apathy, Hyperpyrexia, Respiratory tract infection, Chills, Cyanosis, Pallor, Hypoventilation	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	8 Months Female		Infanrix hexa, Synflorix	3		1 Days	Convulsion, Gaze palsy, Cyanosis, Vaccination complication, Restlessness, Feeling hot, Staring, Muscle twitching, Dyspnoea, Hypotonia, Somnolence, General physical health deterioration, Body temperature increased	Serious	Unknown
	3 Months Male	Premature baby, Anaemia neonatal	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Multivitamin + fluoride	12 Hours	Cyanosis, Screaming, Flushing, Crying	Serious	Resolved
	11 Weeks Female	Splint application, Developmental hip dysplasia, Hypersensitivity	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Simethicone, Ergocalciferol, Sodium Fluoride	Immediate	Cyanosis, Rash macular, Screaming	Not serious	Resolved
	5 Months Male		Infanrix hexa	2		12 Days	Pertussis, Choking, Cyanosis, Apnoea, Bronchopneumonia, Cough, Vomiting	Serious	Unresolved
	15 Months Female	Familial risk factor, Febrile convulsion, Hospitalisation, Cardiac murmur, Underweight, Upper respiratory tract infection	Infanrix hexa	4		0 Days	Febrile convulsion, Pyrexia, Chills, Gaze palsy, Eye movement disorder, Cyanosis, Unresponsive to stimuli, Tremor, Grand mal convulsion, Upper respiratory tract infection	Serious	Resolved
	6 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Synflorix, Vigantol	0 Days	Syncope, Cyanosis, Restlessness, Pallor, Vomiting, Hypotonia, Unresponsive to stimuli	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	12 Weeks Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	2		5 Hours	Cyanosis, Rash macular, Crying, Pain	Serious	Resolved
	13 Months Male	Upper respiratory tract infection, Rhinitis, Cough	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Febrile convulsion, Gastroenteritis, Cyanosis, Cold sweat, Restlessness, Pyrexia, Rash, Myoclonus, Tonic convulsion, Musculoskeletal stiffness, Crying, Vomiting, Dehydration, Diarrhoea	Serious	Unknown
	13 Months Male	Rhinitis, Premature baby, Head titubation	Infanrix hexa	4	Infanrix hexa	9 Hours	Febrile convulsion, Pyrexia, Restlessness, Moaning, Clonic convulsion, Muscle twitching, Staring, Unresponsive to stimuli, Cyanosis, Enuresis, Somnolence, Oxygen saturation decreased, Tachycardia	Serious	Resolved
	19 Months Male	Phimosis	Infanrix hexa	4		7 Months	Pertussis, Cyanosis, Gastroenteritis norovirus, Cough, Dyspnoea, Productive cough, Crying, Ill-defined disorder, Vaccination failure, General physical health deterioration	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	10 Weeks Female	Nervous system disorder, Familial risk factor, Haemangioma of skin	Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		9 Days	Atonic seizures, Apnoea, Hypotonia, Gaze palsy, Choking, Respiration abnormal, Respiratory arrest, Loss of consciousness, Conversion disorder, Fear, Cyanosis, Pallor, Unresponsive to stimuli, Staring, Bronchitis, Gastroenteritis, Rhonchi, Abdominal distension, Abdominal pain, Constipation, Faeces discoloured, Abnormal faeces, Somnolence, Fatigue, Rhinitis, Eye discharge, Abnormal behaviour	Serious	Unresolved
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			48 Hours	Apparent life threatening event, Loss of consciousness, Cyanosis, Unresponsive to stimuli, Respiratory arrest, Hypotonia, Slow response to stimuli, Staring	Serious	Resolved
	3 Months Female	Atrial septal defect	Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Tonic convulsion, Apnoea, Dyspnoea, Screaming, Cyanosis, Musculoskeletal stiffness, Abnormal faeces, Bundle branch block right, Body temperature increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood bilirubin increased	Serious	Unknown
	9 Weeks Female		Infanrix hexa, Synflorix	1	Vitamin D	7 Hours	Convulsion, Syncope, Crying, Gaze palsy, Cyanosis, Pallor, Hypotonia, Fatigue, Listless, Loss of consciousness	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Male	Feeding disorder neonatal, Jaundice neonatal, Craniotabes, Head deformity, Inguinal hernia, Tooth disorder, Surgery, Ear tube insertion, Rash neonatal, Infantile colic	Infanrix hexa	4		0 Months	Convulsion, Febrile convulsion, Speech disorder developmental, Mental retardation, Motor developmental delay, Strabismus, Posture abnormal, Coordination abnormal, Ill-defined disorder, Crying, Restlessness, Slow response to stimuli, Hypotonia, Infection, Abnormal behaviour, Head deformity, Ataxia, Heart sounds abnormal, Hyperhidrosis, Sleep disorder, Cyanosis, Loss of consciousness, Tonic clonic movements, Tongue paralysis, Spinal disorder	Serious	Worse
	18 Weeks Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		21 Days	Congestive cardiomyopathy, Cardiac failure, Atrial septal defect, Cyanosis, Pneumothorax, Bronchopneumonia, Thrombocytosis, Respiratory tract infection, Pyrexia, General physical health deterioration, Tachypnoea, Ill-defined disorder, Cardiomegaly, Dilatation ventricular, Left ventricular dysfunction, Post procedural oedema, Hypertension, C-reactive protein increased	Serious	Unresolved
	11 Weeks Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Rotavirus vaccine	Immediate	Hypotonic-hyporesponsive episode, Cyanosis, Hypotension, Vomiting, Hypotonia, Restlessness, Pallor	Serious	Resolved
	4 Years Female		Infanrix hexa, DTPa-Polio-HIB (Non-GSK)	3		3 Years	Cyanosis, Apnoea, Pertussis, Vomiting, Cough, Vaccination failure	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	4 Years Male	Diabetic relative	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		Unknown	Autism, Pertussis, Pneumonia, Pyrexia, Cough, Vomiting, Cyanosis, Apnoea, Muscle rigidity, Opisthotonus, Diarrhoea, Rales, Pharyngeal erythema, Obstruction, Vaccination failure, Mental impairment, Speech disorder developmental, Abnormal behaviour, Developmental delay	Serious	Unresolved
	20 Months Male	Febrile convulsion, Neurodermatitis, Campylobacter gastroenteritis, Upper respiratory tract infection	Infanrix hexa, Pneumococcal vaccines (Non-GSK)		Prednicarbate	1 Days	Convulsion, Fall, Opisthotonus, Staring, Foaming at mouth, Cyanosis, Dyskinesia, Muscle twitching, Unresponsive to stimuli, Fatigue, Injection site swelling, Injection site erythema, C-reactive protein increased	Serious	Resolved
	3 Months Female	Wound	Infanrix hexa	1		0 Days	Peripheral vascular disorder, Cyanosis, Pallor, Restlessness, Staring	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Pyrexia, Pallor, Hypotonia, Cyanosis, Delirium febrile, Febrile convulsion	Serious	Resolved
	6 Months Male		Infanrix hexa			1 Days	Pyrexia, Apathy, Fluid intake reduced, Decreased appetite, Cold sweat, Cyanosis, Poor peripheral circulation	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Male	Hiccups, Flatulence, Gastrointestinal disorder, Abdominal distension, Constipation	Infanrix hexa	1	Sodium Fluoride, Simethicone	0 Days	Apparent life threatening event, Respiratory arrest, Cyanosis, Epistaxis, Haematemesis, Anoxia, Metabolic acidosis, Brain injury, Mental disorder due to a general medical condition, Respiratory failure, Pupillary reflex impaired, Hyporeflexia, Deafness, Anaemia, Pneumonia, Cerebral atrophy, Asphyxia, Muscle spasms, Muscle spasticity, Urine output decreased, Oedema	Serious	Unresolved
	15 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		1 Days	Febrile convulsion, Pyrexia, Fluid intake reduced, Decreased appetite, Rhinitis, Upper respiratory tract infection, Muscle twitching, Hypotonia, Gaze palsy, Breath sounds abnormal, Fatigue, Somnolence, Crying, Diarrhoea, Cough, Loss of consciousness, Cyanosis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	3 Months Male	Urinary tract disorder	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Death, Multi-organ failure, Encephalopathy, Respiratory failure, Hypertrophic cardiomyopathy, Hypertensive crisis, Epilepsy, Loss of consciousness, Hypotonia, Crying, Hydrophobia, Pyrexia, Dysphagia, Restlessness, Muscle twitching, Cyanosis, Dyspnoea, Blood glucose increased, Acidosis, Acute respiratory failure, Tachycardia, Hypertension, Somnolence, Developmental delay, Myoclonus, Bladder disorder, Sepsis, Systemic inflammatory response syndrome, Ileus, Cerebral atrophy, Quadriparesis, Ventricular hypertrophy	Serious	Fatal
	5 Months Male	Neonatal aspiration, Sepsis neonatal, Streptococcal infection, Retinal haemorrhage, Fever neonatal	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	32 Days	Convulsion, Partial seizures, Hypotonia, Eye movement disorder, Gaze palsy, Bruxism, Unresponsive to stimuli, Oxygen saturation decreased, Cyanosis, Abnormal faeces, Faeces discoloured, Pyrexia, Atonic seizures, Depressed level of consciousness, Neutropenia, Hypertonia, Muscle rigidity	Serious	Unresolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	9 Weeks Female	Jaundice neonatal, Familial risk factor, Foetal monitoring abnormal	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	1	Zymafluor D	1 Days	Sudden infant death syndrome, Febrile convulsion, Cardiac arrest, Pyrexia, Gaze palsy, Cyanosis, Epistaxis	Serious	Fatal
	10 Months Male		Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Apparent life threatening event, Aspiration, Cyanosis	Serious	Resolved
	16 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		1 Days	Febrile convulsion, Pyrexia, Fatigue, Food aversion, Vomiting, Grand mal convulsion, Opisthotonus, Gaze palsy, Cyanosis, Gastroenteritis viral, Rhinitis, Hyponatraemia, Diarrhoea, Abnormal faeces	Serious	Resolved
	4 Months Female		Infanrix hexa, Synflorix, Rotavirus vaccine	1		2 Days	Febrile convulsion, Cyanosis, Staring	Serious	Resolved
	9 Weeks Male		Infanrix hexa, Synflorix			Hours	Convulsion, Pallor, Musculoskeletal stiffness, Cyanosis, Hypotonia	Serious	Resolved
	7 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	2 Days	Crying, Screaming, Muscle spasms, Cyanosis, Musculoskeletal stiffness	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	10 Weeks Female	Premature baby, Jaundice neonatal, Abdominal pain, Flatulence, Rhinitis, Nasopharyngitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	1	Ergocalciferol	2 Days	Convulsion, Cyanosis, Musculoskeletal stiffness, Crying, Dyskinesia, Screaming	Serious	Resolved
[redacted]	2 Months Male	Nervousness, Crying, Dyskinesia, Oligodipsia, Heat stroke, Dehydration, Hyperthermia	Synflorix, Infanrix hexa, Rotavirus vaccine	1		1 Days	Clonic convulsion, Gaze palsy, Cyanosis, Diarrhoea, Pyrexia, Hypotonia, Pallor	Serious	Resolved
[redacted]	2 Years Male		Infanrix hexa	4		13 Months	Pertussis, Pneumonia, Cough, Cyanosis, Lymphadenopathy, Vaccination failure	Serious	Unknown

APPENDIX 7B.10 : Gaze palsy

Vaccines Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Infanrix hexa: Gaze palsy

Date of review	31 October 2013
Vaccine terms included	Infanrix hexa (combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine) GSK drug code: IGA182
Adverse events (MedDRA preferred terms) included	Gaze palsy
Authors	[redacted] Safety Scientist) (Safety Physician)

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AE	Adverse event
AIFA	Agenzia Italiana del Farmaco
HCP	Health Care Professional
HHE	Hypotonic-hyporerspnsive episode
LLT	Lower level Term
MedDRA	Medical Dictionary for Regulatory Activities
PSUR	Periodic Safety Update Report
PT	Preferred term
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
RSI	Reference Safety Information

1. BACKGROUND

1.1. Indication

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b. The primary vaccination schedule consists of three or two doses during the first 6 months of age. After a vaccination with 2 doses (e.g. 3, 5 months) a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age. After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

1.2. Regulatory request

In the context of periodic aggregate safety reports, the Company first described events of gaze palsy in PSUR (periodic safety update report) No 14 (covering the period between 23 October 2008 and 22 October 2009). Since then gaze palsy has been routinely described in periodic Infanrix hexa PSURs. In the assessment report of PSUR 15-16, the European Medicine Agency (EMA) made the following comment and request:

"Since launch, 70 spontaneous cases of Gaze palsy were received by the MAH up to the data lock point of 22 October 2011. The event occurred on the same day of vaccination in 64% cases (45/70). Gaze palsy was one of the presenting symptoms in all cases, the most frequent being convulsions (45), loss/altered or depressed level of consciousness (31) and hypotonia/ hypotonic-hyporesponsive episode (27). Two of these events are listed in the RSI, but gaze palsy is not included.

Since launch, the reporting frequency of gaze palsy is 0.10/100,000 doses administered. However, data provided indicate that the reporting frequency per 100,000 doses distributed substantially increased over this period from 0.04 in PSUR 1-13 (14 cases) to 0.12 in PSUR 14 (14 cases) and 0.17 in PSUR 15 and 16 (42 cases). This increase in rate in PSUR 15-16 is significant (Poisson $p<0.001$), while the reporting frequency of the most frequently associated conditions (convulsions and altered/depressed levels of consciousness) did not vary substantially since launch. This rise can be due to a higher awareness and changes in coding or reporting, but this is not commented by the MAH.

The assessor cannot conclude that the information received with these cases does not provide evidence of a specific safety concern for Gaze Palsy. The MAH is requested to closely monitor Gaze palsy in the next PSURs, and investigate whether other factors may have contributed to this increase in reporting frequency of Gaze Palsy, such as changes in coding system or reporting.

1.3. Reference safety information

Gaze palsy is not listed in the reference safety information (RSI); however events likely to involve other eye movement abnormalities are listed, such as convulsions, collapse or shock-like state (hypotonic-hyporesponsive episode) and syncope.

1.4. Gaze palsy case definition and aetiology

Conjugate gaze palsies are neurological disorders affecting the ability to move both eyes in the same direction. These palsies can affect gaze in a horizontal, upward, or downward direction [Merck Manual, 2013].

Gaze palsies result from lesions due to injury or disease that can disrupt the transmission of signals from the brain to the eye. Almost all conjugate gaze palsies originate from a lesion somewhere in the brain stem, usually the midbrain, or pons. These lesions can be caused by stroke, or conditions such as Koerber-Salus-Elschnig syndrome, Progressive supra nuclear palsy, Olivopontocerebellar syndrome, or Niemann-Pick Disease, Type C [Right Diagnosis, 2013].

1.5. Gaze palsy mapping in MedDRA

The PT Gaze palsy includes 7 current and one non-current lower level term (LLT, Table 1). Beyond being indicative of true gaze palsies resulting from brain lesions (as defined in Section 1.3), these LLTs (mainly Eyeballs raise upward) are often used to report eye movement abnormalities as signs and symptoms in the context of other events such as convulsions, epilepsy, loss of consciousness, hypotonia and hypotonic-hyporesponsive episodes (HHE). Even the LLT Gaze palsy is regularly (and inappropriately) reported to describe eye movement abnormalities in the context of convulsions or HHE.

Table 1 Lower level terms mapping under the PT Gaze palsy in MedDRA

MedDRA LLT mapping under the PT Gaze palsy	Status	Code
Downward deviation of eyes	Current	10056712
Eyeballs raise upward	Current	10015975
Eyes gaze upward	Current	10016007
Feeling of eyeball pulled upward	Non-Current	10016346
Gaze palsy	Current	10056696
Palsy of conjugate gaze	Current	10033562
Spasm of conjugate gaze	Current	10041395
Upward deviation of eyes	Current	10046319

This is a cumulative evaluation of data from spontaneous reporting sources on gaze palsy following administration of Infanrix hexa.

2. POST-MARKETING EXPOSURE TO VACCINE

Infanrix hexa was first approved in European Union on 23 October 2000 (centralized procedure) and is currently licensed in 95 countries (extracted from PSUR No 17, data lock point 22 October 2012). Since launch, more than 100 million doses of Infanrix hexa were distributed worldwide. As vaccination with Infanrix hexa varies between one and four doses per subject, post-marketing exposure to Infanrix hexa since launch until the data lock point of this evaluation (24 October 2013) is estimated as being between 25 and 100 million subjects.

3. SAFETY DATA REVIEWED

This evaluation presents relevant information on reports of gaze palsy from the GSK worldwide safety database.

3.1. Database Search Strategy

The GSK worldwide safety database was searched on 25 October 2013 using the following criteria:

- **Data lock point**: since marketing launch until 24 October 2013
- **Report types**: All spontaneous reports
- **Suspect drug**: Infanrix hexa
- **MedDRA preferred term (PT)**: Gaze palsy

Limitations to quantitative analysis of spontaneous reports
Post-marketing surveillance for suspected adverse reactions is required to characterise the full safety profile of vaccines. Individual case safety reports are the primary source of information to detect potential risks in regular clinical practice. However such reports are anecdotal in nature and do not represent a random sample; they are not suitable as a basis for statistical inference, but statistical methods can provide real value in identifying outstanding reporting patterns for further investigation (signals) and in flagging reporting artefacts that may otherwise be misleading. Indeed invalid information may be generated because of several factors including: biased reporting, under-reporting, secular trends, media effects, missing or limited information, absence of case validation, absence of adequate comparator group.

3.2. Summary of Overall Dataset

A total of 126 cases including the PT Gaze palsy were retrieved from the GSK worldwide safety database (see APPENDIX 1). Of these cases:

- 79 (62.7%) had a healthcare professional as a report source.
- The majority were received from Germany (52.4%), The Netherlands (24.6%) and Italy (15.1%).

Further characteristics are summarised in Table 2. The median age (4 months) of subjects for which gaze palsy was reported was in line with the indicated population (see Section 1). Gaze palsy was reported slightly more frequently for boys than for girls. The median time-to-onset was 12 hours and the most frequent outcome for these cases was 'resolved'. All cases including the PT gaze palsy were serious since gaze palsy is considered an important medical event (IME) by EMA.

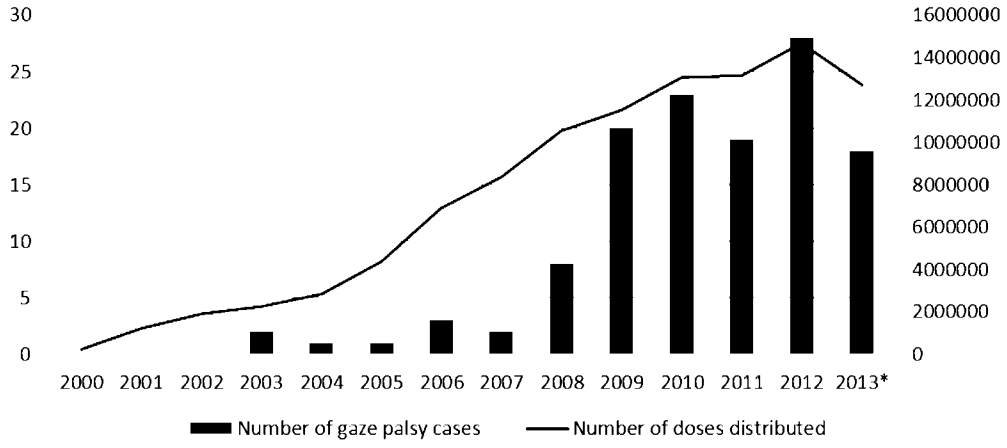
Table 2 Summary of characteristics of cases including the PT Gaze palsy

Patient Age	Median		4 months
	Range		4 weeks to 2 years
	Unknown	n (%)	0 (0%)
Gender	Female	n (%)	59 (46.8%)
	Male	n (%)	66 (52.4%)
	Unknown	n (%)	1 (0.8%)
Time to onset since last dose	Median		12 hours
	Range		3 minutes to 13 months
	Unknown	n (%)	6 (4.8%)
Outcome	Fatal	n (%)	1 (0.8%)
	Improved	n (%)	1 (0.8%)
	Resolved	n (%)	81 (64.3%)
	Resolved with Sequelae	n (%)	1 (0.8%)
	Unknown (at the time of reporting)	n (%)	30 (23.8%)
	Unresolved	n (%)	12 (9.5%)
	Worse	n (%)	0 (0%)
Dose number*	1	n (%)	49 (38.9%)
	2	n (%)	21 (16.7%)
	3	n (%)	21 (16.7%)
	4	n (%)	20 (15.9%)
	Unknown	n (%)	15 (11.9%)
Cases classified as serious		n (%)	126 (100%)

3.3. Reporting trends over time

The blue line and the right vertical axis in Figure 1 show the evolution of the worldwide distribution of Infanrix hexa doses per calendar year, while the red bars and the left vertical axis represent the distribution of the 126 gaze palsy events retrieved by the above search per calendar year[1], and for which a gaze palsy onset date was reported. An increased trend in yearly case reporting was observed in 2008 and 2009, while the trend seemed more stable during the other years. Note that the data for 2013 only covers months January to October and is therefore incomplete compared to the previous years.

Figure 1 Yearly sales and number of spontaneous cases including the PT Gaze palsy

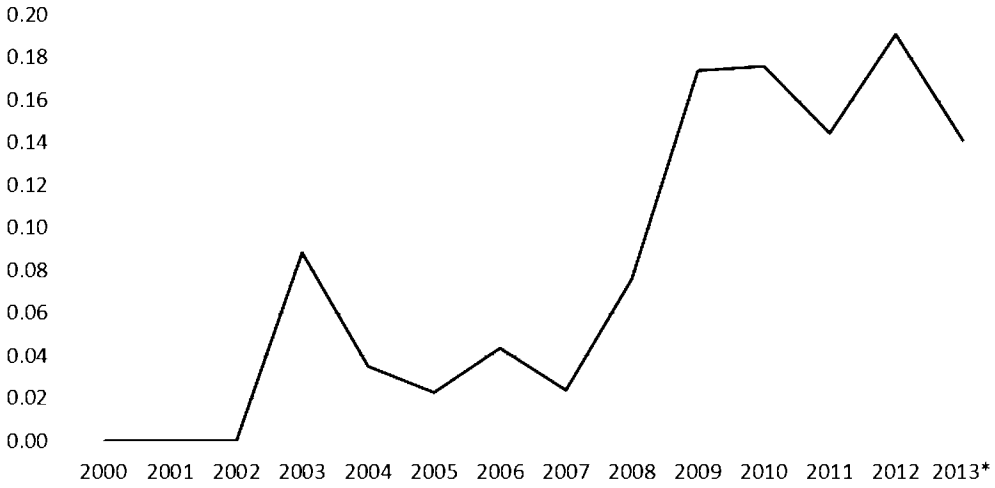


*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

[1] The reporting date used was the gaze palsy onset date, not the case receipt date because for spontaneous cases there might be a long delay between event onset and reporting to GSK. Out of the 126 gaze palsy events, onset date was missing for 1 of them.

Figure 2 shows the yearly reporting frequency for gaze palsy over time[1] expressed in number of cases per 100 000 doses distributed. The reporting frequency varied between 0 and 0.09 cases per 100 000 doses distributed between 2000 and 2007, then increased up to 0.17 between 2008 and 2009 and finally remained between 0.14 and 0.19 as of 2010. Higher fluctuations were observed during the first years following marketing due to lower sales volumes at that time. The increase observed in 2008-2009 is in line with the observation made by EMA (Section 1.2).

Figure 2 Yearly and cumulative reporting frequency in number of cases per 100 000 doses distributed



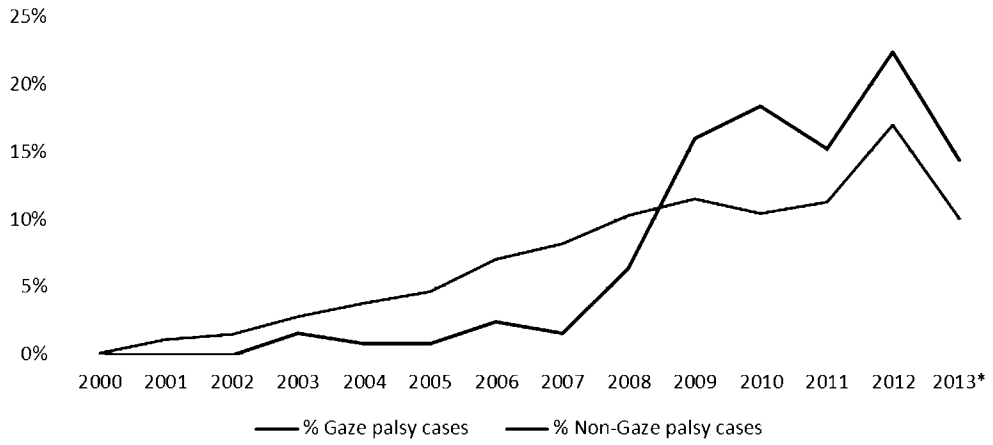
*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

The comparison of gaze palsy reporting with sales data has limitations since the time between dose distribution and actual vaccine administration is unknown. Also, the efficiency of the spontaneous reporting system varies in the different countries where Infanrix hexa is distributed. In order to correct for these limitations, the yearly[1] proportion of gaze palsy cases among the 126 gaze palsy cases was plotted in Figure 3 (red line) and compared to the yearly[2] proportion of non-gaze palsy cases among all[3] non-gaze palsy cases (green line). This approach allows visualizing whether, at some point in time, more gaze palsy cases were received compared to other cases received for Infanrix hexa, while taking into account changes in reporting trends (e.g. following marketing in a high reporting country). Figure 3 confirmed that in 2008 and 2009 more cases including the PT Gaze palsy were reported compared to previous years and compared to cases not including the PT Gaze palsy.

[2] For non-gaze palsy cases, the case onset date, which is the date of occurrence of the first event of the case, was used as reporting date.

[3] Case onset date was reported for 14306 non-gaze palsy cases.

Figure 3 **Proportion of cases including the PT Gaze palsy *versus* cases not including the PT Gaze palsy reported for Infanrix hexa over time**



*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

3.4. Country analysis

As mentioned in Section 3.2, Germany, The Netherlands and Italy mainly accounted for the increase described in Section 3.3. Figure 4 shows that the initial reporting frequency of gaze palsy (before the 2008-2009 increase) was exclusively attributable to Germany. The increase then started in Germany in 2008, followed by The Netherlands in 2009. Finally the reporting frequency stabilised around 0.17 due to cases received from Germany and The Netherlands, as well as from Italy as of 2010.

Figure 4 Breakdown of the worldwide yearly reporting frequency expressed in number of cases including the PT Gaze palsy per 100 000 doses distributed worldwide for Germany, The Netherlands and Italy

3.4.1. Germany

The increase in Germany was expected for the following reasons:

- Before 2006, the local operating company of GSK in Germany distinguished diagnoses from symptoms and coded only diagnoses, not symptoms leading to diagnoses. This approach was changed in 2006 when both diagnoses and symptoms were coded as 'events'. In itself this coding change did not impact the German Gaze palsy reporting frequency since it remained stable in 2006 and 2007.
- Before 2008, the local operating company of GSK in Germany translated German adverse event (AE) terms as literally as possible so that terms related to eye movements in the context of convulsion cases were either coded with the PT Eye movement disorder or the PT Gaze palsy. As of 2008, GSK Germany started to systematically use LLTs mapping into the Gaze palsy PT to code eye movement events in the context of convulsions.
- As of 2010 the German regulatory authority sent cases electronically to GSK via their website. These electronic cases often included detailed medical records and hospital reports, including more details such as signs and symptoms, which were consequently coded more frequently.

- The awareness for AE-reporting and actual AE reporting were and are steadily increasing over the years in Germany.

3.4.2. The Netherlands

The increase in The Netherlands was expected for the following reasons:

- Infanrix hexa was launched in 2006 in The Netherlands leading to an accrual of Dutch cases during the following years.
- The Dutch overall (regardless of event) case reporting frequency was the highest among countries where Infanrix hexa is distributed (54 cases per 100 000 doses distributed[4]). Thus Dutch reporting has a high impact on the global reporting frequency for Infanrix hexa.

Special attention might have further impacted the Dutch reporting frequency due to extension of the target population for Infanrix hexa vaccination from only children at risk for hepatitis B infection in 2006, to children with Down syndrome as of 2008 and finally all new-borns as of 2011. Also, accountability for national case reporting in The Netherlands underwent some changes between 2008 and 2010. Until 2008, GSK received Dutch cases directly from RIVM (National Institute for Public Health and the Environment). Between 2008 and 2010, RIVM cases where first sent to Lareb (Netherlands Pharmacovigilance Centre) for processing before being sent to GSK, while after 2010 Dutch cases were directly received from Lareb. It remains however unknown to what extent these local changes in the national immunization schedule and reporting system impacted the overall Dutch reporting frequency.

3.4.3. Italy

The increase of cases including the Gaze palsy PT in Italy happened nine years after Infanrix hexa (local) commercial launch and was also expected:

- Due to an increased attention of HCPs to report AEs as encouraged by the Italian Drug Agency (AIFA). Since 2008 there has been a steady increase in the Italian case reporting frequency.
- AIFA also encouraged reporting an increasing the level of detail. For example, most cases concerning convulsion episodes now include a high level of detail, such as rolling eyes, deviation of eyes, fixed gaze, together with other signs and symptoms of convulsive episodes. Before 2008, case details were limited to the final diagnosis or to the most relevant signs (e.g. tonic clonic seizures).

[4] Note that this does not mean that most Infanrix hexa cases were received from The Netherlands.

3.5. Medical evaluation of cases including the PT Gaze palsy

Due to the fact that the PT Gaze palsy is in itself unspecific and uninformative (see Section 1.5), a medical evaluation of all cases including the PT Gaze palsy was performed to identify the true medical condition reported. Among the 126 cases including the PT Gaze palsy, 125 (99.2%) actually described events involving eye movement-related signs and symptoms such as convulsions and hypotonia. These cases therefore did not provide any new significant safety information for Infanrix hexa beyond what is already listed in the reference safety information.

Only one case described a potentially true gaze palsy as defined in Section 1.4 which was considered unrelated to vaccination:

- [redacted] **Vaccination complication, Injury, Fluid intake reduced, Fatigue, Listless, Body temperature increased, Vomiting, General physical health deterioration, Insomnia, Crying, Gaze palsy, Dizziness, Haemoglobin decreased, Haemorrhagic anaemia, Thrombosis, Retinal haemorrhage, Haemolysis, Thrombocytopenia**

  This case was reported by a [redacted] regulatory authority and described the occurrence of vaccination complication in a 4-month-old subject who was vaccinated with Infanrix hexa on [redacted] and with Prevenar on [redacted] The subject's medical history included premature delivery after 34 weeks of gestation. The subject was a twin and developed normally. Acute infection was excluded and the subject was supposed to be able to received vaccination. The vaccination with Infanrix hexa was well tolerated and did not cause recognizable acute adverse effects. On [redacted], 1 day after vaccination with Prevenar and 15 days after vaccination with Infanrix hexa, the subject experienced reduced fluid intake, tiredness and listlessness. Body temperature was increased. The subject was treated with paracetamol. On [redacted], the subject experienced vomiting in the evening. General condition further worsened. The subject slept less than normal, cried high-pitched and rolled eyes upward. The subject seemed to be giddy. On [redacted] in the morning, the subject went to see the paediatrician. The paediatrician did not found the cause of disease. The subject was hospitalised for diagnostic examination. At admission examination, the subject was still giddy. Value of haemoglobin was severely decreased (7.4 g/dl). Decreased haemoglobin was interpreted as a result of bleeding and acute haemorrhagic anaemia was diagnosed, but site of bleeding could not be found. The subject was treated immediately with 130 ml blood transfusion. Platelet value and further coagulation factors were uneventfully. Ultrasonic examination showed no larger haematoma. On [redacted], ultrasonic examination showed thrombus at the area of left subarachnoid space (blood clot) and examinations by an ophthalmologist showed several retinal haemorrhages. This was interpreted as signs of shaken impact syndrome (injury). At the time of reporting the outcome of the events was unspecified. The reporter considered that the events were unrelated to vaccination with Infanrix hexa and Prevenar. The possibility of autoimmune reaction to vaccination with Infanrix hexa, which probably led to autoimmune haemolysis and transient thrombocytopenia, was excluded in differential diagnosis. The reporter

considered differential diagnosis as vaccination complication or shaken impact syndrome (injury).

Company comment: This case described a patient of 4 months who had gaze palsy one day after vaccination with Prevenar and 15 days after vaccination with Infanrix hexa. Examinations led to the conclusion that the gaze palsy was the result of haemorrhage in the subarachnoid space, and also some retinal haemorrhages. This was interpreted as the signs of a shaken impact syndrome. This event is not related to vaccination.

4. DISCUSSION AND CONCLUSION

Gaze palsy is not listed in the Infanrix hexa RSI (Section 1.3); however events likely to involve other eye movement abnormalities are listed, such as convulsions, collapse or shock-like state (HHE) and syncope. The PT Gaze palsy is in itself not specific to true gaze palsy as defined in Section 1.4 since it includes LLTs (e.g. Eyeballs raise upward) also indicative of the above mentioned listed events (Section 1.5). Even the LLT Gaze palsy is regularly (and inappropriately) reported to describe eye movement abnormalities in the context of convulsions or HHE. Therefore the PT Gaze palsy is expected to be reported as a sign or symptom of these listed events. For Infanrix hexa, the actual events in cases including the PT Gaze palsy were not truly gaze palsy as defined in Section 1.4, but rather convulsions and collapse or shock-like states such as HHE and/or hypotonia. There was only one case of potentially true gaze palsy after 14 years of post-marketing surveillance which was considered related to subarachnoid and retinal haemorrhages rather than vaccination (Section 3.5).

In 2008 and 2009, the worldwide spontaneous reporting frequency and proportion of cases including the PT Gaze palsy following Infanrix hexa administration increased from ± 0.04 to ± 0.17 cases per 100 000 doses distributed (Section 3.3). Country analysis showed that Germany and The Netherlands mainly accounted for this increase and that Germany, The Netherlands and Italy altogether maintained the reporting frequency around 0.17 afterwards. In Germany and Italy this increase was essentially induced by coding changes and strengthening of local reporting systems, while in The Netherlands market launch of Infanrix hexa and a relatively strong national reporting system increased the worldwide reporting frequency.

Cases including the PT Gaze palsy did not provide any new significant safety information for Infanrix hexa beyond what is already listed in the RSI.

Data currently available to GSK, including the limitations of this evaluation (see Section 3.1), suggest there is no increased risk of Gaze palsy following vaccination with Infanrix hexa. Since the PT Gaze palsy is in itself unspecific and uninformative, GSK will no longer routinely describe gaze palsy in future Infanrix hexa aggregate safety reports.

GSK will continue to employ a routine, pro-active process for identifying safety signals with three main components:

1. Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.

2. Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
3. Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

5. REFERENCES

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APPENDIX 1 LINE LISTING OF GAZE PALSY CASES (N=126)

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	12 Weeks Male		Infanrix hexa	1		7 Hours	Febrile convulsion, Gaze palsy, Musculoskeletal stiffness	Serious	Improved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		3 Minutes	Loss of consciousness, Crying, Pyrexia, Inflammation, Pain, Diarrhoea, Pallor, Gaze palsy, Hypotonia	Serious	Resolved
	2 Months Female	Apnoea	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		3 Minutes	Convulsion, Loss of consciousness, Gaze palsy, Depressed level of consciousness, Respiration abnormal, Injection site swelling, Pyrexia, Crying, Decreased appetite, Oligodipsia	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Convulsion, Loss of consciousness, Depressed level of consciousness, Gaze palsy, Oligodipsia, Hypotonia, Pallor, Pyrexia	Serious	Resolved
	3 Months Male	Nasopharyngitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Depressed level of consciousness, Gaze palsy, Sense of oppression, Pallor, Hypotonia, Vomiting, Pyrexia	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		3 Seconds	Depressed level of consciousness, Crying, Hyperhidrosis, Vasodilatation, Gaze palsy, Pyrexia, Inflammation	Serious	Resolved
	2 Months Male		Infanrix-polio-HIB, Infanrix hexa	1		1 Weeks	Infantile spasms, Gaze palsy, Muscle spasms, Sleep disorder, Condition aggravated, Motor dysfunction, Hypertonia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		5 Hours	Respiration abnormal, Gaze palsy, Loss of consciousness, Pallor, Cyanosis, Hypotonia	Serious	Resolved
	15 Months Female	Psychomotor retardation, Psychomotor skills impaired	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		5 Days	Altered state of consciousness, Gaze palsy, Tonic convulsion, Convulsion, Epilepsy, Gastroenteritis, Febrile convulsion, Hypertonia, Ear infection, Gastritis, Nasopharyngitis, Hypotonia, Body temperature increased, Vomiting, Diarrhoea, Pyrexia	Serious	Unknown
	11 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		2 Hours	Convulsion, Pallor, Gaze palsy, Loss of consciousness, Hypotonia, Pyrexia, Pain, Fatigue	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Gaze palsy, Pyrexia, Mental impairment, Crying	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			6 Hours	Loss of consciousness, Gaze palsy, Pallor, Cyanosis, Hypotonia, Vomiting	Serious	Resolved
	12 Months Male	Nasopharyngitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			1 Days	Convulsion, Gaze palsy, Loss of consciousness, Pyrexia, Otitis media, Pallor	Serious	Resolved
	1 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		8 Hours	Febrile convulsion, Loss of consciousness, Gaze palsy, Pain, Skin warm, Respiration abnormal, Pyrexia, Crying	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	11 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		2 Hours	Pneumonia, Loss of consciousness, Gaze palsy, Convulsion, Nasopharyngitis, Drooling, Pallor, Pyrexia	Serious	Resolved
	2 Years Female		Infanrix hexa	3		5 Hours	Hypotonic-hyporesponsive episode, Depressed level of consciousness, Gaze palsy, Respiration abnormal, Injection site inflammation, Vomiting, Cold sweat, Injection site pain, Pallor, Pyrexia	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		4 Hours	Gaze palsy, Crying, Pyrexia, Myoclonus	Serious	Resolved
	6 Months Male	Haemangioma, Mental impairment	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Epilepsy, Grand mal convulsion, Loss of consciousness, Gaze palsy, Cyanosis, Pyrexia, Salivary hypersecretion, Somnolence, Hyperaemia, Escherichia urinary tract infection, Electroencephalogram abnormal, Drooling, Tremor, Muscle spasms, Partial seizures, Infantile spasms, Hydrocele, Phimosis, Epidermal naevus, Cough, Bronchitis	Serious	Unknown
	16 Months Male		Infanrix hexa			1 Days	Febrile convulsion, Gaze palsy, Unresponsive to stimuli, Pyrexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	12 Months Male	Urticaria	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Cetirizine hydrochloride, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4 Hours	Convulsion, Leukocytosis, Shock, Gaze palsy, Loss of consciousness, Pyrexia	Serious	Unknown
[redacted]	2 Months Female		Infanrix hexa, Meningococcal polysaccharide vaccine group C (Non-GSK), Pneumococcal vaccines (Non-GSK)			2 Hours	Gaze palsy, Hypotonia, Pallor	Serious	Resolved
[redacted]	6 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		Hours	Convulsion, Loss of consciousness, Gaze palsy, Pallor, Pyrexia, Crying	Serious	Unresolved
[redacted]	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Magaldrate, Ranitidine hydrochloride	10 Days	Gaze palsy, Hypotonia	Serious	Resolved
[redacted]	11 Months Male		Infanrix hexa	3	Priorix	2 Days	Loss of consciousness, Gaze palsy, Pallor, Hypotonia	Serious	Resolved
[redacted]	3 Months Male	Dermatitis atopic	Infanrix hexa, Synflorix	1		8 Hours	Hypotonic-hyporesponsive episode, Gaze palsy, Opisthotonus, Pallor, Apathy, Fear, Agitation, Hypotonia, Crying	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	13 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		Hours	Loss of consciousness, Depressed level of consciousness, Convulsion, Gaze palsy, Respiration abnormal, Pallor, Hypotonia, Drooling, Cyanosis, Pyrexia, Vomiting	Serious	Resolved
	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		36 Hours	Loss of consciousness, Apnoea, Depressed level of consciousness, Gaze palsy, Pallor, Cyanosis, Hypotonia, Peripheral coldness, Pyrexia	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		14 Hours	Gaze palsy, Hypertonia, Pyrexia, Dyskinesia, Somnolence, Feeling hot	Serious	Resolved
	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		1 Days	Convulsion, Gaze palsy, Clonus, Pyrexia	Serious	Unknown
	10 Months Female	Milk allergy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Convulsion, Gaze palsy, Conjunctival hyperaemia, Eyelid disorder, Pyrexia, Strabismus	Serious	Unknown
	2 Months Male		Infanrix hexa, Synflorix	1		6 Hours	Febrile convulsion, Convulsion, Body temperature increased, Pallor, Apathy, Crying, Grand mal convulsion, Gaze palsy, Opisthotonus, Feeding disorder	Serious	Resolved
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			32 Days	Simple partial seizures, Gaze palsy	Serious	Unresolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	2 Months Female		Infanrix hexa	1		24 Hours	Gaze palsy, Staring, Hypotonic-hyporesponsive episode	Serious	Resolved
	11 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		1 Days	Febrile convulsion, Grand mal convulsion, Gaze palsy, Salivary hypersecretion, Generalised erythema, Enteritis, Pyrexia, Diarrhoea	Serious	Unknown
	3 Months Male		Infanrix hexa, Synflorix	2		8 Hours	Gaze palsy, Pallor, Hypotonic-hyporesponsive episode, Hypersomnia	Serious	Resolved
	2 Months Male	Syncope	Synflorix, Infanrix hexa	1		0 Minutes	Syncope, Crying, Vaccination complication, Gaze palsy, Pallor, Loss of consciousness	Serious	Resolved
	11 Months Female	Premature baby, Ventricular septal defect repair	Infanrix hexa	4		1 Minutes	Gaze palsy, Cyanosis, Breath holding, Crying, Ill-defined disorder, Pallor	Serious	Resolved
	6 Months Male	Bronchiolitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		1 Days	Loss of consciousness, Crying, Gaze palsy, Tremor, Hypotonia	Serious	Resolved
	8 Weeks Female		Infanrix hexa, Synflorix	1		0 Days	Hypotonic-hyporesponsive episode, Pallor, Fatigue, Hypotonia, Unresponsive to stimuli, Gaze palsy, Ill-defined disorder	Serious	Resolved
	5 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Depressed level of consciousness, Gaze palsy, Hypotonia, Fatigue	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	12 Months Male		Infanrix hexa	3		Hours	Partial seizures with secondary generalisation, Loss of consciousness, Gaze palsy, Grand mal convulsion, Irritability, Change of bowel habit, Hypotonia, Psychomotor hyperactivity, Vomiting, Cyanosis, Staring, Sinus tachycardia, Trismus, Clonus	Serious	Unknown
	8 Weeks Male	Nasopharyngitis, Pyrexia	Infanrix hexa, Synflorix	1		4 Hours	Meningitis, Meningism, Screaming, Cyanosis, Fontanelle bulging, Pyrexia, Gaze palsy, Depressed level of consciousness, Upper respiratory tract infection	Serious	Resolved
	3 Months Female		Rotavirus vaccine, Infanrix hexa			2 Days	Parinaud syndrome, Convulsion, Gaze palsy, Depressed level of consciousness, Altered state of consciousness, Tongue paralysis, Facial pain, Abnormal behaviour, Protrusion tongue	Serious	Resolved
	2 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Gaze palsy, Dyspnoea, Foaming at mouth, Pallor, Paresis, Hypotonia	Serious	Resolved
	10 Months Male		Infanrix hexa	3		0 Days	Gaze palsy, Hypotonia, Syncope	Serious	Resolved
	2 Months Female		Infanrix hexa, Synflorix	1		Immediate	Convulsion, Gaze palsy, Crying, Somnolence, Ill-defined disorder, Pallor, Hyporesponsive to stimuli, Feeding disorder neonatal	Serious	Unresolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	11 Months Male		Infanrix hexa, Synflorix			90 Minutes	Febrile convulsion, Injection site inflammation, Crying, Injection site swelling, Injection site erythema, Chills, Gaze palsy, Hyporesponsive to stimuli, Injection site pain, Staring	Serious	Resolved
	5 Months Female	Cough, Rhinitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Gaze palsy, Musculoskeletal stiffness, Cyanosis, Hypotonia, Drooling	Serious	Resolved
	14 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		0 Days	Febrile convulsion, Gaze palsy, Clonus, Injection site reaction, Crying, Pyrexia	Serious	Unknown
	11 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		3 Hours	Febrile convulsion, Hypertonia, Clonus, Gaze palsy, Cyanosis, Pyrexia	Serious	Resolved
	10 Months Male		Infanrix hexa, Synflorix	4		Hours	Febrile convulsion, Gaze palsy, Unresponsive to stimuli, Dyskinesia, Pyrexia, Pyelonephritis	Serious	Resolved
	15 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Febrile convulsion, Loss of consciousness, Gaze palsy, Cyanosis, Pyrexia, Tremor	Serious	Resolved
	2 Months Female		Infanrix hexa, Synflorix	1		4 Hours	Gaze palsy, Myalgia, Crying, Myoclonus, Pallor, Staring, Injection site pain, Pyrexia	Serious	Resolved
	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			1 Days	Hypotonia, Gaze palsy, Staring, Pallor	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	11 Months Male		Infanrix hexa, Synflorix	2		4 Hours	Febrile convulsion, Injection site inflammation, Injection site erythema, Injection site pain, Extensive swelling of vaccinated limb, Muscle spasms, Loss of consciousness, Gaze palsy, Head titubation, Pallor, Muscle twitching, Sleep disorder, Delirium febrile	Serious	Unknown
	5 Months Male		Synflorix, Infanrix hexa	2		1 Days	Convulsion, Respiratory arrest, Gaze palsy	Serious	Unknown
	6 Months Male		Infanrix hexa	3		1 Days	Gaze palsy, Cyanosis, Drooling, Hypotonia	Serious	Resolved
	4 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		Hours	Febrile convulsion, Crying, Tonic clonic movements, Loss of consciousness, Gaze palsy, Pyrexia	Serious	Resolved
	7 Weeks Male	Somnolence, Pallor	Infanrix hexa, Synflorix	1		2 Hours	Loss of consciousness, Gaze palsy, Hyperpyrexia, Pyrexia, Hypotonic-hyporesponsive episode, Hypophagia, Pallor, Apathy	Serious	Resolved
	2 Months Male		Infanrix hexa, Synflorix	1		0 Days	Hypotonic-hyporesponsive episode, Choking, Gaze palsy, Cyanosis, Pyrexia, Somnolence, Decreased activity	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	2 Months Female	Tobacco user, Alcohol use	Infanrix hexa	1		Same day	Cytomegalovirus infection, Pyrexia, Pallor, Hypotension, Tachypnoea, General physical health deterioration, Gaze palsy, Tachycardia, Hypotonia, Anuria, Transaminases increased, Disseminated intravascular coagulation, Haemolysis, Haematochezia, Hyperkalaemia, Thrombocytopenia, Petechiae, Pneumonia aspiration, Rales, Enteritis, Abdominal distension, Faeces discoloured, Brain injury, Motor dysfunction, Clonus	Serious	Unresolved
	15 Weeks Female		Infanrix hexa	2	Infanrix hexa	4 Hours	Hypotonic-hyporesponsive episode, Crying, Hypotonia, Vomiting, Pallor, Altered state of consciousness, Gaze palsy	Serious	Resolved
	3 Months Female		Infanrix hexa	1		95 Minutes	Tonic convulsion, Opisthotonus, Pallor, Gaze palsy, Muscle twitching, Salivary hypersecretion, Crying	Serious	Resolved
	4 Months Female	Dermatitis atopic	Infanrix hexa	2	Infanrix hexa	9 Days	Nervous system disorder, Developmental delay, Abnormal behaviour, Social avoidant behaviour, Gaze palsy, Syncope, Pallor, Apathy, Extrapyramidal disorder	Serious	Unknown
	2 Months Male	Hyperbilirubinaemia, Strabismus, Jaundice	Infanrix hexa	1		10 Minutes	Hypotonic-hyporesponsive episode, Pallor, Hypotonia, Depressed level of consciousness, Gaze palsy, Immobile, Heart rate increased, Areflexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	5 Months Female		Infanrix hexa	3		12 Hours	Epilepsy, Convulsion, Breath sounds abnormal, Gaze palsy, Staring, Depressed level of consciousness, Muscle twitching, Salivary hypersecretion, Crying, General physical health deterioration, Diarrhoea, Gastroenteritis, Haematochezia, Bronchitis, Nausea, Vomiting	Serious	Unknown
	3 Months Female	Familial risk factor	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Hypotonic-hyporesponsive episode, Febrile convulsion, Pyrexia, Urinary tract infection, Leukocyturia, Haematuria, Hypotonia, Movement disorder, Gaze palsy, Pallor, Vaccination complication	Serious	Resolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		10 Hours	Hypotonic-hyporesponsive episode, Hypotonia, Retching, Vomiting, Pallor, Gaze palsy, Depressed level of consciousness, Vaccination complication, Gastroenteritis, Abnormal faeces, Diarrhoea	Serious	Resolved
	2 Months Male	Vacuum extractor delivery, Foetal monitoring abnormal, Feeding disorder neonatal, Weight decrease neonatal	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Partial seizures, Developmental delay, Hypotonia, Plagiocephaly, Gaze palsy, Salivary hypersecretion, Daydreaming, Fatigue, Oxygen saturation decreased, Pyrexia	Serious	Unresolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Serious-ness	Case Outcome
[redacted]	4 Months Female	Premature baby, Respiratory distress, Sleep apnoea syndrome, Bradycardia, Sepsis, Retinopathy congenital, Familial risk factor	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Zymafluor D, Paracetamol	4 Days	Cerebral haemorrhage, Convulsion, Partial seizures, Status epilepticus, Rhinitis, Somnolence, Oligodipsia, Gaze palsy, Unresponsive to stimuli, Oxygen saturation decreased, Hypothermia, Apnoea, Pallor, Oedema, Pneumonia, Brain oedema, Pyrexia, Pyelonephritis acute, Cerebral hygroma, Oral candidiasis, Candida nappy rash	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	2 Months Female	Microcephaly, Foetal growth restriction, Hyperbilirubinaemia, Urinary tract obstruction	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Epilepsy, Myoclonic epilepsy, Grand mal convulsion, Status epilepticus, Pyrexia, Screaming, Hyperhidrosis, Apathy, Respiration abnormal, Use of accessory respiratory muscles, Gaze palsy, Sleep disorder, Respiratory rate increased, Musculoskeletal stiffness, Apnoea, Clonus, Staring, Strabismus, Binocular eye movement disorder, Pupillary reflex impaired, Eye movement disorder, Conjunctivitis, Infantile spasms, Developmental delay, Fluid intake reduced, Vomiting, Dehydration, Weight decreased, Malnutrition, Pyloric stenosis, Pyelocaliectasis, Thrombocytopenia, Aspartate aminotransferase increased, Anticonvulsant drug level above therapeutic, Iron deficiency anaemia, Respiratory failure, Respiratory acidosis, Metabolic acidosis, Hypothyroidism, Shift to the left, Upper respiratory tract infection	Serious	Unknown
	5 Months Male	Delivery, Jaundice neonatal	Infanrix hexa, DTPa-HepB-IPV-HIB (Non-GSK)	1		2 Months	Infantile spasms, Grand mal convulsion, Developmental delay, Gaze palsy, Salivary hypersecretion, Fatigue, Skin discolouration, Unresponsive to stimuli, Febrile infection, Otitis media, Hypotonia, Illusion, Neurodermatitis, Atopy	Serious	Unresolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	3 Months Male		Infanrix hexa	1		0 Days	Depressed level of consciousness, Gaze palsy, Somnolence, Vomiting projectile, Pyrexia, Asthenia, Pallor	Serious	Unknown
	4 Months Unknown	Premature delivery	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		15 Days	Vaccination complication, Injury, Fluid intake reduced, Fatigue, Listless, Body temperature increased, Vomiting, General physical health deterioration, Insomnia, Crying, Gaze palsy, Dizziness, Haemoglobin decreased, Haemorrhagic anaemia, Thrombosis, Retinal haemorrhage, Haemolysis, Thrombocytopenia	Serious	Unknown
	4 Months Female	Flatulence, Delivery	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Dimethicone	9 Days	Epilepsy, Crying, Gaze palsy, Asthenia, Dyskinesia, Body temperature increased, Gastroenteritis adenovirus, Gastroenteritis norovirus, Dermatitis diaper, Motor developmental delay	Serious	Resolved with Sequelae
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		1 Days	Gaze palsy, Chills, Pyrexia, Vomiting	Serious	Resolved
	14 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	0 Days	Febrile convulsion, Pyrexia, Opisthotonus, Gaze palsy, Tremor, Unresponsive to stimuli, Fatigue, Agitation, Crying	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	3 Months Male	Impetigo, Iron deficiency anaemia, Coordination abnormal, Physiotherapy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Rotavirus vaccine, Paracetamol, Ergocalciferol, Ferrous glycine sulphate	14 Days	Convulsion, Gaze palsy, Crying, Opisthotonus, Benign familial neonatal convulsions, Epilepsy, Hypertonia, Unresponsive to stimuli, Dyskinesia, Lividity, Psychomotor hyperactivity, Excessive masturbation	Serious	Unresolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		1 Days	Convulsion, Cyanosis, Apnoea, Musculoskeletal stiffness, Gaze palsy	Serious	Resolved
	9 Weeks Male	Plagiocephaly	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		36 Hours	Convulsion, Gaze palsy, Staring, Unresponsive to stimuli, Opisthotonus, Hypotonia, Abnormal faeces	Serious	Resolved
	2 Years Male	Fall, Haematoma	Infanrix hexa	4		1 Days	Febrile convulsion, Pyrexia, Convulsion, Loss of consciousness, Depressed level of consciousness, Musculoskeletal stiffness, Gaze palsy, Cyanosis, Disorientation, Viral infection, Injection site erythema, Injection site swelling	Serious	Unknown
	2 Months Female		Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		0 Days	Febrile convulsion, Pyrexia, Gaze palsy, Muscle twitching	Serious	Resolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Rotavirus vaccine	0 Days	Apparent life threatening event, Cyanosis, Hypotonia, Gaze palsy, Fatigue, Somnolence, Sleep apnoea syndrome, Gastroenteritis rotavirus, Apnoea, Apathy	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	5 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Ergocalciferol	0 Days	Convulsion, Febrile convulsion, Atonic seizures, Grand mal convulsion, Pyrexia, Diarrhoea, Gaze palsy, Cyanosis, Disturbance in attention, Staring, Pharyngeal erythema, Rhinitis, Leukocytosis, Gastroenteritis, Gastroenteritis norovirus	Serious	Unresolved
	2 Months Female	Premature baby	Synflorix, Infanrix hexa	1	Ferrous glycine sulphate, Vitamin D	6 Hours	Convulsion, Gaze palsy, Muscle spasms, Tremor	Serious	Resolved
	14 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		0 Days	Febrile convulsion, Loss of consciousness, Cataplexy, Gaze palsy, Pyrexia, Vaccination complication	Serious	Resolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		1 Days	Convulsion, Gaze palsy, Musculoskeletal stiffness, Cyanosis	Serious	Resolved
	5 Months Male	Abnormal weight gain, Rhinitis, Productive cough, Vomiting, Gastrooesophageal reflux disease, Testicular retraction	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		0 Days	Hypotonic-hyporesponsive episode, Gaze palsy, Hypotonia, Mental impairment, Feeling abnormal, Neutropenia	Serious	Resolved
	23 Months Male	Febrile infection, Gastroenteritis, Vomiting	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		0 Days	Febrile convulsion, Pyrexia, Diarrhoea, Gaze palsy, Grand mal convulsion, Pallor, Vomiting, Gastroenteritis	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	8 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		1 Days	Febrile convulsion, Gaze palsy, Respiratory arrest, Respiratory tract infection, Pharyngeal erythema, Feeling of relaxation, Skin discolouration, Vaccination complication	Serious	Resolved
	13 Months Male	Cyanosis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		0 Weeks	Convulsion, Gaze palsy, Depressed level of consciousness, Pyrexia, Musculoskeletal stiffness, Fall, Concussion, Contusion, Hypotonia	Serious	Unknown
	14 Months Female	Therapy change	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	0 Days	Febrile convulsion, Pyrexia, Fatigue, Gaze palsy, Loss of consciousness, Grand mal convulsion, Oxygen saturation decreased, Disorientation, Somnolence, Tachycardia, Pharyngeal erythema	Serious	Resolved
	4 Months Male	Cardiac murmur	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		0 Days	Febrile convulsion, Pyrexia, Musculoskeletal stiffness, Gaze palsy, Somnolence, Transaminases increased, Pharyngeal erythema, Tympanic membrane hyperaemia	Serious	Unknown
	3 Months Male		Rotavirus vaccine, Infanrix hexa, Synflorix	1		1 Days	Thalamus haemorrhage, Convulsion, Facial paresis, Hemiparesis, Hypophagia, Restlessness, Pyrexia, Screaming, Somnolence, Pallor, Hyperaesthesia, Eyelid oedema, Abdominal distension, Hypotonia, Apnoea, Gaze palsy	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	6 Months Female	Premature baby, Neonatal respiratory distress syndrome, Neonatal respiratory failure, Apnoea neonatal, Bradycardia neonatal, Hyperbilirubinaemia neonatal, Regurgitation	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Intubation, Mechanical ventilation	1 Days	Apnoea, Cyanosis, Febrile convulsion, Gaze palsy, Altered state of consciousness, Convulsion, Body temperature increased, Breath holding, Moaning, Erythema, Swelling, Hypokinesia, Pain, Pyrexia, Dyspnoea, Infection	Serious	Unknown
	12 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		1 Days	Convulsion, Depressed level of consciousness, Gaze palsy, Hypochromic anaemia, Pyrexia, Injection site erythema, Musculoskeletal stiffness, Iron deficiency	Serious	Unknown
	8 Months Female		Infanrix hexa, Synflorix	3		1 Days	Convulsion, Gaze palsy, Cyanosis, Vaccination complication, Restlessness, Feeling hot, Staring, Muscle twitching, Dyspnoea, Hypotonia, Somnolence, General physical health deterioration, Body temperature increased	Serious	Unknown
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	0 Days	Hypotonic-hyporesponsive episode, Eye movement disorder, Convulsion, Gaze palsy, Opisthotonus, Crying	Serious	Resolved
	4 Months Female	Bronchitis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Salbutamol sulphate	1 Days	Febrile convulsion, Muscle rigidity, Opisthotonus, Gaze palsy, Pyrexia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	15 Months Female	Familial risk factor, Febrile convulsion, Hospitalisation, Cardiac murmur, Underweight, Upper respiratory tract infection	Infanrix hexa	4		0 Days	Febrile convulsion, Pyrexia, Chills, Gaze palsy, Eye movement disorder, Cyanosis, Unresponsive to stimuli, Tremor, Grand mal convulsion, Upper respiratory tract infection	Serious	Resolved
	16 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			48 Hours	Convulsion, Pallor, Gaze palsy, Depressed level of consciousness, Joint hyperextension, Loss of consciousness, Hypotonia	Serious	Unknown
	5 Months Male	Posture abnormal, Agitation, Bronchitis, Familial risk factor, Osteopathic treatment, Physiotherapy, Nervousness	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1 Days	Convulsion, Gaze palsy, Juvenile myoclonic epilepsy, Myoclonic epilepsy, Opisthotonus, Dyskinesia, Muscle tightness, Head titubation, Tension, Tremor	Serious	Resolved
	18 Months Male	Hypocalcaemia, Vitamin D deficiency, Rickets, Convulsion	Infanrix hexa, Priorix Tetra	4	Vitamin D	0 Days	Febrile convulsion, Pyrexia, Pallor, Gaze palsy, Dyskinesia	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	10 Weeks Female	Nervous system disorder, Familial risk factor, Haemangioma of skin	Rotavirus vaccine, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		9 Days	Atonic seizures, Apnoea, Hypotonia, Gaze palsy, Choking, Respiration abnormal, Respiratory arrest, Loss of consciousness, Conversion disorder, Fear, Cyanosis, Pallor, Unresponsive to stimuli, Staring, Bronchitis, Gastroenteritis, Rhonchi, Abdominal distension, Abdominal pain, Constipation, Faeces discoloured, Abnormal faeces, Somnolence, Fatigue, Rhinitis, Eye discharge, Abnormal behaviour	Serious	Unresolved
	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	6 Hours	Loss of consciousness, Vomiting projectile, Diarrhoea, Pyrexia, Circulatory collapse, Hypotonia, Unresponsive to stimuli, Gaze palsy, Cardiovascular disorder, Gastroenteritis	Serious	Resolved
	4 Months Female		Infanrix hexa	2		8 Hours	Febrile convulsion, Gaze palsy, Muscle spasms, Skin discolouration, Musculoskeletal stiffness, Sensation of pressure, Asthenia, Hypopnoea, Pyrexia, Mood altered	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	4 Months Female		Infanrix hexa, Rotavirus vaccine, Pneumococcal vaccines (Non-GSK), Topiramate	2	D-fluoretten	15 Days	Epilepsy, Partial seizures, Eye movement disorder, Depressed level of consciousness, Retching, Oral disorder, Psychomotor skills impaired, Metabolic acidosis, Hypocitraturia, Gaze palsy, Tardive dyskinesia, Hypotonia, Joint hyperextension, Hypertonia, Visual acuity reduced, Polymicrogyria, Apathy, General physical health deterioration, Oligodipsia, Choking, Nystagmus, Pyrexia, Rash, Blindness cortical	Serious	Unknown
	9 Weeks Male	Menkes' syndrome, Epilepsy, Blindness cortical, Deafness, Mental retardation, Crying, Life expectancy shortened	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			2 Days	Gaze palsy, Epilepsy, Agitation, Pyrexia, Crying	Serious	Resolved
	9 Weeks Female		Infanrix hexa, Synflorix	1	Vitamin D	7 Hours	Convulsion, Syncope, Crying, Gaze palsy, Cyanosis, Pallor, Hypotonia, Fatigue, Listless, Loss of consciousness	Serious	Resolved
	14 Months Male		Infanrix hexa, Meningococcal polysaccharide vaccine group C (Non-GSK)	4		0 Days	Febrile convulsion, Pyrexia, Grand mal convulsion, Muscle twitching, Salivary hypersecretion, Gaze palsy, Listless, Unresponsive to stimuli, Tachycardia, Agitation, Crying	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	20 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Status epilepticus, Febrile convulsion, Grand mal convulsion, Gaze palsy, Depressed level of consciousness, Upper respiratory tract infection, Pyrexia, Heart rate increased, Crying, Somnolence, Hypertonia, Pharyngeal erythema	Serious	Unknown
	15 Months Female	Premature baby, Sleep apnoea syndrome, Bradycardia, Respiratory disorder	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		Hours	Febrile convulsion, Grand mal convulsion, Gaze palsy, Vomiting, Pyrexia, General physical health deterioration	Serious	Resolved
	6 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		1 Days	Convulsion, Gaze palsy	Serious	Resolved
	24 Months Female	Respiratory tract infection	Infanrix hexa			3 Hours	Convulsion, Gaze palsy, Unresponsive to stimuli, Hypotonia, Pallor, Hypotonic-hyporesponsive episode	Serious	Resolved
	15 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	4		1 Days	Febrile convulsion, Pyrexia, Fluid intake reduced, Decreased appetite, Rhinitis, Upper respiratory tract infection, Muscle twitching, Hypotonia, Gaze palsy, Breath sounds abnormal, Fatigue, Somnolence, Crying, Diarrhoea, Cough, Loss of consciousness, Cyanosis	Serious	Resolved
	18 Months Male		Infanrix hexa	4	Infanrix hexa	2 Days	Febrile convulsion, Pyrexia, Eye movement disorder, Gaze palsy	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	5 Months Male	Neonatal aspiration, Sepsis neonatal, Streptococcal infection, Retinal haemorrhage, Fever neonatal	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	32 Days	Convulsion, Partial seizures, Hypotonia, Eye movement disorder, Gaze palsy, Bruxism, Unresponsive to stimuli, Oxygen saturation decreased, Cyanosis, Abnormal faeces, Faeces discoloured, Pyrexia, Atonic seizures, Depressed level of consciousness, Neutropenia, Hypertonia, Muscle rigidity	Serious	Unresolved
	9 Weeks Female	Jaundice neonatal, Familial risk factor, Foetal monitoring abnormal	Infanrix hexa, Pneumococcal vaccines (Non-GSK), Rotavirus vaccine (Non-GSK)	1	Zymafluor D	1 Days	Sudden infant death syndrome, Febrile convulsion, Cardiac arrest, Pyrexia, Gaze palsy, Cyanosis, Epistaxis	Serious	Fatal
	4 Months Female	Viral upper respiratory tract infection	Infanrix hexa, Pneumococcal vaccines (Non-GSK)			1 Days	Grand mal convulsion, Epilepsy, Restlessness, Respiration abnormal, Hypertonia, Myoclonus, Gaze palsy, Muscle tightness, Hypotonia, Listless, Salivary hypersecretion, Pyrexia	Serious	Resolved
	4 Weeks Female	Kinematic imbalances due to suboccipital strain, Fluid intake reduced, Gastroenteritis norovirus, Pharyngitis, Infection, Streptococcal infection, Umbilical cord around neck, Torticollis	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Rotavirus vaccine (Non-GSK)	0 Months	Aggression, Developmental delay, Screaming, Head injury, Sleep disorder, Nervousness, Opisthotonus, Meningitis, Movement disorder, Convulsion, Gastrointestinal disorder, Hypermobility syndrome, Cardiovascular disorder, Gaze palsy, Vomiting, Pyrexia, Muscle disorder, Condition aggravated	Serious	Unknown

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	16 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3		1 Days	Febrile convulsion, Pyrexia, Fatigue, Food aversion, Vomiting, Grand mal convulsion, Opisthotonus, Gaze palsy, Cyanosis, Gastroenteritis viral, Rhinitis, Hyponatraemia, Diarrhoea, Abnormal faeces	Serious	Resolved
	4 Months Female	Developmental delay, Antidiuretic hormone abnormality, Hypotonia, Weight gain poor, Hypersomnia, Hospitalisation, Blood sodium increased, Blood chloride increased, Gastroenteritis, Flatulence, Fluid retention	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		3 Days	Infantile spasms, Opisthotonus, Gaze palsy, Cognitive disorder, Musculoskeletal stiffness, Crying, Haemangioma	Serious	Unresolved
	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		1 Days	Convulsion, Pyrexia, Gaze palsy, Dyskinesia, Unresponsive to stimuli	Serious	Resolved
	2 Months Male	Nervousness, Crying, Dyskinesia, Oligodipsia, Heat stroke, Dehydration, Hyperthermia	Synflorix, Infanrix hexa, Rotavirus vaccine	1		1 Days	Clonic convulsion, Gaze palsy, Cyanosis, Diarrhoea, Pyrexia, Hypotonia, Pallor	Serious	Resolved

Case ID + Country Of Reporter	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Seriousness	Case Outcome
[redacted]	16 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK), Priorix Tetra	4		1 Days	Partial seizures, Infective myositis, Encephalopathy, Developmental delay, Amaurotic familial idiocy, Mitochondrial cytopathy, Blood creatine phosphokinase increased, Pyrexia, Hemiplegia, Restlessness, Unresponsive to stimuli, Gaze palsy, Tremor, Gastroenteritis norovirus, Iron deficiency anaemia, Hearing impaired, Hypotonia	Serious	Unresolved
	8 Weeks Male	Familial risk factor, Gastroenteritis	Infanrix hexa, Rotavirus vaccine, Pneumococcal vaccines (Non-GSK)	1		Hours	Convulsion, Partial seizures, Convulsions local, Gaze palsy, Pachygyria, Polymicrogyria, Microcephaly, Methylmalonic aciduria, Vitamin B12 deficiency, Metabolic disorder, Myoclonus, Plagiocephaly, Subdural hygroma	Serious	Unknown

APPENDIX 7B.11 : Haematochezia

Vaccines Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Infanrix hexa: Haematochezia

Date of review	11 November 2013
Vaccine terms included	Infanrix hexa (combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and *Haemophilus influenzae* type b vaccine) GSK drug code: IGA182
Adverse events (MedDRA preferred terms) included	Chronic gastrointestinal bleeding Diarrhoea haemorrhagic Gastrointestinal haemorrhage Haematochezia Intestinal haemorrhage Intra-abdominal haemorrhage Large intestinal haemorrhage Lower gastrointestinal haemorrhage Melaena Melaena neonatal Neonatal gastrointestinal haemorrhage Rectal haemorrhage Upper gastrointestinal haemorrhage
Authors	[redacted]afety Scientist) [redacted]Safety Physician)

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LIST OF ABBREVIATIONS

AE	Adverse event
HHE	Hypotonic-hyporerspnsive episode
HLT	Higher level Term
MedDRA	Medical Dictionary for Regulatory Activities
PSUR	Periodic Safety Update Report
PT	Preferred term
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
RSI	Reference Safety Information

1. BACKGROUND

1.1. Indication

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b. The primary vaccination schedule consists of three or two doses during the first 6 months of age. After a vaccination with 2 doses (e.g. 3, 5 months) a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age. After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) of Infanrix hexa a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

1.2. Regulatory request

In the context of periodic aggregate safety reports, the Company first described events of haematochezia in PSUR (periodic safety update report) No 14 (covering the period between 23 October 2008 and 22 October 2009). Since then haematochezia has been routinely described in periodic Infanrix hexa PSURs. In PSUR 14 the following case was reported:

- [redacted] **Haematochezia, Iron deficiency, Stool analysis abnormal**

  This case was reported by a physician and described the occurrence of bloody stools in a 3-month-old female who was vaccinated with a first dose of Infanrix hexa on 21 November 2008. At unknown date, a pneumococcal vaccine (Prevenar, Other) was coadministrated with an Infanrix hexa. The subject did not receive a rotavirus vaccine. As of 23 November 2008, two days after vaccination with Infanrix hexa, the subject experienced intermittent episodes of bloody stools. Local examination (not otherwise specified) was normal. After an unspecified time, the event improved. In January 2009, the subject received a second dose of Infanrix hexa. In January 2009, an unspecified time after the second vaccination with Infanrix hexa, bloody stool episodes increased (positive rechallenge). Blood occurred only at defecation. Bloody stools were not associated with constipation, diarrhea, abdominal pain or intestinal invagination. Bowel movement was normal. The subject had a normal weight and height growth. At an unspecified date, allergological test to cow's milk proteins was negative. Stool culture was negative. Stool analysis was positive for alpha-tumor necrosis factor and of alpha-1 antitrypsin (coded stool analysis abnormal). Blood albumin and C reactive protein were normal. Blood iron was slightly decreased (coded iron deficiency) without anemia. A coloscopy was not performed. At the time of the initial report, the event was unresolved; at the time of the follow-up report the outcome of the events was unspecified, the physician had not seen the child again. The physician reported a few other similar cases without causality relationship demonstrated.

  Company comment: This case described a patient who presented bloody stools after vaccination with the first and second dose Infanrix hexa. There is a temporal association to vaccination. The presence of alpha-tumour necrosis factor indicates intestinal inflammation; most likely the child presented a gastrointestinal condition

that caused the events described. A causal role of the vaccinations is however considered unlikely due to the type and nature of this event.

In the assessment report of PSUR 14, the European Medicine Agency (EMA) made the following comment and request:

In this case, there is a positive rechallenge. The TTO after the 2nd dose of infanrix hexa and the event is not known. Haematochezia should be monitored in the next PSUR.

1.3. Reference safety information

Haematochezia is not listed in the Infanrix hexa reference safety information (RSI); however it is listed in the RSI of rotavirus vaccines.

1.4. Haematochezia definition and aetiology

Haematochezia is the passage of fresh blood through the anus, usually in or with stools. Haematochezia is commonly associated with lower gastrointestinal bleeding in contrast to Melaena i.e. black faeces that are associated with upper gastrointestinal haemorrhage; the black colour being caused by oxidation of the iron in haemoglobin during its passage through the ileum and colon. In babies, haematochezia in conjunction with abdominal pain is associated with intussusception.

1.5. Haematochezia in MedDRA

Preferred terms (PTs) that might be indicative of haematochezia where identified in three different HLT (high level term) groups. Table 1 shows the PTs included in these three HLTs (MedDRA version 16.1). The 13 PTs considered indicative of haematochezia and thus retained for the present evaluation are highlighted in bold italic font.

Table 1 PTs retained for the present evaluation (bold italic)

MedDRA HLT	MedDRA PT
Intestinal haemorrhages	Anal haemorrhage
	Colonic haematoma
	Intestinal haematoma
	Intestinal haemorrhage
	Large intestinal haemorrhage
	Mesenteric haematoma
	Mesenteric haemorrhage
	Portal hypertensive enteropathy
	Rectal haemorrhage
	Small intestinal haemorrhage
Non-site specific gastrointestinal haemorrhages	***Chronic gastrointestinal bleeding***
	Gastrointestinal haemorrhage
	Haematemesis
	Haematochezia
	Intra-abdominal haemorrhage
	Lower gastrointestinal haemorrhage
	Melaena
	Melaena neonatal
	Neonatal gastrointestinal haemorrhage
	Upper gastrointestinal haemorrhage
Diarrhoea (excl infective)	Diarrhoea
	Diarrhoea haemorrhagic
	Diarrhoea neonatal

This is a cumulative evaluation of data from spontaneous reporting sources on haematochezia following administration of Infanrix hexa.

2. POST-MARKETING EXPOSURE TO VACCINE

Infanrix hexa was first approved in European Union on 23 October 2000 (centralized procedure) and is currently licensed in 95 countries (extracted from PSUR No 17, data lock point 22 October 2012). Since launch, more than 100 million doses of Infanrix hexa were distributed worldwide. As vaccination with Infanrix hexa varies between one and four doses per subject, post-marketing exposure to Infanrix hexa since launch until the data lock point of this evaluation (24 October 2013) is estimated as being between 25 and 100 million subjects.

3. SAFETY DATA REVIEWED

This evaluation presents relevant information on reports of haematochezia from the GSK worldwide safety database.

3.1. Database Search Strategy

The GSK worldwide safety database was searched on 12 November 2013 using the following criteria:

- **Data lock point**: since marketing launch until 11 November 2013

- **Report types**: All spontaneous reports
- **Suspect drug**: Infanrix hexa
- **MedDRA PTs**: Intestinal haemorrhage, Large intestinal haemorrhage, Rectal haemorrhage, Chronic gastrointestinal bleeding, Gastrointestinal haemorrhage, Haematochezia, Intra-abdominal haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Melaena neonatal, Neonatal gastrointestinal haemorrhage, Upper gastrointestinal haemorrhage, Diarrhoea haemorrhagic

Limitations to quantitative analysis of spontaneous reports
Post-marketing surveillance for suspected adverse reactions is required to characterise the full safety profile of vaccines. Individual case safety reports are the primary source of information to detect potential risks in regular clinical practice. However such reports are anecdotal in nature and do not represent a random sample; they are not suitable as a basis for statistical inference, but statistical methods can provide real value in identifying outstanding reporting patterns for further investigation (signals) and in flagging reporting artefacts that may otherwise be misleading. Indeed invalid information may be generated because of several factors including: biased reporting, under-reporting, secular trends, media effects, missing or limited information, absence of case validation, absence of adequate comparator group.

3.2. Summary of Overall Dataset

A total of 67 cases including the PT haematochezia were retrieved from the GSK worldwide safety database. In 26 of these, a rotavirus vaccine was reported as co-suspect (25) or concomitant (1) vaccine (data not shown). Since haematochezia is a listed event for rotavirus vaccines, these 26 cases were not further analysed in the context of the present safety evaluation for haematochezia in association with Infanrix hexa.

Among the 41 remaining cases where rotavirus vaccine co-administration was not reported (see also APPENDIX 1):

- 25 (60.9%) had a healthcare professional as a report source.
- The majority were received from Germany (41.5%), France and Italy (14.6% each).
- 4 involved a positive re-challenge ([redacted])

The PTs indicative of haematochezia coded in these cases were Diarrhoea haemorrhagic, Gastrointestinal haemorrhage, Haematochezia, Melaena and Rectal haemorrhage. Further characteristics are summarised in Table 2. The median age (3 months) of subjects for which haematochezia was reported was in line with the indicated population (see Section 1). Haematochezia was reported slightly more frequently for boys than for girls. The median time-to-onset was within one day of vaccination and the most frequent outcome for these cases was 'resolved'. Most cases including at least one PT indicative of haematochezia were categorised as serious since Diarrhoea haemorrhagic, Gastrointestinal haemorrhage, Haematochezia, Melaena and Rectal haemorrhage are considered important medical events (IMEs) by EMA. The reason why not all cases were coded as serious in the safety database is because the automated assessment of

seriousness was not implemented in GSK during the entire time period covered by the present evaluation.

Table 2 Summary of characteristics of cases including at least one PT indicative of haematochezia

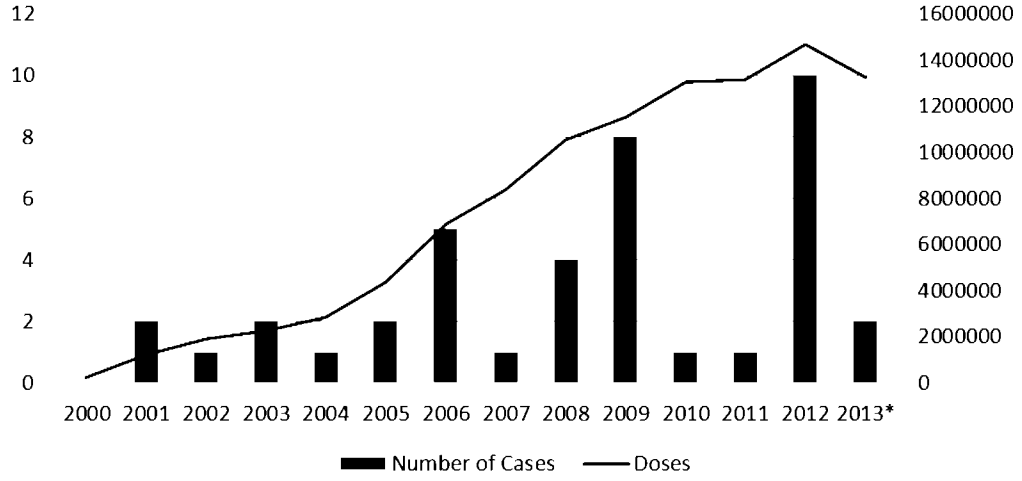
Patient Age	Median		3 months
	Range		2 - 13 months
	Unknown	n (%)	1 (2.4%)
Gender	Female	n (%)	18 (43.9%)
	Male	n (%)	23 (56.1%)
	Unknown	n (%)	0 (0.0%)
Time to onset since last dose	Median		1 Day
	Range		0 - 27 Days
	Unknown	n (%)	1 (2.4%)
Outcome	Fatal	n (%)	0 (0.0%)
	Improved	n (%)	2 (4.9%)
	Resolved	n (%)	24 (58.5%)
	Resolved with Sequelae	n (%)	1 (2.4%)
	Unknown (at the time of reporting)	n (%)	9 (22.0%)
	Unresolved	n (%)	5 (12.2%)
	Worse	n (%)	0 (0.0%)
Dose number*	1	n (%)	18 (40.0%)
	2	n (%)	12 (26.7%)
	3	n (%)	5 (11.1%)
	4	n (%)	1 (2.2%)
	Unknown	n (%)	9 (20.0%)
Cases classified as serious		n (%)	35 (85.4%)

In 4 cases haematochezia was reported twice, following 2 different doses; therefore the total number of doses is 45

3.3. Reporting trends over time

The blue line and the right vertical axis in Figure 1 show the evolution of the worldwide distribution of Infanrix hexa doses per calendar year, while the red bars and the left vertical axis represent the distribution of the 41 haematochezia cases (where no rotavirus vaccine was co-reported) retrieved by the above search per calendar year[1], and for which a haematochezia onset date was reported. Overall, the increased trend in yearly case reporting followed the increase of sales over time. Reporting peaks were observed every three years in 2006, 2009 and 2012. Note that the data for 2013 only covers months January to 11 November and is therefore incomplete compared to the previous years.

Figure 1 Yearly Infanrix hexa sales and number of spontaneous cases including at least one PT indicative of haematochezia

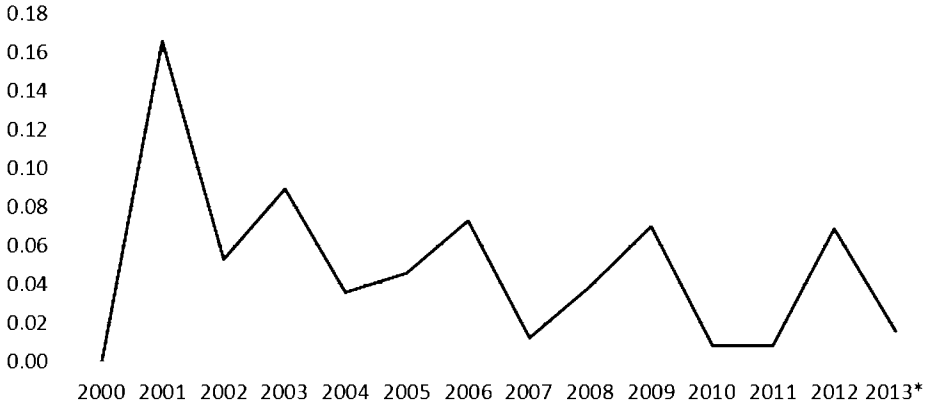


*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

[1] The reporting date used was the haematochezia onset date, not the case receipt date because for spontaneous cases there might be a long delay between event onset and reporting to GSK. Out of the 41 haematochezia cases, onset date was missing for 1 of them.

Figure 2 shows the yearly reporting frequency for haematochezia over time[1] expressed in number of cases per 100 000 doses distributed. The reporting frequency stabilized between 0.01 and 0.07 cases per 100 000 doses distributed since 2004. Higher fluctuations were observed during the first years following marketing due to lower sales volumes at that time. No increased reporting trend was observed over the past 14 years.

Figure 2 Yearly and cumulative reporting frequency in number of cases per 100 000 doses distributed



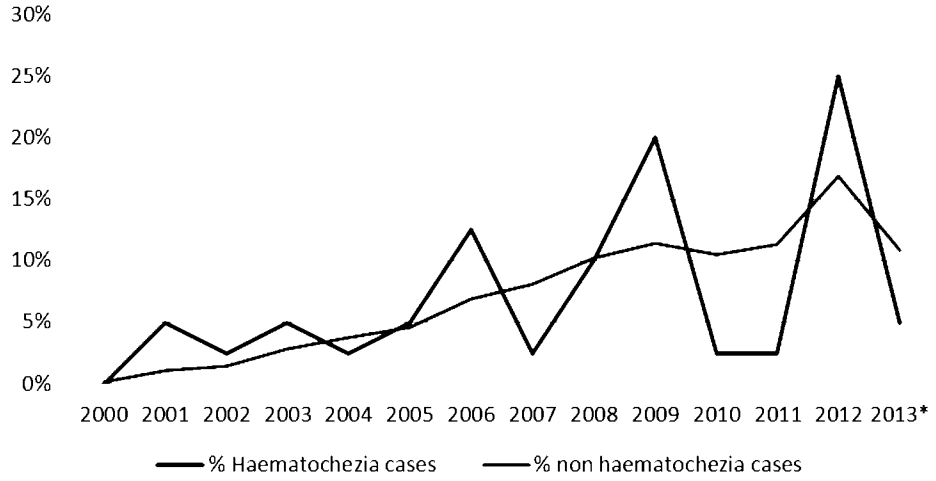
*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

The comparison of haematochezia reporting with sales data has limitations since the time between dose distribution and actual vaccine administration is unknown. Also, the efficiency of the spontaneous reporting system varies in the different countries where Infanrix hexa is distributed. In order to correct for these limitations, the yearly[1] proportion of haematochezia cases among the 41 haematochezia cases was plotted in Figure 3 (red line) and compared to the yearly[2] proportion of non-haematochezia cases among all[3] non- haematochezia cases (green line). This approach allows visualizing whether, at some point in time, more haematochezia cases were received compared to other cases received for Infanrix hexa, while taking into account changes in reporting trends (e.g. following marketing in a high reporting country). The fact that proportion of haematochezia cases crossed several times the proportion of non- haematochezia cases in Figure 3 suggests that there was no disproportionate reporting of haematochezia since the past 14 years; and that the changes in reporting trends observed in Figure 1 and Figure 2 were random fluctuations.

[2] For non-haematochezia cases, the case onset date, which is the date of occurrence of the first event of the case, was used as reporting date.

[3] Case onset date was reported for 16088 non-gaze palsy cases.

Figure 3 **Proportion of cases including at least one PT indicative of haematochezia *versus* cases not including any PT indicative of haematochezia reported for Infanrix hexa over time**



*The data for 2013 only covers months January to October and is therefore incomplete compared to the previous years

3.4. Medical evaluation

Among the 41 cases including at least on PT indicative of haematochezia, 14 were reported with insufficient clinical evidence to relate haematochezia to vaccination, 20 were reported with more plausible causes of haematochezia/melaena than vaccination such as symptoms/signs/indications (pyrexia, vomiting, diarrhoea with or without blood and/or mucus, anti-diarrhoeic medication) of a concurrent infection, gastroenteritis, enteritis, rotavirus infection, intussusception, allergic colitis, other gastrointestinal condition (indicated by the presence of alpha-tumour necrosis factor), or haematochezia/ melaena occurred already before vaccination. In eight (8) cases the reporter considered the haematochezia/melaena unrelated to vaccination. Three (3) cases described rectal haemorrhages (rather than haematochezia) likely to have been caused by concomitantly reported idiopathic thrombocytopenic purpura (IPT) or autoimmune thrombocytopenia. These cases are identified in Table 3. Note that four cases ([redacted], [redacted], [redacted] and [redacted]) matched two of these assessments simultaneously.

Table 3 Medical assessments by case ID

Medical assessment	Case ID
Insufficient clinical evidence to relate haematochezia to vaccination	[redacted]
Other more likely causes co-reported: symptoms/signs/indications (pyrexia, vomiting, diarrhoea with or without blood and/or mucus, anti-diarrhoeic medication) of a concurrent infection, gastroenteritis, enteritis, rotavirus infection, intussusception, allergic colitis, other gastrointestinal condition (indicated by presence of alpha-tumour necrosis factor), or haematochezia/melaena occurred already before vaccination	[redacted]
Reporter considered the haematochezia/melaena **unrelated** to vaccination	[redacted]
Cases describing rectal haemorrhages (rather than haematochezia) likely to have been caused by concomitantly reported idiopathic thrombocytopenic purpura (IPT) or autoimmune thrombocytopenia	[redacted]

*Involved positive re-challenge

4. DISCUSSION AND CONCLUSION

Haematochezia is the passage of fresh blood through the anus, usually in or with stools. Haematochezia is commonly associated with lower gastrointestinal bleeding. In babies, haematochezia in conjunction with abdominal pain is associated with intussusception.

The biological plausibility for an injectable (intramuscular) vaccine such as Infanrix hexa to cause a gastrointestinal event such as haematochezia is low. In line with this is the high proportion of cases (77.5%) which were co-reported with other more likely causes of haematochezia, considered unrelated to vaccination by the reporter, or didn't describe true haematochezia. The remaining cases included insufficient clinical evidence to relate haematochezia to vaccination. The four cases involving positive re-challenges were all part of those co-reported with other more likely causes of haematochezia.

During the past 14 years the reporting frequency did not tend to increase or decrease beyond random fluctuations.

Data currently available to GSK, including the limitations of this evaluation (see Section 3.1), suggest there is no increased risk of haematochezia following vaccination with Infanrix hexa. GSK will no longer routinely describe haematochezia in future Infanrix hexa aggregate safety reports.

GSK will continue to employ a routine, pro-active process for identifying safety signals with three main components:

1. Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
2. Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
3. Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

APPENDIX 1 - LINE LISTING OF HAEMATOCHEZIA CASES WHERE ROTAVIRUS VACCINE WAS NOT ADMINISTERED (N=41)

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 02Dec2004	3 Months Male		Infanrix hexa	2	Infanrix hexa	3 Days	Haematochezia	[redacted]	Not serious	Resolved
[redacted] 10Nov2005	Infant Male		Infanrix hexa			Unknown	Diarrhoea haemorrhagic		Serious	Unknown
[redacted] 14Jun2006	13 Months Female		Infanrix hexa			2 Days	Diarrhoea haemorrhagic, Decreased appetite, Irritability, Diarrhoea		Serious	Resolved
[redacted] 09May2007	11 Months Male		Infanrix hexa	1 and 2		7 Days and Unknown	Diarrhoea haemorrhagic, Diarrhoea		Serious	Resolved
[redacted] 09Feb2009	4 Months Female		Infanrix hexa			1 Days	Diarrhoea haemorrhagic, Vomiting, Diarrhoea, Pyrexia, Ill-defined disorder		Serious	Resolved
[redacted] 25Feb2009	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1 and 2		2 Days and unkown	Haematochezia, Iron deficiency, Stool analysis abnormal		Not serious	Unknown
[redacted] 06Oct2009	6 Months Male	Premature baby	Infanrix hexa	3		1 Days	Diarrhoea haemorrhagic		Serious	Unknown
[redacted] 12Oct2009	11 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			2 Days	Melaena		Serious	Resolved
[redacted] 11Dec2009	3 Months Male	Gastroenteritis	Infanrix hexa	2		0 Days	Haematochezia, Diarrhoea, Pyrexia		Not serious	Resolved

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 21Dec2009	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Infanrix-polio-HIB	0 Days	Idiopathic thrombocytopenic purpura, Haematoma, Rectal haemorrhage, Purpura	[redacted]	Serious	Resolved
[redacted] 07Jan2010	2 Months Male		Infanrix hexa			0 Days	Melaena, Oesophagitis, Pyrexia, Vomiting, Irritability		Serious	Resolved
[redacted] 17Aug2010	2 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		2 Days	Rectal haemorrhage, Abdominal pain, Haematochezia		Serious	Resolved
[redacted] 21Sep2011	2 Months Male	Milk allergy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Neocate	0 Days	Rectal haemorrhage		Serious	Resolved
[redacted] 03Sep2012	2 Months Male		Infanrix hexa, Synflorix	1		36 Hours	Haematochezia, Injection site inflammation		Serious	Resolved
[redacted] 03Sep2012	2 Months Female		Infanrix hexa, Synflorix	1		3 Days	Haematochezia, Pyrexia		Serious	Resolved
[redacted] 26Oct2012	Infant Female		Infanrix hexa			0 Days	Drug eruption, Restlessness, Abdominal pain, Diarrhoea, Haematochezia, Mucous stools, Crying		Serious	Resolved
[redacted] 28Oct2012	6 Months Female	Milk allergy, Food allergy	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		6 Hours	Haematochezia, Generalised oedema, Pyrexia		Serious	Improved

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 02Nov2012	2 Months Female		Infanrix hexa	1		10 Hours	Milk allergy, Haematochezia, Gastroenteritis, Diarrhoea, Vomiting, Abdominal pain, Decreased appetite, Agitation, Somnolence, Lethargy, Weight decreased, Restlessness, Crying	[redacted]	Serious	Resolved
[redacted] 22Oct2012	4 Months Female		Infanrix hexa	2		0 Days	Enteritis, Diarrhoea haemorrhagic		Serious	Unknown
[redacted] 29Nov2012	2 Months Male	Bronchiolitis, Stridor, Congenital tracheomalacia, Gastrooesophageal reflux disease, Takayasu's arteritis, Surgery, Chest discomfort	Infanrix-polio-HIB, Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1	Esomeprazole	2 Days	Idiopathic thrombocytopenic purpura, Rectal haemorrhage, Haemoptysis, Petechiae, Epistaxis, Pallor		Serious	Resolved
[redacted] 27Nov2012	3 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)			0 Days	Urinary tract infection, Neutropenia, Milk allergy, Enterocolitis, Haematochezia, Diarrhoea, Somnolence, Vomiting, Dehydration		Serious	Resolved with Sequelae
[redacted] 13Dec2012	Infant Female	Lactose intolerance, Milk allergy, Gastrooesophageal reflux disease, Hypersensitivity	Infanrix-polio-HIB, Infanrix hexa	1	Domperidone	0 Days	Diarrhoea haemorrhagic, Diarrhoea		Serious	Resolved

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 31Dec2012	6 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)		Infanrix-polio-HIB, Pneumococcal vaccines (Non-GSK)	1 Days	Viral infection, Haematochezia, Rash erythematous, Rash maculo-papular, Faeces hard, Hyperaemia	[redacted]	Serious	Resolved
[redacted] 06Jun2013	12 Months Female	Lip oedema, Milk allergy, Diarrhoea haemorrhagic	Infanrix hexa	4	Infanrix hexa	2 Days	Diarrhoea haemorrhagic, Hypersensitivity, Product quality issue		Serious	Resolved
[redacted] 02Oct2001	3 Months Male		Infanrix hexa	1 and 2		7 Days and 3 Days	Enteritis, Haematochezia		Not serious	Resolved
[redacted] 24Oct2001	5 Months Male		Infanrix hexa	1		2 Days	Diarrhoea haemorrhagic, Pyrexia, Crying, Decreased appetite, Fatigue, Restlessness		Serious	Unknown
[redacted] 30Oct2002	Male		Infanrix hexa	1		2 Days	Rash, Diarrhoea haemorrhagic		Not serious	Unknown

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 04Nov2003	2 Months Female	Tobacco user, Alcohol use	Infanrix hexa	1		Same day	Cytomegalovirus infection, Pyrexia, Pallor, Hypotension, Tachypnoea, General physical health deterioration, Gaze palsy, Tachycardia, Hypotonia, Anuria, Transaminases increased, Disseminated intravascular coagulation, Haemolysis, Haematochezia, Hyperkalaemia, Thrombocytopenia, Petechiae, Pneumonia aspiration, Rales, Enteritis, Abdominal distension, Faeces discoloured, Brain injury, Motor dysfunction, Clonus	[redacted]	Serious	Unresolved
[redacted] 13Nov2003	3 Months Male		Infanrix hexa	1		Same day	Haematochezia		Not serious	Resolved
[redacted] 14Jun2005	3 Months Male	Pneumonia	Infanrix hexa	1 and 3	Infanrix hexa	1 Day and 1 Day	Diarrhoea haemorrhagic, Enteritis infectious, Viral test positive, Adenovirus infection, Restlessness, Gastroenteritis norovirus, Dermatitis diaper		Serious	Resolved
[redacted] 21Feb2006	3 Months Female	Blood bilirubin increased	Infanrix hexa	1		15 Days	Haematochezia, Transaminases increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Thrombocytosis		Serious	Improved

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 09May2006	5 Months Female		Infanrix hexa	3		12 Hours	Epilepsy, Convulsion, Breath sounds abnormal, Gaze palsy, Staring, Depressed level of consciousness, Muscle twitching, Salivary hypersecretion, Crying, General physical health deterioration, Diarrhoea, Gastroenteritis, Haematochezia, Bronchitis, Nausea, Vomiting	[redacted]	Serious	Unknown
[redacted] 15May2006	3 Months Male		Infanrix hexa			Unknown	Abscess, Oedema peripheral, Hyperaesthesia, Pyrexia, Restlessness, Bronchitis, Pneumonia, Abdominal pain, Haemorrhagic anaemia, Gastrointestinal haemorrhage		Serious	Unknown

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 31Jul2006	4 Months Female	Premature baby, Small for dates baby, Hospitalisation	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2		4 Days	Resuscitation, Systemic inflammatory response syndrome, Sepsis, Staphylococcal infection, Respiratory syncytial virus infection, Rotavirus infection, Disseminated intravascular coagulation, Thrombocytopenia, Anaemia, Pneumonia aspiration, Respiratory distress, Multi-organ failure, Renal failure acute, Acute hepatic failure, Hypertension, Cerebral hygroma, Atrial septal defect acquired, Cyanosis, Hypotonia, Haematochezia	[redacted]	Serious	Unresolved
[redacted] 05Jan2009	2 Months Male	Pallor, Iron deficiency anaemia, Breast feeding	Infanrix hexa	1	Ferrous glycine sulphate	3 Days	Thrombocytopenia, Granulocytopenia, Haematochezia, Abdominal discomfort		Serious	Unknown

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 08Jun2009	5 Months Male	Sick relative	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	3	Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1 Days	Viral infection, Gastroenteritis, Mucous stools, Haematochezia, Diarrhoea, Vomiting, Kawasaki's disease, Fluid intake reduced, Dehydration, Restlessness, Pyrexia, Eye discharge, Conjunctivitis, Rash, General physical health deterioration, Cough, Bronchitis, Pneumonia, Meningitis bacterial, Leukocytosis, Pain, Lymphadenopathy, Vasculitis, Coronary artery disease, Aneurysm	[redacted]	Serious	Unresolved
[redacted] 14Jul2009	4 Months Male	Respiratory disorder neonatal, Craniocerebral injury, Hospitalisation, Fall, Developmental coordination disorder	Infanrix hexa	2	Ergocalciferol, Infanrix hexa	3 Days	Autoimmune thrombocytopenia, Petechiae, Haematoma, Haematochezia, Mucosal haemorrhage, Conjunctival haemorrhage, Anaemia, Lymphadenopathy		Serious	Resolved

Case ID + Country + Company receipt date	Age + Gender	Medical Conditions PT Comma	Suspect Drugs PT Comma Sep	Dose No	Concurrent Drugs PT Comma Sep	Time To Onset Since Last Dose	Events PT Comma Sep	Haemato-chezia Onset Date	Serious-ness	Case Outcome
[redacted] 18Aug2009	4 Months Male		Synflorix, Infanrix hexa	3		6 Hours	Intussusception, Pyrexia, Faeces discoloured, Crying, Abnormal faeces, Haematochezia, Fatigue, Restlessness, Vomiting, Fluid intake reduced, Pallor, Fontanelle depressed, Abdominal pain, Tachycardia, Pain, Intestinal mucosal hypertrophy, Ascites, Abdominal lymphadenopathy	[redacted]	Serious	Resolved
[redacted] 13Aug2010	3 Months Male		Infanrix hexa, Synflorix	2		0 Days	Haematochezia, Mucous stools, Faeces discoloured, Crying		Serious	Resolved
[redacted] 26Apr2012	4 Months Male		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	2	Ergocalciferol	1 Days	Intussusception, Haematochezia, Abdominal rigidity, Intestinal obstruction, Lymphadenitis, Pyrexia, Abdominal pain, Umbilical hernia, Vomiting, Skin discolouration, General physical health deterioration		Serious	Unresolved
[redacted] 18Sep2013	3 Months Female		Infanrix hexa, Pneumococcal vaccines (Non-GSK)	1		10 Days	Haematochezia, Rectal discharge, Flatulence, Screaming, Restlessness, Blood immunoglobulin A decreased		Serious	Unresolved

APPENDIX 7B.12 : Injection site nodule

Vaccines' Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Infanrix hexa: Injection site nodule

Date of review	13 January 2015
Product Family	DTPa-HBV-IPV+Hib
Adverse events (MedDRA preferred terms) included	Application site nodule Injection site nodule Nodule Vaccination site nodule
Authors	[redacted] (Safety Physician) [redacted] Safety Scientist)

1. BACKGROUND

1.1. Indication

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b. The primary vaccination schedule consists of three or two doses during the first 6 months of age. After a vaccination with 2 doses (e.g. 3, 5 months) a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age. After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

1.2. Regulatory request

In the context of periodic aggregate safety reports, the Company first specifically described events of injection site nodule in PSUR (periodic safety update report) No 14 (covering the period between 23 October 2008 and 22 October 2009). Since then injection site nodule has been routinely described in periodic Infanrix hexa PSURs.

In the assessment report of PSUR 15-16, the European Medicine Agency (EMA) made the following comment and request:

The following adverse events of interest should be closely monitored and kept under review: (...) injection site nodule (...).

1.3. Reference safety information

Injection site nodule is not listed *per se* in the Infanrix hexa reference safety information (RSI); however injection site reactions in general (with a frequency of common, i.e. from ≥ 1/100 to < 1/10) are listed.

1.4. Clinical characteristics of injection site nodule

Published clinical characteristics of injection site nodules include: firmness, tenderness or pain, and pruritus. Nodules at injection site have also been described as being asymptomatic. There are several review papers about the role of aluminium salts in vaccines and the development of nodules at injection sites, especially when the vaccine is administered subcutaneously. [Rothstein, 2004] The Working Group of Brighton Collaboration for injection site reactions after vaccination agreed that the discrete (ie. well demarcated) clinical feature of a nodule at injection site sufficiently differentiates it from the more common clinical picture of acute induration and swelling, which are more diffuse and of shorter duration. The Working Group as well recognizes as well, that a nodule at injection site may progress to a sterile abscess.

Granuloma is a subcategory of a nodule at injection site. A biopsy of a nodule at injection site is not routinely necessary or recommended. Although to make a diagnosis of granuloma at injection site, it is needed to obtain histopathologic confirmation of granulomatous inflammation and granuloma, as well the histology will help to establish

the aetiology of different types of granuloma (ie. immune mediated, infectious, or foreign body).

2. EXPOSURE TO VACCINE

Infanrix hexa was first approved in European Union on 23 October 2000 (centralized procedure) and is currently licensed in 100 countries (extracted from the Infanrix hexa PBRER covering the reporting period from 23 October 2011 to 22 October 2014). Since launch, 120 million doses of Infanrix hexa were distributed worldwide. As vaccination with Infanrix hexa varies between one and four doses per subject, post-marketing exposure to Infanrix hexa since launch until the data lock point of this evaluation (22 October 2014) is estimated as being between 30 and 120 million subjects.

3. SAFETY DATA REVIEWED

3.1. Database Search Strategy

The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred terms (PTs)**: Application site nodule, Injection site nodule, Nodule, Vaccination site nodule

3.2. Summary of Overall Dataset

A total of 206 reports (cases) were retrieved from the GSK worldwide safety database. The PT Injection site nodule was reported in most (88%) of these cases, while the PTs Nodule (9%), Vaccination site nodule (3%) were rarely reported. Application site nodule was reported in none of these cases. Some of these cases have been reported as injection site nodule while medical review of the narratives rather suggests occurrence of injection site abscess.

The majority was received from France (30 %), Italy (19%), Germany (18%) and the Netherlands (15%).

Further characteristics are summarised in Table 1. The median age (1 year) of subjects for which injection site nodule was reported was in line with the indicated population (see Section 1.1). Injection site nodule was similarly reported for boys and girls. The median time-to-onset was 1 day. Among cases with a reported outcome, the outcome was resolved, resolved with sequelae or improved in 55% of cases and unresolved or worse in 45% of cases. 19% of these cases were serious. No new or unexpected information has been received with these cases.

Table 1 Summary of characteristics of cases including the PT Nodule, Injection site nodule or Vaccination site nodule (N=206)

Patient Age	Median		1 year	
	Range		7 weeks - 16 years	
	Unknown	n (%)	46	22%
Gender	Female	n (%)	90	44%
	Male	n (%)	95	46%
	Unknown	n (%)	21	10%
Time to onset since last dose	Median		3 Days	
	Range		Same day to 10 months	
	Unknown	n (%)	62	30%
Dose*	1	n (%)	38	18%
	2	n (%)	31	15%
	3	n (%)	46	22%
	4	n (%)	38	18%
	Unknown (at the time of reporting)	n (%)	38	18%
Outcome	Fatal	n (%)	0	0.0%
	Improved	n (%)	27	13%
	Resolved	n (%)	51	25%
	Resolved with Sequelae	n (%)	14	7%
	Unknown (at the time of reporting)	n (%)	38	18%
	Unresolved	n (%)	74	36%
	Worse	n (%)	1	0.5%
Cases classified as serious		n (%)	39	19%

* In 4 cases injection site nodule was reported twice, following 2 different doses; therefore the total number of doses is 210.

3.3. Reporting frequency over time

Figure 1 shows that the worldwide reporting frequency of cases including the PTs Injection site nodule, Nodule or Vaccination site nodule progressively increased from 0.11 cases per 100000 doses sold in 2005 to 0.25 in 2014, with a peak at 0.31 in 2012.

The analysis of respective contributions of the four countries from which most injection site nodule cases were reported shows mainly random variations over time. No consistent reporting tendency was observed among the four countries displayed.

The increase in the Netherlands in 2012 was one of the main triggers of the overall increase in 2012. However this increase was not specific to injection site nodule as all events reported from the Netherlands increased in 2012 (Figure 2). This was due to the extension of the Dutch target population for Infanrix hexa vaccination from only children at risk for hepatitis B infection in 2006, to children with Down syndrome as of 2008 and finally to all new-borns as of 2011. Also, overall reporting in the Netherlands decreased again after 2013, which was expected in view of decreasing sales as of 2014 (data not shown).

Local reporting of injection site nodule in France, Italy and Germany was not characterised by any increased tendency when compared to reporting of other events (Figure 2). Reporting of injection site nodule varied above and below the reporting of other cases, suggesting random variations.

Figure 1 **Yearly reporting frequency for cases including the PTs Injection site nodule, Nodule or Vaccination site nodule, and respective contributions of the four countries from which most cases were reported**

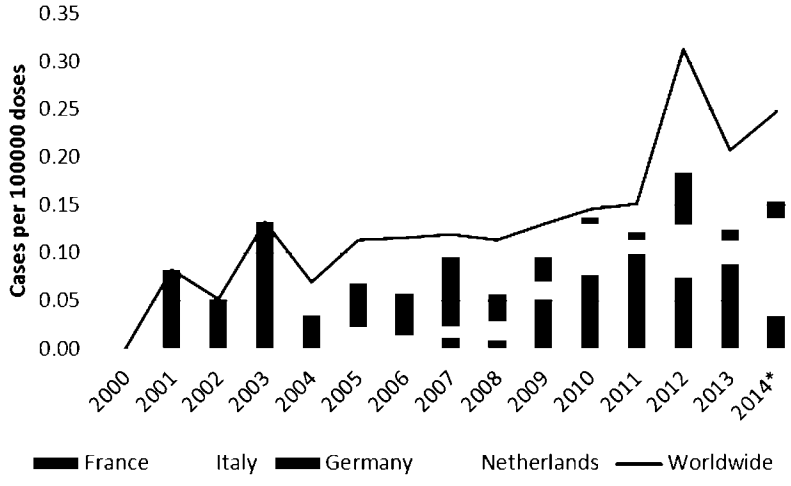
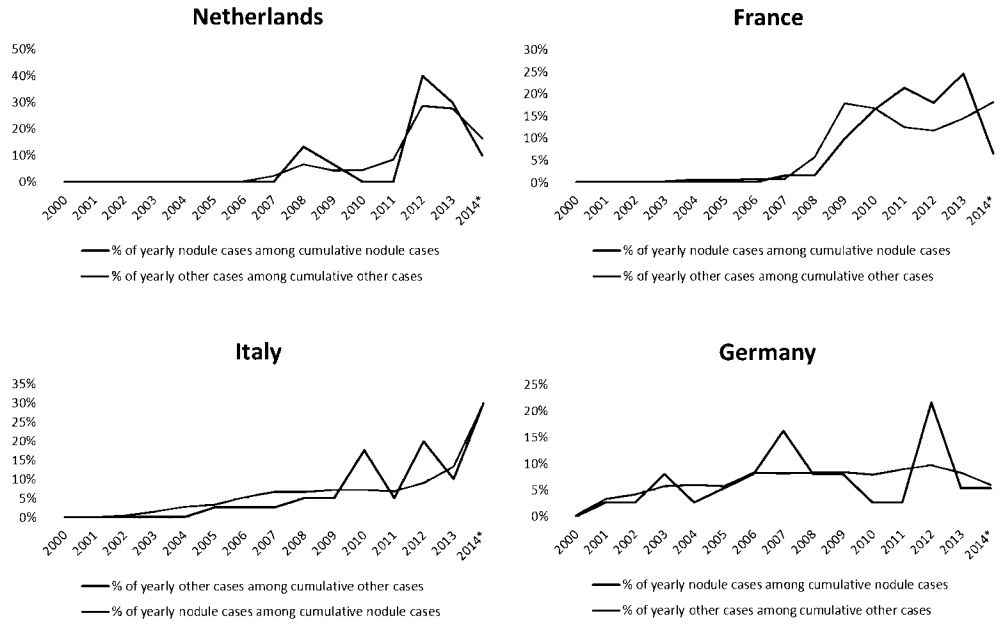


Figure 2 **Proportion of cases including the PTs Injection site nodule, Nodule or Vaccination site nodule versus non-nodule cases reported for Infanrix hexa over time in the Netherlands, France, Italy and Germany**



4. CONCLUSION

Data currently available to GSK suggest that injection site nodule is very rarely associated with Infanrix hexa vaccination. The highest yearly reporting frequency observed was 3 reports per 1 million doses sold (in 2012). The pathophysiology of the large local reactions seen after (primary or booster) injections of DTaP vaccine is probably multifactorial and may present a cumulative increased response to several component antigens [Plotkin, 2008] and the injection itself.

Injection site nodule is covered by vaccination site reactions which are listed in the Infanrix hexa RSI.

GSK will no longer routinely describe injection site nodule in future Infanrix hexa aggregate safety reports. GSK will continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.

- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

5. REFERENCES

Plotkin S, Orenstein W, Offit PA. Vaccines, 5th edition, Philadelphia: Saunders, 2008.

Rothstein E., Nodule at injection site as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation, Vaccine 22 (2004) 575–585

APPENDIX 7B.13 : Injection site abscess

Vaccines' Clinical Safety and Pharmacovigilance

Safety Evaluation and Risk Management

Infanrix hexa: Injection site abscess

Date of review	13 January 2015
Product Family	DTPa-HBV-IPV+Hib
Adverse events (MedDRA preferred terms) included	Abscess Abscess limb Abscess sterile Administration site abscess Application site abscess Injection site abscess Injection site abscess sterile Vaccination site abscess Vaccination site abscess sterile
Authors	[redacted] (Safety Physician) Safety Scientist)

1. BACKGROUND

1.1. Indication

Infanrix hexa is indicated for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and *Haemophilus influenzae* type b. The primary vaccination schedule consists of three or two doses during the first 6 months of age. After a vaccination with 2 doses (e.g. 3, 5 months) a booster dose must be given at least 6 months after the last priming dose, preferably between 11 and 13 months of age. After vaccination with 3 doses (e.g. 2, 3, 4 months; 3, 4, 5 months; 2, 4, 6 months) a booster dose may be given at least 6 months after the last priming dose and preferably before 18 months of age.

1.2. Regulatory request

In the context of periodic aggregate safety reports, the Company first specifically described events of injection site abscess in PSUR (periodic safety update reports) No 9 (covering the period between 23 October 2000 and 22 April 2005). Since PSUR No 11 (covering the period between 23 October 2005 and 22 October 2006) injection site abscess has been routinely described in periodic Infanrix hexa PSURs.

In the assessment report of PSUR 15-16, the European Medicine Agency (EMA) made the following comment and request:

The following adverse events of interest should be closely monitored and kept under review: (...) abscess and injection site abscess (...).

1.3. Reference safety information

Injection site abscess is not listed *per se* in the Infanrix hexa reference safety information (RSI); however injection site reactions in general (with a frequency of common, i.e. from ≥ 1/100 to < 1/10) are listed.

1.4. Clinical characteristics of injection site abscess

Abscess at an injection site involving a localized soft tissue collection of material at the site of immunization is a rare local reaction. Despite its rarity, the Brighton Collaboration Working Group developed standardized diagnostic criteria to guide appropriate public health interventions, in order to improve global comparability of vaccine safety data on abscess [Kohl , 2007]. The case definition is structured in several levels of diagnostic certainty and the guidelines are structured according to the steps of data collection, analysis and presentation.

The working group of Brighton Collaboration recognizes that in several health systems it is not possible to do a microbiological confirmation for cases of abscess. There is also general consideration that cases with sterile abscess can be considered under the same terminology, as it is difficult to distinguish practically among abscess due to infectious aetiology or sterile abscess, as the difference cannot always be made out of clinical symptoms. For example redness and tenderness, have been reported in sterile abscess and

in some infectious abscess, there is clinical representation of redness or warm around the injection site, i.e. the so called cold abscesses. The term 'sterile abscess' was also used when the patient was pre-treated with antibiotics prior to microbiological culture. By the time drainage is performed on an abscess, a prolonged inflammatory reaction may occur precluding the recovery of organisms. In addition, 'sterile abscess' is also used to describe an inflammatory delayed-type hypersensitivity reaction to one or more components of the vaccine, although limited data are availabe in the literature to support the aetiology [Kohl , 2007].

The Brighton Collaboration Working Group was aware of the potential overlap (both temporally and clinically) of signs and symptoms across the various local reactions, particularly with nodules, cellulitis or lymphangitis in the case of abscess.

It is general medical knowledge that any injection might lead to injection site abscess.

2. EXPOSURE TO VACCINE

Infanrix hexa was first approved in European Union on 23 October 2000 (centralized procedure) and is currently licensed in 100 countries (extracted from the Infanrix hexa PBRER covering the reporting period from 23 October 2011 to 22 October 2014). Since launch, 120 million doses of Infanrix hexa were distributed worldwide. As vaccination with Infanrix hexa varies between one and four doses per subject, post-marketing exposure to Infanrix hexa since launch until the data lock point of this evaluation (22 October 2014) is estimated as being between 30 and 120 million subjects.

3. SAFETY DATA REVIEWED

3.1. Database Search Strategy

The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred terms (PTs)**: Abscess, Abscess limb, Abscess sterile, Administration site abscess, Application site abscess, Injection site abscess, Injection site abscess sterile, Vaccination site abscess, Vaccination site abscess sterile

3.2. Summary of Overall Dataset

A total of 318 reports (cases) were retrieved from the GSK worldwide safety database. The PT Injection site abscess was reported in most (52%) of these cases, while the PTs Abscess (14%), Abscess sterile (8%), Injection site abscess sterile (8%), Vaccination site abscess (6%), Vaccination site abscess sterile (6%), Abscess limb (5%) and Application site abscess (1%) were rarely reported. Administration site abscess was reported in none of these cases.

The majority was received from Germany (61%) and the Netherlands (9%).

Further characteristics are summarised in Table 1. The median age (8 months) of subjects for which abscess was reported was in line with the indicated population (see Section 1.1). Abscess was similarly reported for boys and girls. The median time-to-onset was 45 days. Among cases with a reported outcome, the outcome was resolved, resolved with sequelae or improved in 77% of cases and unresolved or worse in 23% of cases. 71% of these cases were serious. No new or unexpected information has been received with these cases.

Table 1 Summary of characteristics of cases including the PTs Abscess, Abscess limb, Abscess sterile, Administration site abscess, Application site abscess, Injection site abscess, Injection site abscess sterile, Vaccination site abscess or Vaccination site abscess sterile (N=318)

Patient Age	Median		8 months	
	Range		1 month to 8 years	
	Unknown	n (%)	28	9%
Gender	Female	n (%)	156	49%
	Male	n (%)	144	45%
	Unknown	n (%)	18	6%
Time to onset since last dose	Median		45 Days	
	Range		Same day to 17 months	
	Unknown	n (%)	56	16%
Dose*	1	n (%)	37	11%
	2	n (%)	56	16%
	3	n (%)	117	34%
	4	n (%)	60	17%
	Unknown (at the time of reporting)	n (%)	75	22%
Outcome	Improved	n (%)	43	14%
	Not Recovered/Not Resolved	n (%)	4	1%
	Recovered/Resolved	n (%)	3	1%
	Resolved	n (%)	106	33%
	Resolved with Sequelae	n (%)	37	12%
	Unchanged	n (%)	1	0%
	Unknown	n (%)	73	23%
	Unresolved	n (%)	50	16%
	Worse	n (%)	1	0%
Cases classified as serious		n (%)	227	71%

* In 17 cases abscess was reported twice following 2 different doses, and 5 cases abscess was reported three times following 3 different doses; therefore the total number of doses is 345.

3.3. Reporting frequency over time

Figure 1 shows that, over the past 10 years, the worldwide reporting frequency of cases including the PTs Abscess, Abscess limb, Abscess sterile, Administration site abscess, Application site abscess, Injection site abscess, Injection site abscess sterile, Vaccination site abscess or Vaccination site abscess sterile was stable and varied between 0.15 and 0.35 cases per 100000 doses sold.

Figure 1 **Yearly reporting frequency for cases including the PTs Abscess, Abscess limb, Abscess sterile, Administration site abscess, Application site abscess, Injection site abscess, Injection site abscess sterile, Vaccination site abscess or Vaccination site abscess sterile**

4. CONCLUSION

Data currently available to GSK suggest that abscess is very rarely associated with Infanrix hexa vaccination. The highest yearly reporting frequency observed was 7 reports per 1 million doses sold (2003). The pathophysiology of the large local reactions seen after booster injections of DTaP vaccine is probably multifactorial and may present a cumulative increased response to several component antigens [Plotkin, 2008] and the injection itself.

Injection site abscess is covered by vaccination site reactions which are listed in the Infanrix hexa RSI.

GSK will no longer routinely describe injection site abscess in future Infanrix hexa aggregate safety reports. GSK will continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.

- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

5. REFERENCES

Kohl et al, Abcess at injection site: Case definition and guidelines for collection, analysis and presentation of immunization safety data, Vaccine 25, 5821-5838, 2007.

Plotkin S, Orenstein W, Offit PA. Vaccines, 5th edition, Philadelphia: Saunders, 2008.

APPENDIX 7B.14 : Anaemia haemolytic autoimmune and Haemolysis anemia

The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred terms (PTs)**: Autoimmune haemolytic anaemia, Haemolytic anaemia, Warm type haemolytic anaemia

A total of 13 reports (cases) were retrieved from the GSK worldwide safety database since launch in 2000, of which 5 were reported during the period between 23 October 2011 and 22 October 2014 (Table 1). In four of these cases, there was not enough clinical evidence to relate these events to vaccination with Infanrix hexa, and in one case [redacted] a mycoplasma infection was more likely to have caused autoimmune haemolytic anaemia.

Figure 1 shows that, since launch, the worldwide reporting frequency of cases including the PTs Autoimmune haemolytic anaemia, Haemolytic anaemia or Warm type haemolytic anaemia was stable and varied between 0.00 and 0.04 cases per 100000 doses sold. These variations result from the fact that very low numbers of cases were reported per year, i.e. between zero (e.g. in 2012) and 3 per year (only in 2014). Reporting frequency tendencies cannot reliably be interpreted based on such low numbers.

Figure 1 Yearly reporting frequency for cases including the PTs Autoimmune haemolytic anaemia, Haemolytic anaemia or Warm type haemolytic anaemia

*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

Table 1 **Line listing of cases including the PTs Autoimmune haemolytic anaemia, Haemolytic anaemia or Warm type haemolytic anaemia received during the period (N=5)**

Case ID, Age (years), Gender and Country	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Male	Physician		[Infanrix hexa]		[10PN-PD-Dit vaccine]	Haemolytic anaemia		Yes Unknown
[redacted] .5 Male	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	2	[Infanrix hexa], [Prevenar 13]	Haemolytic anaemia, Diarrhoea, Decreased appetite, Pallor, Gastric dilatation	12 Days	Yes Improved
[redacted] 3 Female	Regulatory Authority, Physician		[Rotarix liquid formulation], [Infanrix hexa], [Prevenar 13]	1		Haemolytic anaemia	4 Weeks	Yes Unknown
[redacted] .5 Male	Regulatory Authority, Other Health Professional, Physician		[Infanrix hexa], [Prevenar 13], [Paracetamol], [Lidocaine jelly]	3		Autoimmune haemolytic anaemia, Bladder fibrosis, Mycoplasma infection, Hypotonia, Fatigue, Jaundice, Pyrexia, Vomiting, Fluid intake reduced, General physical health deterioration, Heart rate increased	15 Days	Yes Unknown
[redacted] .92 Female	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Haemolytic anaemia	2 Days	Yes Resolved

Data currently available to GSK suggest there is no increased risk of autoimmune haemolytic anaemia following vaccination with Infanrix hexa.

GSK will continue to monitor and describe autoimmune haemolytic anaemia in future Infanrix hexa aggregate safety reports. GSK will also continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

APPENDIX 7B.15 : Thrombocytopenia, Thrombocytopenic purpura, Autoimmune thrombocytopenia and Idiopathic thrombocytopenic purpura

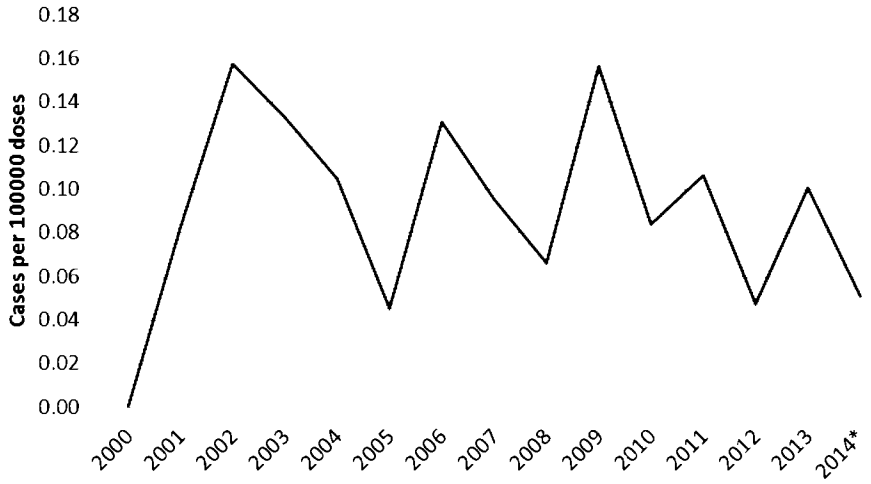
The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred terms (PTs)**: Immune thrombocytopenic purpura, Thrombocytopenia, Thrombocytopenia neonatal, Thrombocytopenic purpura

A total of 109 reports (cases) were retrieved from the GSK worldwide safety database since launch in 2000, of which 31 were reported during the period between 23 October 2011 and 22 October 2014 (Table 1).

Figure 1 shows that, since launch, the worldwide reporting frequency of cases including the PTs Immune thrombocytopenic purpura, Thrombocytopenia, Thrombocytopenia neonatal or Thrombocytopenic purpura was stable and varied between 0.04 and 0.16 cases per 100000 doses sold. In most cases there was not enough clinical evidence to relate the event to vaccination with Infanrix hexa. In some cases the causal relationship was confounded by other conditions (e.g. upper respiratory tract infection, viral illnesses).

Figure 1 **Yearly reporting frequency for cases including the PTs Immune thrombocytopenic purpura, Thrombocytopenia, Thrombocytopenia neonatal or Thrombocytopenic purpura**



*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

Data currently available to GSK suggest there is no increased risk of Thrombocytopenia, Thrombocytopenic purpura, Autoimmune thrombocytopenia[1] and Idiopathic thrombocytopenic purpura[1] following vaccination with Infanrix hexa.

GSK will continue to monitor and describe Thrombocytopenia, Thrombocytopenic purpura, Autoimmune thrombocytopenia[1] and Idiopathic thrombocytopenic purpura[1] in future Infanrix hexa aggregate safety reports. GSK will also continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

[1] In the current MedDRA version (v17.1), both Autoimmune thrombocytopenia and Idiopathic thrombocytopenic purpura are lower level terms (LLTs) mapping into the preferred term 'Immune thrombocytopenic purpura'.

Table 1 **Line listing of cases including the PTs Immune thrombocytopenic purpura, Thrombocytopenia, Thrombocytopenia neonatal, Thrombocytopenic purpura received during the period (N=31)**

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .92 Female [redacted]	28 Nov 11	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar]			Thrombocytopenic purpura, Thrombocytopenia, Ecchymosis, Contusion, Petechiae	9 Days	Yes Resolved
[redacted] .25 Male [redacted]	1 Jun 12	Physician, Consumer		[Infanrix hexa]	1		Death, Thrombocytopenia		Yes Fatal
[redacted] .17 Male [redacted]	7 Jun 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	1		Thrombocytopenia, Crying, Erythema, Peripheral swelling, Pyrexia, Rash, Skin discolouration		Yes Improved
[redacted] .42 Male [redacted]	29 Jun 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	2		Thrombocytopenic purpura, Thrombocytopenia, Petechiae	6 Days	Yes Resolved
[redacted] .33 UNK [redacted]	18 Sep 12	Regulatory Authority, Physician	Historical Condition: Varicella	[Infanrix hexa]	1		Thrombocytopenia, Petechiae	4 Days	Yes Improved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .17 Male [redacted]	29 Nov 12	Regulatory Authority	Current Condition: Bronchiolitis, Stridor, Congenital tracheomalacia, Gastrooesophageal reflux disease, Takayasu's arteritis, Surgery, Chest discomfort;Historical Condition:No adverse event	[Infanrixquinta], [Infanrix hexa], [Prevenar 13]	1	[Inexium]	Immune thrombocytopenic purpura, Rectal haemorrhage, Haemoptysis, Petechiae, Epistaxis, Pallor	2 Days	Yes Resolved
[redacted] .25 Male [redacted]	24 Jan 13	Physician, Consumer	Current Condition: Thrombocytopenic purpura	[Infanrix hexa], [RotaTeq]	1		Thrombocytopenic purpura, Skin haemorrhage	4 Days	Yes Resolved
[redacted] .33 Male [redacted]	27 Mar 13	Regulatory Authority, Physician		[Infanrix hexa]			Immune thrombocytopenic purpura, Petechiae, Thrombocytopenia	12 Days	Yes Resolved
[redacted] .5 Female [redacted]	12 Apr 13	Physician, Consumer		[Infanrix hexa]	3		Thrombocytopenic purpura		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .42 Male [redacted]	16 Apr 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Immune thrombocytopenic purpura, Petechiae, Haematoma		Yes Unknown
[redacted] 6 Female [redacted]	23 Apr 13	Physician, Consumer	Historical Drug: Infanrix hexa, Rotarix lyophilized formulation, Avaxim, Vaxigrip	[Infanrix hexa], [Rotarix lyophilized formulation], [Rouvax], [Avaxim], [Pentaxim], [Vaxigrip]	3		Immune thrombocytopenic purpura, Contusion, Dehydration	1885 Days	Yes Unknown
[redacted] .19 Female [redacted]	10 May 13	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Prevenar 13]			Immune thrombocytopenic purpura	14 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .15 Male [redacted]	12 Jul 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Petechiae, Thrombocytopenia	3 Days	Yes Unknown
[redacted] .92 Female [redacted]	26 Aug 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	4		Immune thrombocytopenic purpura, Petechiae, Haematoma	9 Days	Yes Resolved
[redacted] .42 Female [redacted]	1 Oct 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	2		Immune thrombocytopenic purpura, Petechiae, Haematoma, Thrombocytopenia	11 Days	Yes Resolved
[redacted] .25 Male [redacted]	10 Oct 13	Regulatory Authority	Current Condition: Rhinitis;Historical Condition: No adverse event	[Infanrix hexa], [Prevenar]			Immune thrombocytopenic purpura, Petechiae, Thrombocytopenia, Drug administered to patient of inappropriate age	14 Days	Yes Resolved
[redacted] 1.58 Female [redacted]	10 Oct 13	Regulatory Authority	Current Condition: Conjunctivitis	[Infanrix hexa], [Meningitec]		[Rifampicine]	Immune thrombocytopenic purpura, Incorrect route of drug administration	32 Days	Yes Improved
[redacted] .42 Male [redacted]	15 Oct 13	Regulatory Authority	Current Condition: Viral infection	[Infanrix hexa]		[Prevenar]	Immune thrombocytopenic purpura, Petechiae, Haematoma, Thrombocytopenia	1 Months	Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 17 Male [redacted]	21 Oct 13	Regulatory Authority	Current Condition:Ecchymosis, Acute lymphocytic leukaemia, Obesity	[Infanrix hexa]		[Hydrocortisone], [Diffu k]	Thrombocytopenia, Epistaxis, Off label use		Yes Unknown
[redacted] .17 UNK [redacted]	8 Nov 13	Physician, Consumer		[Infanrix hexa]		[Rotarix], [Pneumococcal vaccine]	Thrombocytopenic purpura	5 Days	Yes Resolved
[redacted] .25 Male [redacted]	14 Nov 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]			Petechiae, Thrombocytopenia	1 Weeks	No Unknown
[redacted] .08 Female [redacted]	30 Jan 14	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]			Thrombocytopenia	4 Days	No Resolved
[redacted] .29 Male [redacted]	28 Apr 14	Regulatory Authority, Other Health Professional		[Infanrix hexa]	2		Immune thrombocytopenic purpura	21 Days	Yes Improved
[redacted] 1.33 Female [redacted]	16 May 14	Regulatory Authority	Current Condition: Generalised tonic-clonic seizure, Varicella	[Infanrix hexa]			Pyrexia, Vomiting, Rash vesicular, Thrombocytopenic purpura, Neutropenia, Drug administered to patient of inappropriate age	1 Days	Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .17 Female [redacted]	16 Jun 14	Regulatory Authority	Current Condition: Premature baby, Cerebral dysgenesis, Single umbilical artery, Cytomegalovirus test positive, Atrophy, Inguinal hernia	[Infanrix hexa], [Infanrixquinta], [Prevenar 13]	1	[Ursolvan], [Levothyrox], [Tocopherol d-alpha]	Thrombocytopenia, Incorrect route of drug administration	9 Days	Yes Resolved
[redacted] .5 Male [redacted]	8 Jun 12	Physician	Historical Condition:Premature baby, Twin pregnancy, Hospitalisation; Current Condition: Naevus flammeus	[Infanrix hexa]			Respiratory arrest, Petechiae, Respiratory distress, Vasculitis, Thrombocytopenia, Gastroenteritis, Body temperature increased, Diarrhoea, Vomiting, Somnolence, Fluid intake reduced, Pallor, Rash, Lymphadenopathy	1 Days	Yes Unknown
[redacted] 2.17 Male [redacted]	6 Jul 12	Regulatory Authority		[Infanrix hexa]			Pneumonia, Immune thrombocytopenic purpura, Tachypnoea, Rales, Haematoma	5 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .92 Male [redacted]	29 Jan 13	Physician, Consumer	Historical Condition: Febrile infection	[Priorix Tetra], [Infanrix hexa]	4		Immune thrombocytopenic purpura, Thrombocytopenia, Petechiae, Haematoma, Platelet count decreased, Bleeding time prolonged	20 Days	Yes Resolved
[redacted] .92 Male [redacted]	8 Apr 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	4	[Infanrix hexa], [Prevenar 13]	Immune thrombocytopenic purpura	4 Days	Yes Unresolved
[redacted] .33 Female [redacted]	24 Sep 14	Physician, Consumer	Current Condition: Rhinitis	[Infanrix hexa], [Rotarix liquid formulation], [PREVENAR 13]	1	[D-FLUORETTEN], [VITAMIN K]	Thrombocytopenia, Autoimmune neutropenia, Petechiae, Haematoma, Muscle haemorrhage, Immune thrombocytopenic purpura, Mouth haemorrhage	47 Days	Yes Unknown
[redacted] .17 Female [redacted]	30 Sep 14	Physician	Historical Condition: Breech delivery, Premature baby, Hospitalisation	[Infanrix hexa]		[Hepatitis B vaccine], [BCG VACCINE]	Immune thrombocytopenic purpura, Neutropenia, Rash, Contusion, Mouth haemorrhage, Petechiae		Yes Recovered/Resolved

APPENDIX 7B.16 : Important neurological events (including encephalitis and encephalopathy)

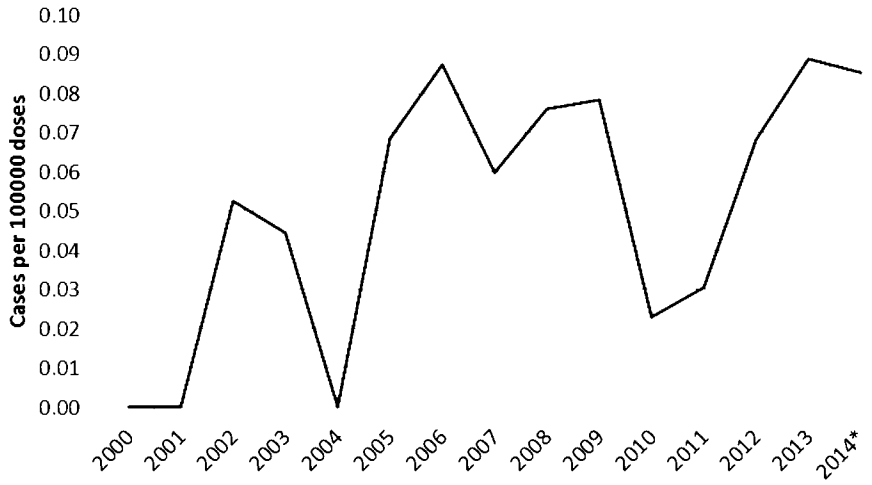
The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred terms (PTs)**: Acute disseminated encephalomyelitis, Acute haemorrhagic leukoencephalitis, Encephalitis, Encephalitis autoimmune, Encephalitis haemorrhagic, Encephalitis post immunisation, Encephalomyelitis, Encephalopathy, Encephalopathy allergic, Encephalopathy neonatal, Leukoencephalopathy, Panencephalitis

A total of 75 reports (cases) were retrieved from the GSK worldwide safety database since launch in 2000, of which 36 were reported during the period between 23 October 2011 and 22 October 2014 (Table 1). These cases have different time to onsets and symptomatologies. Most of these cases are related to an inborn defect, a brain malformation, an underlying disease or infection, or even a genetic-metabolic disease disorder. In other cases there is not enough clinical evidence to relate the event to vaccination with Infanrix hexa.

Figure 1shows that, since launch, the worldwide reporting frequency of cases including the PTs Acute disseminated encephalomyelitis, Acute haemorrhagic leukoencephalitis, Encephalitis, Encephalitis autoimmune, Encephalitis haemorrhagic, Encephalitis post immunisation, Encephalomyelitis, Encephalopathy, Encephalopathy allergic, Encephalopathy neonatal, Leukoencephalopathy or Panencephalitis was stable and varied between 0.00 and 0.09 cases per 100000 doses sold.

Figure 1 **Yearly reporting frequency for cases including the PTs Acute disseminated encephalomyelitis, Acute haemorrhagic leukoencephalitis, Encephalitis, Encephalitis autoimmune, Encephalitis haemorrhagic, Encephalitis post immunisation, Encephalomyelitis, Encephalopathy, Encephalopathy allergic, Encephalopathy neonatal, Leukoencephalopathy or Panencephalitis**



*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

Data currently available to GSK suggest there is no increased risk of important neurological events (including encephalitis and encephalopathy) following vaccination with Infanrix hexa.

It is GSK's position that Encephalopathy remains a potential risk in all DTP line vaccines, as a precautionary measure, especially considering that encephalopathy seven days following a previous pertussis vaccination is a contraindication listed in the Infanrix hexa reference safety information (RSI).

GSK will continue to monitor and describe important neurological events (including encephalitis and encephalopathy) in future Infanrix hexa aggregate safety reports. GSK will also continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

Table 1 **Line listing of cases including the PTs Acute disseminated encephalomyelitis, Acute haemorrhagic leukoencephalitis, Encephalitis, Encephalitis autoimmune, Encephalitis haemorrhagic, Encephalitis post immunisation, Encephalomyelitis, Encephalopathy, Encephalopathy allergic, Encephalopathy neonatal, Leukoencephalopathy or Panencephalitis received during the period (N=36)**

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 1 Female [redacted]	21 Dec 11	Regulatory Authority, Physician, Other Health Professional	Current Condition: Growth retardation, Psychomotor retardation;Historical Drug:Infanrix hexa, Pneumococcal vaccines, Pneumococcal vaccine, Hepatitis A vaccine	[Infanrix hexa], [Menjugate]	3		Encephalopathy, Myoclonic epilepsy, Cerebral atrophy, Lower respiratory tract infection, Vomiting, Pyrexia, Tremor, Dyskinesia, Drooling, Sleep apnoea syndrome, Condition aggravated, Hypotonia, Dystonia, Respiratory disorder, Asthenia	2 Days	Yes Unresolved
[redacted] .12 Male [redacted]	20 Mar 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Encephalopathy, Loss of consciousness, Apathy, Somnolence, Decreased appetite		Yes Resolved
[redacted] .25 Male [redacted]	17 May 12	Regulatory Authority, Physician		[Infanrix hexa]	2		Encephalitis, Altered state of consciousness, Loss of consciousness, Decreased appetite, Pharyngitis, Crying, Hypotonic-hyporesponsive episode, Coma scale, Somnolence, Apathy, Central nervous system haemorrhage	2 Days	Yes Unknown
[redacted] .42 Male [redacted]	18 Jul 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	2		Encephalopathy, Epilepsy, Autism spectrum disorder, Convulsion, Hypotonia		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .13 Male [redacted]	29 Aug 12	Physician	Current Condition: Premature baby, Low birth weight baby, Blood bilirubin increased	[Infanrix hexa]	1	[BCG vaccine]	Sepsis, Multi-organ failure, Encephalitis, Encephalopathy, Apnoea, Crying, Condition aggravated, Cold sweat	1 Days	Yes Fatal
[redacted] .5 Male ITALY	18 Oct 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	2		Encephalopathy		Yes Resolved
[redacted] .92 Male [redacted]	17 Oct 12	Consumer, Regulatory Authority	Current Condition: Drug hypersensitivity, Poisoning;Historical Drug:Infanrix hexa	[Infanrix hexa]	3		Encephalopathy, Gastroenteritis, Decreased appetite, Developmental delay, Speech disorder developmental		Yes Resolved
[redacted] .33 Male [redacted]	14 Feb 13	Regulatory Authority, Physician	Current Condition: Coarctation of the aorta, Atrioventricular septal defect, Premature baby	[Infanrix hexa], [Prevenar 13]		[Surgery]	Encephalitis, Oculogyric crisis, Cyanosis, Dyspnoea, Irritability, Hypertonia, Pyrexia		Yes Resolved
[redacted] .42 Female [redacted]	14 Feb 13	Regulatory Authority, Consumer		[Infanrix hexa], [Meningitec], [ProQuad]	2 & 3		Acute disseminated encephalomyelitis, Multiple sclerosis, Hypokinesia, Pyrexia, Nervousness, Insomnia, Decreased appetite		Yes Unresolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .42 Female [redacted]	10 Apr 13	Physician, Regulatory Authority		[Infanrix hexa], [Prevenar]	1, 2 & 3	[Rotarix], [Prevenar]	Encephalitis, Pyrexia, Meningism, Crying, Hyperaesthesia, Fontanelle bulging, Tachypnoea, Erythema, Injection site pain, Injection site induration, Photophobia, Muscle contractions involuntary, Moaning, Hypertonia, Cough, Lacrimation increased, Rhinitis		Yes Resolved
[redacted] .5 Female [redacted]	11 Apr 13	Regulatory Authority, Physician		[Infanrix hexa], [Rotarix liquid formulation], [Prevenar 13]	2		Infantile spasms, Encephalopathy, Immobile, Staring, Circadian rhythm sleep disorder, Crying	16 Days	Yes Worse
[redacted] .25 Female [redacted]	19 Jun 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	1	[Nutritional supplement]	Infantile spasms, Crying, Psychomotor retardation, Hypotonia, Encephalopathy	1 Days	Yes Unknown
[redacted] .5 Male [redacted]	15 Jul 13	Regulatory Authority, Physician, Consumer	Current Condition: Congenital torticollis, Hypotonia, Hyperbilirubinaemia neonatal;Historical Drug:Hepatitis B vaccine, Infanrix-polio-HIB, Neisvac-C	[Infanrix hexa]		[Infanrix-polio-HIB], [Neisvac-C], [Pneumococcal vaccine], [RotaTeq]	Encephalopathy, Petit mal epilepsy, Microcephaly, Myoclonus, Developmental delay, Muscle spasms, Hypotonia, Antisocial behaviour, Atrophy, Visual impairment, Sensory disturbance, Weight gain poor, Death	19 Days	Yes Fatal

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .5 Male [redacted]	11 Sep 13	Physician, Consumer, Lawyer	Current Condition: Developmental delay	[Infanrix hexa]	2	[Infanrix hexa]	Encephalitis, Intentional self-injury, Psychomotor retardation, Hypotonia, Dyspnoea, Gaze palsy		Yes Unknown
[redacted] 1 Male [redacted]	4 Nov 13	Consumer, Regulatory Authority, Physician	Historical Drug: Infanrix hexa	[Infanrix hexa], [Synflorix]	3		Encephalitis, Injection site pain, Body temperature increased, Initial insomnia, Rash generalised, Psychomotor hyperactivity, Tremor, Decreased appetite, Anxiety, Disturbance in attention, Decreased eye contact, Micturition disorder, Change of bowel habit, Crying, Dyspnoea, Aggression		Yes Unknown
[redacted] .25 Male [redacted]	15 Nov 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	1		Encephalopathy, Decreased eye contact, Nervous system disorder, Eczema, Multiple allergies, Gastrointestinal disorder, Dermatitis atopic	7 Days	Yes Resolved with Sequelae
[redacted] .92 Male [redacted]	18 Nov 13	Regulatory Authority	Current Condition: Breast feeding	[Infanrix hexa], [Prevenar 13]	3		Encephalopathy, Gastrointestinal motility disorder, Eczema, Multiple allergies, Dermatitis atopic	9 Days	Yes Resolved with Sequelae
[redacted] .17 Female [redacted]	27 Nov 13	Regulatory Authority	Current Condition: Psychomotor skills impaired	[Infanrix hexa], [Prevenar 13]	1		Encephalopathy, Status epilepticus, Myoclonic epilepsy, Clonic convulsion		Yes Resolved with Sequelae
[redacted] .33 Male [redacted]	21 Jan 14	Physician, Other Health Professional , Regulatory Authority	Current Condition: Severe myoclonic epilepsy of infancy, Infection;Historical Condition: No adverse event	[Infanrix hexa], [Prevenar]	1	[Prevenar], [BCG], [Infanrixquinta]	Encephalopathy, Developmental delay, Convulsion, Loss of consciousness, Disorientation, Incontinence, Drug administered to patient of inappropriate age, Inappropriate schedule of drug administration	78 Days	Yes Unresolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Female [redacted]	23 Jan 14	Regulatory Authority	Current Condition: Developmental delay, Pharyngitis	[Infanrix hexa], [Prevenar 13]		[Zimox]	Encephalopathy, Infantile spasms, Dyskinesia, Decreased eye contact, Somnolence, Slow response to stimuli, Tremor, Gastrointestinal motility disorder, Respiratory tract inflammation, Arrhythmia, Pyrexia, Motor dysfunction, Cardiovascular disorder	70 Days	Yes Unresolved
[redacted] .17 UNK [redacted]	14 Apr 14	Regulatory Authority, Physician		[Infanrix hexa]			Apnoea, Hypotonic-hyporesponsive episode, Encephalopathy, Cyanosis, Salivary hypersecretion, Hypotonia, Irritability	2 Days	Yes Resolved
[redacted] 1.33 Male [redacted]	6 Jun 14	Regulatory Authority, Physician		[Infanrix hexa]	4		Encephalitis post immunisation, Body temperature increased, Tremor, Pyrexia, Hypersomnia		Yes Unknown
[redacted] .33 Male [redacted]	23 Jun 14	Regulatory Authority, Physician	Current Condition: Psychomotor retardation, Neurodevelopmental disorder	[Infanrix hexa]	2		Encephalopathy, Nystagmus, Muscle tone disorder	3 Days	Yes Resolved
[redacted] .17 Male [redacted]	8 Jul 14	Physician, Consumer		[Infanrix hexa]		[BCG], [HBV vaccine]	Encephalitis, Hydrocephalus, Strabismus, Febrile convulsion, Pyrexia, Loss of consciousness, Gaze palsy, Muscle twitching, Blepharospasm, Movement disorder, Disorientation, Somnolence	1 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .5 Male [redacted]	21 Aug 14	Lawyer, Consumer, Other Health Professional	Current Condition: Immunodeficiency; Historical Drug: Infanrix hexa, BCG	[Infanrix hexa]	3	[Infanrix hexa]	Encephalitis, Loss of consciousness, Encephalopathy, Epilepsy, Hypotonia, Muscle tone disorder, Dyspnoea, Erythema, Pallor, Developmental delay, Heterophoria, Hypersensitivity, Balance disorder, Hypermetropia, Astigmatism, Disturbance in attention, Upper respiratory tract infection, Daydreaming, Hand-eye coordination impaired		Yes Unknown
[redacted] .75 Female [redacted]	25 Aug 14	Consumer	Historical Condition: Altered state of consciousness	[Infanrix hexa]	1 & 2	[Diazepam]	Encephalitis, Insomnia, Speech disorder, Crying, Apathy	114 Days	Yes Not Recovered/Not Resolved
[redacted] .25 Female [redacted]	15 Feb 12	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	1		Encephalopathy, Crying, Movement disorder	2 Days	Yes Resolved
[redacted] .12 Female [redacted]	30 Jul 12	Regulatory Authority		[Infanrix hexa], [RotaTeq]			Developmental delay, Infantile spasms, Visual impairment, Akathisia, Encephalopathy, Crying, Gastrooesophageal reflux disease, Nervousness, Abdominal pain, Eye movement disorder		Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Male [redacted]	23 Nov 12	Lawyer	Current Condition: Urinary tract disorder	[Infanrix hexa], [Prevenar]	1		Death, Multi-organ failure, Encephalopathy, Respiratory failure, Hypertrophic cardiomyopathy, Hypertensive crisis, Epilepsy, Loss of consciousness, Hypotonia, Crying, Hydrophobia, Pyrexia, Dysphagia, Restlessness, Muscle twitching, Cyanosis, Dyspnoea, Blood glucose increased, Acidosis, Acute respiratory failure, Tachycardia, Hypertension, Somnolence, Developmental delay, Myoclonus, Bladder disorder, Sepsis, Systemic inflammatory response syndrome, Ileus, Cerebral atrophy, Quadriparesis, Ventricular hypertrophy, Osteopenia, Pathological fracture	130 Days	Yes Fatal
[redacted] 1.17 Male [redacted]	13 Dec 12	Regulatory Authority, Physician	Current Condition: Bronchitis	[Infanrix hexa], [Synflorix]	3	[Antibiotic]	Encephalitis, Ataxia	7 Days	Yes Improved
[redacted] .23 Male [redacted]	2 May 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	1		Acute hepatic failure, Pulmonary haemorrhage, Adenovirus infection, General physical health deterioration, Vomiting, Body temperature increased, Transaminases increased, Lactic acidosis, Hypoglycaemia, Hepatic function abnormal, Hyperammonaemia, Encephalopathy, Renal failure, Circulatory collapse	4 Days	Yes Fatal

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 1.33 Male [redacted]	30 Jul 13	Lawyer, Physician	Historical Drug: Infanrix hexa, Prevenar, Priorix Tetra, Meningococcal vaccine	[Infanrix hexa], [Prevenar 13], [Priorix Tetra]	4		Partial seizures, Infective myositis, Encephalopathy, Developmental delay, Neuronal ceroid lipofuscinosis, Mitochondrial cytopathy, Blood creatine phosphokinase increased, Pyrexia, Hemiplegia, Restlessness, Unresponsive to stimuli, Gaze palsy, Tremor, Gastroenteritis norovirus, Iron deficiency anaemia, Hearing impaired, Hypotonia, Muscular weakness, Heart disease congenital, Speech disorder developmental, Stereotypy		Yes Unresolved
[redacted] 1 Male [redacted]	9 Sep 13	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Prevenar 13]	4	[Infanrix hexa], [Prevenar 13]	Encephalitis, Gait disturbance, Pyrexia	1 Days	Yes Resolved
[redacted] .5 Male [redacted]	8 Nov 13	Other Health Professional	Historical Condition: Abdominal distension, Cough, Conjunctival haemorrhage, Upper respiratory tract infection, Complication of pregnancy; Current Condition:S kull malformation, Strabismus, Dyskinesia	[Infanrix hexa], [Prevenar 13]	3	[Infanrix hexa], [Prevenar 13]	Severe mental retardation, Developmental delay, Restlessness, Hypotonia, Motor developmental delay, Opisthotonus, Developmental coordination disorder, Hand-eye coordination impaired, Coordination abnormal, Microcephaly, Brain scan abnormal, Extrapyramidal disorder, Quadriparesis, Cerebral palsy, Leukoencephalopathy, Febrile convulsion, Upper respiratory tract infection, Pyrexia, Visual impairment, Hearing impaired	379 Days	Yes Unresolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .42 Female [redacted]	20 Jun 14	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Prevenar]	2	[Infanrix hexa], [Prevenar]	Encephalopathy, Delayed fontanelle closure	1 Days	Yes Unknown
[redacted] .92 Female [redacted]	15 Oct 14	Physician	Historical Condition: Clonus;Current Condition: Psychomotor retardation, Quadriparesis	[Infanrix hexa]	3		Encephalopathy, Hypotonia, Hyporesponsive to stimuli, Regressive behaviour		Yes Resolved with Sequelae

APPENDIX 7B.17 : Henoch-Schönlein purpura

The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred term (PT)**: Henoch-Schönlein purpura

A total of 9 reports (cases) were retrieved from the GSK worldwide safety database since launch in 2000, of which 2 were reported during the period between 23 October 2011 and 22 October 2014 (Table 1). There was not enough clinical evidence to relate the event to vaccination with Infanrix hexa.

Figure 1shows that, since launch, the worldwide reporting frequency of cases including the PT Henoch-Schönlein purpura decreased over time. These variations result from the fact that very low numbers of cases were reported per year, i.e. between zero (e.g. in 2013 and 2014) and 2 per year (only in 2011 and 2012). Reporting frequency tendencies cannot reliably be interpreted based on such low numbers.

Figure 1 **Yearly reporting frequency for cases including the PT Henoch-Schönlein purpura**

*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

Data currently available to GSK suggest there is no increased risk of Henoch-Schönlein purpura following vaccination with Infanrix hexa.

GSK will continue to monitor and describe Henoch-Schönlein purpura in future Infanrix hexa aggregate safety reports. GSK will also continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.

- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

Table 1 Line listing of cases including the PT Henoch-schonlein purpura received during the period (N=2)

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 1 Male	31 Jul 12	Regulatory Authority, Physician		[Infanrix hexa]			Vasculitis, Henoch-Schonlein purpura, Rash		Yes Resolved
[redacted] .5 Male	23 Apr 12	Regulatory Authority, Physician		[Infanrix hexa]			Henoch-Schonlein purpura, Petechiae, Oedema peripheral	21 Days	Yes Unknown

APPENDIX 7B.18 : Petechiae

The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred term (PT)**: Petechiae

A total of 226 reports (cases) were retrieved from the GSK worldwide safety database since launch in 2000, of which 105 were reported during the period between 23 October 2011 and 22 October 2014 (Table 1). Some of these events were reported in cases with infectious diseases, autoimmune reactions or thrombocytopenia triggered by an infectious disease or underlying condition. Beyond a temporal association there was not enough clinical evidence to relate petechiae to vaccination with Infanrix hexa.

Figure 1 shows that, since launch, the worldwide reporting frequency of cases including the PT Petechiae was stable and varied between 0.13 and 0.26 cases per 100000 doses sold.

Figure 1 Yearly reporting frequency for cases including the PT Petechiae

*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

Data currently available to GSK suggest there is no increased risk of Petechiae following vaccination with Infanrix hexa.

GSK will continue to monitor and describe petechiae in future Infanrix hexa aggregate safety reports. GSK will also continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative

methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.

- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

Table 1 Line listing of cases including the PT Henoch-schonlein purpura received during the period (N=105)

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .17 Male [redacted]	28 Oct 11	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Synflorix]	1		Petechiae		No Unresolved
[redacted] .17 Male [redacted]	10 Nov 11	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	1		Skin discolouration, Pyrexia, Petechiae, Screaming, Erythema	15 Days	No Resolved
[redacted] .92 Female [redacted]	28 Nov 11	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar]			Thrombocytopenic purpura, Thrombocytopenia, Ecchymosis, Contusion, Petechiae	15 Days	Yes Resolved
[redacted] .33 Male [redacted]	30 Nov 11	Regulatory Authority, Physician	Current Condition: Milk allergy, Renal disorder	[Infanrix hexa], [Synflorix]			Meningitis, Pyrexia, Petechiae		Yes Resolved
[redacted] .33 Male [redacted]	13 Jan 12	Regulatory Authority, Physician	Historical Condition: Anaemia neonatal;Current Condition:Influenza like illness	[Synflorix], [Infanrix hexa]	2	[Palivizumab]	Petechiae		No Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Male [redacted]	24 Feb 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix], [Rotarix liquid formulation]		[Vigantol]	Waterhouse-Friderichsen syndrome, Multi-organ failure, Septic shock, Disseminated intravascular coagulation, Altered state of consciousness, Meningitis, Shock, Cardiac failure, Meningococcal sepsis, Petechiae, Cough, Body temperature increased, Nasopharyngitis, Dyspnoea, Cyanosis, Arrhythmia, Bradycardia, Tachycardia, Hypotension, Faeces discoloured, Terminal state, Somnolence	2 Days	Yes Fatal
[redacted] .25 UNK [redacted]	20 Mar 12	Regulatory Authority, Physician		[Infanrix hexa]			Petechiae, Extensive swelling of vaccinated limb, Pyrexia, Crying, Oedema peripheral		Yes Resolved
[redacted] .33 Male [redacted]	2 Apr 12	Regulatory Authority, Physician	Current Condition: Pyrexia;Historical Condition: Premature baby	[Infanrix hexa], [Synflorix]	3		Petechiae, Purpura	2 Days	No Unknown
[redacted] .23 Female [redacted]	10 Apr 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]			Screaming, Skin discolouration, Crying, Petechiae, Erythema		No Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .42 Male [redacted]	23 Apr 12	Regulatory Authority, Physician		[Infanrix hexa]	1		Oedema peripheral, Erythema, Petechiae		Yes Resolved
[redacted] .5 Male [redacted]	23 Apr 12	Regulatory Authority, Physician		[Infanrix hexa]			Henoch-Schonlein purpura, Petechiae, Oedema peripheral	21 Days	Yes Unknown
[redacted] .33 Female [redacted]	15 May 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	3		Purpura, Peripheral swelling, Petechiae, Pyrexia, Upper respiratory tract infection	4 Weeks	No Unknown
[redacted] .25 Female [redacted]	25 May 12	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	2		Petechiae, Influenza like illness, Cough, Productive cough, Somnolence, Body temperature increased, Malaise	2 Days	Yes Resolved
[redacted] .42 Male [redacted]	29 Jun 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	2		Thrombocytopenic purpura, Thrombocytopenia, Petechiae	6 Days	Yes Resolved
[redacted] .25 UNK [redacted]	19 Jul 12	Regulatory Authority, Physician		[Infanrix hexa]			Apnoea, Hypotonic-hyporesponsive episode, Petechiae		Yes Unknown
[redacted] .25 Female [redacted]	8 Aug 12	Regulatory Authority, Physician		[Infanrix hexa]			Hypotonic-hyporesponsive episode, Apnoea, Petechiae		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .42 Female [redacted]	10 Aug 12	Regulatory Authority, Physician	Current Condition: Developmental hip dysplasia	[Infanrix hexa], [Synflorix]	1		Skin discolouration, Petechiae, Extensive swelling of vaccinated limb, Erythema, Rash, Injection site induration, Crying		No Resolved
[redacted] 5 Female [redacted]	16 Aug 12	Regulatory Authority	Current Condition: Gastrooesophageal reflux disease, Asthma; Historical Condition: Bronchiolitis, Laryngitis, No adverse event	[Infanrix hexa], [Infanrixquinta]	4	[Aerius], [Singulair]	Pertussis, Skin plaque, Cough, Petechiae, Dyspnoea, Vomiting, Rhinorrhoea, Vaccination failure	1366 Days	Yes Improved
[redacted] .25 Female [redacted]	24 Jul 12	Regulatory Authority		[Infanrix hexa], [Prevenar]			Petechiae		No Improved
[redacted] .4 Female [redacted]	27 Aug 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	3		Skin discolouration, Peripheral swelling, Feeling hot, Petechiae		No Resolved
[redacted] .33 UNK [redacted]	18 Sep 12	Regulatory Authority, Physician	Historical Condition: Varicella	[Infanrix hexa]	1		Thrombocytopenia, Petechiae	4 Days	Yes Improved
[redacted] .17 Female [redacted]	19 Sep 12	Physician, Regulatory Authority	Historical Condition: No adverse event	[Infanrix hexa]	1	[Emla patch]	Petechiae, Oedema peripheral, Cyanosis, Papule, Hypersensitivity	1 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Female [redacted]	1 Oct 12	Regulatory Authority, Consumer	Current Condition: Respiratory tract infection, Pyrexia	[Synflorix], [Infanrix hexa]	2		Skin discolouration, Pyrexia, Petechiae	10 Days	Yes Unknown
[redacted] .15 Female [redacted]	11 Oct 12	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	1		Petechiae, Macule		No Improved
[redacted] .33 Female [redacted]	16 Oct 12	Regulatory Authority, Other Health Professional , Physician, Consumer		[Infanrix hexa], [Synflorix]	3		Screaming, Panic reaction, Erythema, Peripheral coldness, Skin discolouration, Petechiae	3 Days	No Resolved
[redacted] Male [redacted]	25 Oct 12	Physician, Consumer	Current Condition: Premature baby	[Infanrix hexa], [Prevenar 13]	3	[Infanrix hexa], [Rotarix], [Prevenar 13], [Vigantol], [Kanavit], [Aktiferrin]	Anti-neutrophil cytoplasmic antibody positive vasculitis, Petechiae	1 Weeks	Yes Improved
[redacted] .25 Male [redacted]	25 Oct 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	2		Petechiae, Crying		No Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .17 Male [redacted]	29 Nov 12	Regulatory Authority	Current Condition: Bronchiolitis, Stridor, Congenital tracheomalacia, Gastrooesophageal reflux disease, Takayasu's arteritis, Surgery, Chest discomfort; Historical Condition: No adverse event	[Infanrixquinta], [Infanrix hexa], [Prevenar 13]	1	[Inexium]	Immune thrombocytopenic purpura, Rectal haemorrhage, Haemoptysis, Petechiae, Epistaxis, Pallor	4 Days	Yes Resolved
[redacted] .33 Female [redacted]	4 Dec 12	Regulatory Authority	Current Condition: Premature baby; Historical Condition: Neonatal respiratory distress syndrome, Petechiae, Ultrasound scan, No adverse event	[Infanrix hexa], [Rotarix lyophilized formulation], [Prevenar 13]	3		Petechiae, Neutropenia	5 Days	Yes Resolved
[redacted] .25 Female [redacted]	3 Dec 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Petechiae	14 Days	Yes Resolved
[redacted] .33 Male [redacted]	20 Nov 12	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Synflorix]	3		Pyrexia, Crying, Skin discolouration, Screaming, Injection site erythema, Injection site pain, Extensive swelling of vaccinated limb, Petechiae, Peripheral swelling, Erythema, Somnolence		No Improved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 0 Female	21 Nov 12	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	2		Pyrexia, Crying, Petechiae		No Resolved
[redacted] .23 Male	17 Jan 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	2		Erythema nodosum, Pyrexia, Moaning, Skin mass, Petechiae		Yes Improved
[redacted] .33 Male	9 Jan 13	Consumer, Physician		[Infanrix hexa]			Petechiae	1 Days	No Improved
[redacted] .33 Male	17 Jan 13	Regulatory Authority, Consumer	Current Condition: Laryngomalacia	[Infanrix hexa], [Synflorix]	3		Injection site inflammation, Skin discolouration, Pyrexia, Gastrointestinal disorder, Vomiting, Diarrhoea, Erythema, Feeling hot, Petechiae, Crying, Injection site swelling		No Resolved
[redacted] 1.08 Female	28 Jan 13	Regulatory Authority, Consumer		[Synflorix], [Infanrix hexa]	2		Influenza like illness, Petechiae, Malaise, Cough, Productive cough, Somnolence, Pyrexia	3 Days	Yes Resolved
[redacted] .5 Female	18 Feb 13	Regulatory Authority	Historical Drug: Infanrix hexa	[Infanrix hexa], [Prevenar 13]		[Infanrix hexa]	Petechiae, Dyspnoea, Crying, Erythema, Peripheral swelling, Induration		No Resolved
[redacted] .33 Male	27 Mar 13	Regulatory Authority, Physician		[Infanrix hexa]			Immune thrombocytopenic purpura, Petechiae, Thrombocytopenia	12 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .42 Male [redacted]	16 Apr 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Immune thrombocytopenic purpura, Petechiae, Haematoma	3 Days	Yes Unknown
[redacted] .25 Male [redacted]	24 Jan 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]			Oedema peripheral, Petechiae, Erythema, Pyrexia		No Resolved
[redacted] .17 Female [redacted]	4 Apr 13	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Synflorix]	1		Petechiae		No Resolved
[redacted] .33 UNK [redacted]	3 Jun 13	Regulatory Authority, Physician		[Infanrix hexa]	2		Injection site extravasation, Petechiae, Injection site erythema, Injection site rash, Injection site oedema, Extensive swelling of vaccinated limb, Pyrexia	3 Days	Yes Improved
[redacted] .25 Female [redacted]	23 Apr 13	Regulatory Authority, Other Health Professional , Consumer	Historical Condition: Gastrooesophageal reflux disease	[Infanrix hexa], [Synflorix]	2	[Infanrix hexa], [Synflorix]	Injection site inflammation, Petechiae, Pyrexia, Miliaria, Vomiting, Pallor, Body temperature decreased, Rash erythematous, Injection site discolouration, Somnolence		No Resolved
[redacted] .42 Male [redacted]	2 Jul 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	2		Petechiae, Irritability		No Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 2 UNK [redacted]	9 Jul 13	Regulatory Authority, Physician		[Infanrix hexa]			Extensive swelling of vaccinated limb, Petechiae, Injection site warmth, Injection site erythema, Injected limb mobility decreased	1 Days	Yes Resolved
[redacted] .15 Male [redacted]	12 Jul 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Petechiae, Thrombocytopenia	3 Days	Yes Unknown
[redacted] .33 Female [redacted]	16 Jul 13	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Synflorix]	3		Petechiae	1 Days	No Unresolved
[redacted] .31 Male [redacted]	18 Jul 13	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	2		Petechiae	4 Days	No Improved
[redacted] .27 Female [redacted]	17 Jul 13	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	2		Petechiae	1 Days	No Resolved
[redacted] .17 Female [redacted]	18 Jul 13	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	1, 2 & 3		Respiratory syncytial virus infection, Petechiae	4 Days	Yes Resolved
[redacted] .23 Female [redacted]	30 Jul 13	Regulatory Authority, Consumer	Current Condition: Hypotonia	[Synflorix], [Infanrix hexa]	2		Petechiae, Injection site haemorrhage	4 Days	No Improved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .13 Male [redacted]	7 Aug 13	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	1		Petechiae	2 Days	No Improved
[redacted] .23 Female [redacted]	8 Aug 13	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Synflorix]	2		Petechiae	1 Days	No Resolved
[redacted] .33 Male [redacted]	15 Aug 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	3		Petechiae, Purpura		Yes Improved
[redacted] .92 Female [redacted]	26 Aug 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	4		Immune thrombocytopenic purpura, Petechiae, Haematoma	9 Days	Yes Resolved
[redacted] .15 Male [redacted]	27 Aug 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	1 & 2		Petechiae, Pyrexia, Listless	1 Days; 1 Days	Yes Improved
[redacted] .42 Male [redacted]	3 Sep 13	Physician	Historical Condition: No adverse event	[Infanrix hexa]	2	[Infanrix hexa]	Erythema, Crying, Livedo reticularis, Petechiae, Drug administered to patient of inappropriate age		No Resolved
[redacted] .33 Female [redacted]	6 Sep 13	Regulatory Authority, Physician		[Infanrix hexa]		[Meningitis vaccine (strain not stated)]	Petechiae, Injection site induration	2 Days	Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Male [redacted]	5 Sep 13	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Synflorix]	3		Petechiae	1 Days	No Resolved
[redacted] .25 Male [redacted]	18 Sep 13	Consumer, Contact	Current Condition: Food allergy; Historical Condition: No adverse event	[Infanrix hexa], [Infanrixquinta], [Prevenar]	1		Serum sickness, Oedema peripheral, Erythema, Pain in extremity, Petechiae, Rash macular, Inappropriate schedule of drug administration	9 Days	No Resolved
[redacted] .19 Male [redacted]	24 Sep 13	Regulatory Authority	Current Condition: Hypertonia, Osteomyelitis, Bovine tuberculosis; Historical Condition: No adverse event	[Infanrix hexa], [Prevenar], [RotaTeq]			Pyrexia, Injection site induration, Irritability, Livedo reticularis, Petechiae, Musculoskeletal stiffness, Fontanelle bulging, Drug administered to patient of inappropriate age		Yes Resolved
[redacted] 1.25 Male [redacted]	27 Sep 13	Regulatory Authority	Current Condition: Viral infection, Macule; Historical Condition: No adverse event	[Infanrix hexa]			Injection site inflammation, Injection site erythema, Pyrexia, Rash maculo-papular, Injection site oedema, Injection site warmth, Chills, Ecchymosis, Petechiae, Drug administered to patient of inappropriate age		Yes Improved
[redacted] .17 Female [redacted]	25 Sep 13	Physician, Consumer		[Infanrix hexa], [Rotarix liquid formulation], [Prevenar 13]			Petechiae	6 Days	Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .42 Female [redacted]	1 Oct 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	2		Immune thrombocytopenic purpura, Petechiae, Haematoma, Thrombocytopenia	11 Days	Yes Resolved
[redacted] .25 Male [redacted]	10 Oct 13	Regulatory Authority	Current Condition: Rhinitis; Historical Condition: No adverse event	[Infanrix hexa], [Prevenar]			Immune thrombocytopenic purpura, Petechiae, Thrombocytopenia, Drug administered to patient of inappropriate age	14 Days	Yes Resolved
[redacted] .15 Female [redacted]	7 Oct 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	1 & 2		Skin discolouration, Petechiae	64 Days, 11 Days	No Resolved
[redacted] .42 Male [redacted]	15 Oct 13	Regulatory Authority	Current Condition: Viral infection	[Infanrix hexa]		[Prevenar]	Immune thrombocytopenic purpura, Petechiae, Haematoma, Thrombocytopenia	1 Months	Yes Unknown
[redacted] .17 Female [redacted]	17 Oct 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	1		Petechiae, Body temperature	1 Days	No Resolved
[redacted] .25 Male [redacted]	14 Nov 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]			Petechiae, Thrombocytopenia	1 Weeks	No Unknown
[redacted] .15 Female [redacted]	17 Dec 13	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	1		Petechiae		No Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 1.5 UNK [redacted]	7 Jan 14	Regulatory Authority		[Infanrix hexa]	4		Erythema multiforme, Injection site erythema, Rash, Petechiae	1 Days	Yes Unknown
[redacted] .17 Male [redacted]	10 Mar 14	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Synflorix]	1		Injection site inflammation, Skin discolouration, Petechiae, Crying	8 Days	No Unresolved
[redacted] .5 Male [redacted]	12 Mar 14	Physician, Consumer	Historical Drug: Infanrix hexa, Meningitis c vaccination, Rotarix lyophilized formulation	[Infanrix hexa]	3	[Infanrix hexa], [Rotarix lyophilized formulation], [Pneumococcal vaccine], [Meningitis c vaccination]	Dermatitis allergic, Extensive swelling of vaccinated limb, Injection site erythema, Erythema, Oedema peripheral, Petechiae, Vomiting, Anxiety, Pruritus, Irritability		No Resolved
[redacted] .92 Female [redacted]	8 Apr 14	Regulatory Authority, Consumer	Current Condition: Haematoma	[Infanrix hexa], [Synflorix]	1, 2, 3 & 4		Petechiae, Pyrexia, Nasopharyngitis	4 Weeks, 8 Days, 2 Days, 3 Days	No Resolved
[redacted] .15 Female [redacted]	27 May 14	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]		[Nexium], [Lactulose]	Petechiae, Crying, Injection site pain		No Improved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Female	8 Jul 14	Regulatory Authority		[Infanrix hexa], [Prevenar 13]			Petechiae		No Unknown
[redacted] .17 Male	5 Aug 14	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	1		Petechiae	2 Days	No Resolved
[redacted] .33 Female	6 Aug 14	Regulatory Authority, Consumer		[Infanrix hexa], [Synflorix]	3		Petechiae	4 Days	No Unresolved
[redacted] .92 Female	6 Aug 14	Consumer		[Infanrix hexa], [Synflorix]	4		Petechiae, Injection site inflammation		No Recovered/Resolved
[redacted] .42 Female	27 Aug 14	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Prevenar 13]			Peripheral swelling, Petechiae, Pallor, Pyrexia, Crying		Yes Unresolved
[redacted] .19 Male	11 Sep 14	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Synflorix]			Petechiae, Pyrexia	1 Days	No Resolved
[redacted] 1 Female	12 Sep 14	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	3	[Dietary supplement], [Fluoril]	Vasculitis, Pyrexia, Rash, Petechiae	31 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .42 UNK	15 Sep 14	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Petechiae, Pyrexia, Crying, Oedema peripheral, Anxiety, Somnolence		Yes Improved
[redacted] .42 Male	9 Dec 11	Physician		[Infanrix hexa]	2		Petechiae, Purpura	4 Days	No Resolved
[redacted] .33 Female	21 Dec 11	Regulatory Authority, Physician	Current Condition: Pharyngeal erythema	[Infanrix hexa], [Prevenar 13], [RotaTeq]	3		Hypersensitivity vasculitis, Petechiae, Leukocytosis, Body temperature increased		Yes Unknown
[redacted] .25 Female	23 Apr 12	Pharmacist, Physician, Regulatory Authority		[Infanrix hexa], [Prevenar 13]	1		Vasculitis, Erythema, Petechiae, Crying, Restlessness, Generalised erythema		Yes Resolved
[redacted] .25 Male	27 Apr 12	Physician		[Infanrix hexa], [Prevenar 13], [RotaTeq]	1		Erythema, Petechiae, Extensive swelling of vaccinated limb		No Resolved
[redacted] .5 Male [redacted]	8 Jun 12	Physician	Historical Condition: Premature baby, Twin pregnancy, Hospitalisation; Current Condition: Naevus flammeus	[Infanrix hexa]			Respiratory arrest, Petechiae, Respiratory distress, Vasculitis, Thrombocytopenia, Gastroenteritis, Body temperature increased, Diarrhoea, Vomiting, Somnolence, Fluid intake reduced, Pallor, Rash, Lymphadenopathy	1 Days	Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Female	14 Jun 12	Regulatory Authority		[Infanrix hexa], [Prevenar 13], [RotaTeq]	3	[Infanrix hexa], [Prevenar 13], [RotaTeq]	Petechiae	1 Days	Yes Unresolved
[redacted] .25 Female	28 Jun 12	Physician, Consumer, Regulatory Authority	Current Condition: Pulmonary valve stenosis; Historical Condition: Atrial septal defect	[Rotarix liquid formulation], [Infanrix hexa], [Prevenar 13]	2	[Rotarix liquid formulation], [Infanrix hexa], [Prevenar 13]	Petechiae, Pyrexia, Skin haemorrhage, Skin turgor decreased		Yes Resolved
[redacted] .33 Female	5 Sep 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar], [RotaTeq]	1		Pyrexia, Diarrhoea, Rash, Abdominal pain, Hypotonia, Petechiae	1 Days	Yes Unknown
[redacted] .19 Female [redacted]	27 Sep 12	Regulatory Authority	Historical Condition: Hospitalisation, Mobility decreased	[Infanrix hexa], [Prevenar 13]	1		Status epilepticus, Inappropriate antidiuretic hormone secretion, Hypothermia, Convulsion, Loss of consciousness, Coma, Oxygen saturation decreased, Pallor, Fontanelle bulging, Cold sweat, Abdominal distension, Blood glucose increased, Petechiae	1 Days	Yes Resolved
[redacted] .21 Female [redacted]	14 Jan 13	Physician		[Infanrix hexa], [Prevenar 13]	1		Pyrexia, Somnolence, Petechiae		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .92 Male [redacted]	29 Jan 13	Physician, Consumer	Historical Condition: Febrile infection	[Priorix Tetra], [Infanrix hexa]	4		Immune thrombocytopenic purpura, Thrombocytopenia, Petechiae, Haematoma, Platelet count decreased, Bleeding time prolonged	20 Days	Yes Resolved
[redacted] .21 Female [redacted]	3 Jul 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	1		Petechiae	4 Days	No Resolved
[redacted] .25 Female [redacted]	2 Aug 13	Physician, Consumer, Regulatory Authority	Historical Condition: Premature baby, Respiratory tract infection; Current Condition: Developmental hip dysplasia, Familial risk factor	[Infanrix hexa], [Prevenar 13]	1	[Zymafluor D]	Petechiae, Crying, Screaming, Ecchymosis		Yes Resolved
[redacted] .23 Male [redacted]	28 Aug 13	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Prevenar 13], [RotaTeq]			Petechiae, Restlessness	2 Days	Yes Resolved
[redacted] .25 Male [redacted]	14 Jan 14	Physician, Consumer	Historical Condition: Premature baby, Continuous positive airway pressure, Hyperbilirubinaemia	[Infanrix hexa], [Synflorix], [Rotarix liquid formulation]	1	[Vigantol]	Vasculitis, Purpura, Decreased appetite, Petechiae, Rash, Platelet count increased, Skin haemorrhage	1 Days	Yes Improved
[redacted] .25 Female [redacted]	24 Feb 14	Physician, Regulatory Authority		[Infanrix hexa], [Prevenar 13], [RotaTeq]	2	[Infanrix hexa], [Prevenar 13], [RotaTeq]	Cutaneous vasculitis, Petechiae	3 Days	No Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Female [redacted]	21 Mar 14	Physician, Consumer		[Infanrix hexa], [Prevenar 13]	1	[Sab simplex]	Skin haemorrhage, Petechiae	30 Days	No Resolved
[redacted] .23 Male [redacted]	1 Aug 14	Regulatory Authority, Other Health Professional	Current Condition: Neurodermatitis, Upper respiratory tract infection, Abdominal pain	[Infanrix hexa], [Rotarix liquid formulation], [Prevenar 13]			Petechiae, Restlessness, Hyperaesthesia, Angiopathy	20 Days	Yes Resolved
[redacted] .33 Female [redacted]	24 Sep 14	Physician, Consumer	Current Condition: Rhinitis	[Infanrix hexa], [Rotarix liquid formulation], [PREVENAR 13]	1	[D-FLUORETTEN], [VITAMIN K]	Thrombocytopenia, Autoimmune neutropenia, Petechiae, Haematoma, Muscle haemorrhage, Immune thrombocytopenic purpura, Mouth haemorrhage		Yes Unknown
[redacted] 11 Female	6 Oct 14	Physician	Current Condition: Wound	[Infanrix hexa], [DTP vaccine]	4		Pertussis, Cough, Bronchial obstruction, Petechiae, Pyrexia, Vomiting, Rhinitis, Asthma, Vaccination failure		Yes Unknown
[redacted] .13 Male	3 Oct 14	Consumer		[Synflorix], [Infanrix hexa]	1		Injection site swelling, Petechiae, Crying		No Recovering/Resolving
[redacted] .17 Female [redacted]	30 Sep 14	Physician	Historical Condition: Breech delivery, Premature baby, Hospitalisation	[Infanrix hexa]		[Hepatitis B vaccine], [BCG VACCINE]	Immune thrombocytopenic purpura, Neutropenia, Rash, Contusion, Mouth haemorrhage, Petechiae		Yes Recovered/Resolved

APPENDIX 7B.19 : Purpura

The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred term (PT)**: Chronic pigmented purpura, Henoch-schonlein purpura, Immune thrombocytopenic purpura, Palpable purpura, Purpura, Purpura cerebri, Purpura fulminans, Purpura neonatal, Purpura non-thrombocytopenic, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura, Vascular purpura

A total of 119 reports (cases) were retrieved from the GSK worldwide safety database since launch in 2000, of which 39 were reported during the period between 23 October 2011 and 22 October 2014 (Table 1). Some of these events were reported in cases with infectious diseases, autoimmune reactions or thrombocytopenia triggered by an infectious disease or underlying condition. Beyond a temporal association there was not enough clinical evidence to relate petechiae to vaccination with Infanrix hexa.

Figure 1 shows that, since launch, the worldwide reporting frequency of cases including the PTs Chronic pigmented purpura, Henoch-schonlein purpura, Immune thrombocytopenic purpura, Palpable purpura, Purpura, Purpura cerebri, Purpura fulminans, Purpura neonatal, Purpura non-thrombocytopenic, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura or Vascular purpura was stable and varied between 0.05 and 0.17 cases per 100000 doses sold.

Figure 1 **Yearly reporting frequency for cases including the PTs Chronic pigmented purpura, Henoch-schonlein purpura, Immune thrombocytopenic purpura, Palpable purpura, Purpura, Purpura cerebri, Purpura fulminans, Purpura neonatal, Purpura non-thrombocytopenic, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura or Vascular purpura**

*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

Data currently available to GSK suggest there is no increased risk of purpura following vaccination with Infanrix hexa.

GSK will continue to monitor and describe purpura in future Infanrix hexa aggregate safety reports. GSK will also continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.
- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

Table 1 **Line listing of cases including the PT Chronic pigmented purpura, Henoch-schonlein purpura, Immune thrombocytopenic purpura, Palpable purpura, Purpura, Purpura cerebri, Purpura fulminans, Purpura neonatal, Purpura non-thrombocytopenic, Thrombocytopenic purpura, Thrombotic thrombocytopenic purpura or Vascular purpura received during the period (N=39)**

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Female [redacted]	10 Nov 11	Pharmacist, Other Health Professional, Consumer, Physician	Current Condition: Nasopharyngitis, Premature baby	[Infanrix hexa], [Rotarix], [Prevenar]	1		Meningococcal bacteraemia, Purpura fulminans, Sepsis, Hypoglycaemia, Pyrexia, Diarrhoea, Purpura, Irritability, Decreased appetite, Insomnia, Tachycardia, Tachyarrhythmia, Tympanic membrane hyperaemia, Faeces discoloured, Bradycardia, Poor peripheral circulation, Respiratory disorder, Moaning, Asthenia	8 Days	Yes Fatal
[redacted] .92 Female [redacted]	28 Nov 11	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar]			Thrombocytopenic purpura, Thrombocytopenia, Ecchymosis, Contusion, Petechiae	9 Days	Yes Resolved
[redacted] .33 Male [redacted]	2 Apr 12	Regulatory Authority, Physician	Current Condition: Pyrexia; Historical Condition: Premature baby	[Infanrix hexa], [Synflorix]	3		Petechiae, Purpura	2 Days	No Unknown
[redacted] .5 Male [redacted]	23 Apr 12	Regulatory Authority, Physician		[Infanrix hexa]			Henoch-Schonlein purpura, Petechiae, Oedema peripheral	21 Days	Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Female	15 May 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	3		Purpura, Peripheral swelling, Petechiae, Pyrexia, Upper respiratory tract infection	11 Days	No Unknown
[redacted] .25 Male	25 Jun 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	2		Purpura	2 Days	Yes Resolved
[redacted] .42 Male	29 Jun 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	2		Thrombocytopenic purpura, Thrombocytopenia, Petechiae	6 Days	Yes Resolved
[redacted] .33 Male	17 Jul 12	Regulatory Authority	Historical Condition: No adverse event	[Infanrix hexa], [Prevenar 13]			Livedo reticularis, Purpura, Tachycardia, Pallor, Peripheral coldness		Yes Unresolved
[redacted] 1 Male	31 Jul 12	Regulatory Authority, Physician		[Infanrix hexa]			Vasculitis, Henoch-Schonlein purpura, Rash		Yes Resolved
[redacted] .42 Female	13 Aug 12	Regulatory Authority	Historical Condition: No adverse event	[Infanrix hexa], [Infanrixquinta], [Prevenar]			Purpura	9 Days	Yes Resolved
[redacted] .17 Male	15 Aug 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	1		Purpura, Pyrexia, Haematoma, Pigmentation disorder	1 Days	No Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 1.42 Male [redacted]	19 Oct 12	Physician		[Infanrix hexa], [Priorix]			Injection site erythema, Purpura, Pyrexia		Yes Resolved
[redacted] .17 Female [redacted]	22 Nov 12	Regulatory Authority	Historical Condition: No adverse event	[Infanrix hexa], [Prevenar 13]	1	[Emla patch]	Injection site inflammation, Injection site erythema, Injection site warmth, Injection site pain, Purpura, Crying		Yes Resolved
[redacted] .17 Male [redacted]	29 Nov 12	Regulatory Authority	Current Condition: Bronchiolitis, Stridor, Congenital tracheomalacia, Gastrooesophageal reflux disease, Takayasu's arteritis, Surgery, Chest discomfort; Historical Condition: No adverse event	[Infanrixquinta], [Infanrix hexa], [Prevenar 13]	1	[Inexium]	Immune thrombocytopenic purpura, Rectal haemorrhage, Haemoptysis, Petechiae, Epistaxis, Pallor	2 Days	Yes Resolved
[redacted] .25 Male [redacted]	24 Jan 13	Physician, Consumer	Current Condition: Thrombocytopenic purpura	[Infanrix hexa], [RotaTeq]	1		Thrombocytopenic purpura, Skin haemorrhage	4 Days	Yes Resolved
[redacted] .33 Male [redacted]	27 Mar 13	Regulatory Authority, Physician		[Infanrix hexa]			Immune thrombocytopenic purpura, Petechiae, Thrombocytopenia	12 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 2 Female [redacted]	12 Apr 13	Regulatory Authority	Historical Drug: Infanrix hexa, Priorix, Prevenar; Historical Condition: No adverse event	[Infanrix hexa], [Infanrixquinta], [Priorix], [Prevenar]	4		Acute lymphocytic leukaemia, Hepatosplenomegaly, Lymphadenopathy, Purpura, Fatigue	3 Months	Yes Improved
[redacted] .5 Female [redacted]	12 Apr 13	Physician, Consumer		[Infanrix hexa]	3		Thrombocytopenic purpura		Yes Resolved
[redacted] .42 Male [redacted]	16 Apr 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Immune thrombocytopenic purpura, Petechiae, Haematoma		Yes Unknown
[redacted] 6 Female [redacted]	23 Apr 13	Physician, Consumer	Historical Drug: Infanrix hexa, Rotarix lyophilized formulation, Avaxim, Vaxigrip	[Infanrix hexa], [Rotarix lyophilized formulation], [Rouvax], [Avaxim], [Pentaxim], [Vaxigrip]	3		Immune thrombocytopenic purpura, Contusion, Dehydration	1885 Days	Yes Unknown
[redacted] .19 Female [redacted]	10 May 13	Regulatory Authority, Other Health Professional		[Infanrix hexa], [Prevenar 13]			Immune thrombocytopenic purpura	14 Days	Yes Resolved
[redacted] .92 Male [redacted]	27 May 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	3		Cellulitis, Purpura, Pyrexia	3 Days	Yes Improved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Male [redacted]	15 Aug 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	3		Petechiae, Purpura		Yes Improved
[redacted] .92 Female [redacted]	26 Aug 13	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	4		Immune thrombocytopenic purpura, Petechiae, Haematoma	9 Days	Yes Resolved
[redacted] .42 Female [redacted]	1 Oct 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	2		Immune thrombocytopenic purpura, Petechiae, Haematoma, Thrombocytopenia	11 Days	Yes Resolved
[redacted] .25 Male [redacted]	10 Oct 13	Regulatory Authority	Current Condition: Rhinitis; Historical Condition: No adverse event	[Infanrix hexa], [Prevenar]			Immune thrombocytopenic purpura, Petechiae, Thrombocytopenia, Drug administered to patient of inappropriate age	14 Days	Yes Resolved
[redacted] 1.58 Female [redacted]	10 Oct 13	Regulatory Authority	Current Condition: Conjunctivitis	[Infanrix hexa], [Meningitec]		[Rifampicine]	Immune thrombocytopenic purpura, Incorrect route of drug administration	32 Days	Yes Improved
[redacted] .42 Male [redacted]	15 Oct 13	Regulatory Authority	Current Condition: Viral infection	[Infanrix hexa]		[Prevenar]	Immune thrombocytopenic purpura, Petechiae, Haematoma, Thrombocytopenia	1 Months	Yes Unknown
[redacted] .17 UNK [redacted]	8 Nov 13	Physician, Consumer		[Infanrix hexa]		[Rotarix], [Pneumococcal vaccine]	Thrombocytopenic purpura	5 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .29 Male [redacted]	28 Apr 14	Regulatory Authority, Other Health Professional		[Infanrix hexa]	2		Immune thrombocytopenic purpura	21 Days	Yes Improved
[redacted] 1.33 Female [redacted]	16 May 14	Regulatory Authority	Current Condition: Generalised tonic-clonic seizure, Varicella	[Infanrix hexa]			Pyrexia, Vomiting, Rash vesicular, Thrombocytopenic purpura, Neutropenia, Drug administered to patient of inappropriate age	1 Days	Yes Unknown
[redacted] Male	27 May 14	Physician	Historical Condition: No adverse event	[Infanrix hexa]		[Prevenar]	Purpura, Vaccination site reaction		No Resolved
[redacted] .42 Male	9 Dec 11	Physician		[Infanrix hexa]	2		Petechiae, Purpura	4 Days	No Resolved
[redacted] 2.17 Male	6 Jul 12	Regulatory Authority		[Infanrix hexa]			Pneumonia, Immune thrombocytopenic purpura, Tachypnoea, Rales, Haematoma	5 Days	Yes Resolved
[redacted] .92 Male	29 Jan 13	Physician, Consumer	Historical Condition: Febrile infection	[Priorix Tetra], [Infanrix hexa]	4		Immune thrombocytopenic purpura, Thrombocytopenia, Petechiae, Haematoma, Platelet count decreased, Bleeding time prolonged	24 Days	Yes Resolved
[redacted] .92 Male [redacted]	8 Apr 13	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	4	[Infanrix hexa], [Prevenar 13]	Immune thrombocytopenic purpura	4 Days	Yes Unresolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Male [redacted]	14 Jan 14	Physician, Consumer	Historical Condition: Premature baby, Continuous positive airway pressure, Hyperbilirubinaemia	[Infanrix hexa], [Synflorix], [Rotarix liquid formulation]	1	[Vigantol]	Vasculitis, Purpura, Decreased appetite, Petechiae, Rash, Platelet count increased, Skin haemorrhage	1 Days	Yes Improved
[redacted] .19 Male	15 May 14	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	1		Urticaria, Purpura	2 Days	No Unknown
[redacted] .17 Female [redacted]	30 Sep 14	Physician	Historical Condition: Breech delivery, Premature baby, Hospitalisation	[Infanrix hexa]		[Hepatitis B vaccine], [BCG VACCINE]	Immune thrombocytopenic purpura, Neutropenia, Rash, Contusion, Mouth haemorrhage, Petechiae		Yes Recovered/Resolved

APPENDIX 7B.20 : Allergic reaction (including anaphylactic and anaphylactoid reactions)

The GSK worldwide clinical safety database was searched using the following criteria:

- **Data lock point:** since launch until 22 October 2014
- **Report types:** All spontaneous reports
- **Suspect vaccine**: Infanrix hexa (DTPa-HBV-IPV+Hib)
- **MedDRA preferred term (PT)**: all PTs included in the narrow SMQ (Standard MedDRA Query) Anaphylactic reaction

A total of 114 reports (cases) were retrieved from the GSK worldwide safety database since launch in 2000, of which 41 were reported during the period between 23 October 2011 and 22 October 2014 (Table 1).

Figure 1 shows that, since launch, the worldwide reporting frequency of cases including at least one PT from the narrow SMQ Anaphylactic reaction was stable and varied between 0.04 and 0.23 cases per 100000 doses sold.

Figure 1 Yearly reporting frequency for cases including at least one PT from the narrow SMQ Anaphylactic reaction

*The data for 2014 does not cover the entire year as the data lock point was 22 October 2014

Data currently available to GSK suggest that allergic reaction is very rarely associated with Infanrix hexa vaccination. The highest yearly reporting frequency observed was 2.3 reports per 1 million doses sold (2005).

Hypersensitivity is a contraindication listed in the Infanrix hexa RSI.

GSK will continue to monitor and describe allergic reactions in future Infanrix hexa aggregate safety reports. GSK will also continue to employ a routine, pro-active process for identifying safety signals with three main components:

- Ongoing awareness and review of important individual cases, including all reports with a fatal outcome.

- Systematic, regular and proactive review of aggregate safety data. This includes trend analysis to detect increased frequency of reporting and quantitative methodologies to detect drug interactions and signals in overdose/medication errors, paediatrics and the elderly.
- Systematic, regular review of the literature.

Sources screened for signals as part of GSK's routine pharmacovigilance include the GSK safety database, disproportionality analysis, global scientific literature, clinical study data, epidemiology study data and pre-clinical information.

Table 1 **Line listing of cases including at least one PT from the narrow SMQ Anaphylactic reaction received during the period (N=41)**

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Female [redacted]	29 Dec 11	Regulatory Authority, Physician	Historical Condition: Premature baby, Neonatal respiratory distress syndrome, Low birth weight baby; Current Condition: Congenital hypothyroidism, Bronchopulmonary dysplasia	[Infanrix hexa], [Prevenar 13]		[Synagis], [Iron], [Vitamin]	Cardiac arrest, Cardiopulmonary failure, Loss of consciousness, Shock, Slow response to stimuli, Cyanosis, Hypotonia, Mydriasis, Clonus, Anuria		Yes Fatal
[redacted] .15 UNK [redacted]	9 Jan 12	Other Health Professional		[Infanrix hexa], [Synflorix], [Rotarix]			Circulatory collapse, Respiratory arrest	10 Minutes	Yes Unknown
[redacted] .17 Male [redacted]	17 Jan 12	Regulatory Authority, Physician	Current Condition: Bronchopneumonia, Premature baby, Patent ductus arteriosus, Atrial septal defect, Cardiac septal defect	[Infanrix hexa], [Prevenar 13]			Cardiac arrest, Vomiting, Shock, Hypoxia, Altered state of consciousness, Aspiration tracheal	3 Days	Yes Fatal
[redacted] .25 Male [redacted]	31 Jan 12	Regulatory Authority, Physician	Current Condition: Nasopharyngitis	[Infanrix hexa], [Synflorix]	2		Hypotonic-hyporesponsive episode, Pyrexia, Ill-defined disorder, Pallor, Depressed level of consciousness, Circulatory collapse		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Male [redacted]	24 Feb 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix], [Rotarix liquid formulation]		[Vigantol]	Waterhouse-Friderichsen syndrome, Multi-organ failure, Septic shock, Disseminated intravascular coagulation, Altered state of consciousness, Meningitis, Shock, Cardiac failure, Meningococcal sepsis, Petechiae, Cough, Body temperature increased, Nasopharyngitis, Dyspnoea, Cyanosis, Arrhythmia, Bradycardia, Tachycardia, Hypotension, Faeces discoloured, Terminal state, Somnolence	3 Days	Yes Fatal
[redacted] .25 Male [redacted]	24 Feb 12	Other Health Professional		[Infanrix hexa], [Synflorix]		[Glucose]	Loss of consciousness, Hypotonic-hyporesponsive episode, Pallor, Faecal incontinence, Cold sweat, Dyspnoea, Diarrhoea, Shock		Yes Improved
[redacted] .58 Male [redacted]	20 Mar 12	Other Health Professional		[Infanrix hexa]	3		Anaphylactic reaction, Incorrect route of drug administration, Cyanosis, Emotional distress, Tachypnoea, Wheezing, Dyspnoea		Yes Resolved
[redacted] .33 Male [redacted]	31 May 12	Regulatory Authority, Physician		[Infanrix hexa], [Neisvac-C]	2		Anaphylactic reaction, Conjunctival irritation, Bronchospasm, Oedema, Hypotonia, Conjunctival oedema		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .17 Female [redacted]	27 Jun 12	Regulatory Authority, Consumer	Current Condition: Ill-defined disorder	[Infanrix hexa], [Synflorix]	1		Loss of consciousness, Hypotonic-hyporesponsive episode, Injection site pain, Injection site swelling, Circulatory collapse, Injection site inflammation, Pallor		Yes Improved
[redacted] .17 Male [redacted]	6 Jul 12	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar]			Cyanosis, Loss of consciousness, Shock, Pallor, Cold sweat, Dyspnoea		Yes Resolved
[redacted] .25 Female [redacted]	27 Aug 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]			Hypotonic-hyporesponsive episode, Circulatory collapse, Pyrexia, Pallor, Ill-defined disorder, Eye movement disorder, Heart rate decreased, Hyporesponsive to stimuli, Otitis media		Yes Resolved
[redacted] .13 Male [redacted]	12 Sep 12	Regulatory Authority, Physician		[Infanrix hexa], [Synflorix]	1	[Paracetamol]	Circulatory collapse, Viral infection, Pallor, Ill-defined disorder, Somnolence, Pyrexia		Yes Resolved
[redacted] .33 Female [redacted]	26 Oct 12	Other Health Professional, Consumer	Current Condition: Rash	[Infanrix hexa]	1	[DTPa-Polio-HIB (Non-GSK)]	Anaphylactic reaction, Pyrexia, Extensive swelling of vaccinated limb, Rash generalised, Injection site erythema	1 Days	Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Male [redacted]	3 Dec 12	Other Health Professional, Consumer, Physician		[Rotarix liquid formulation], [Infanrix hexa], [Prevenar 13]			Anaphylactic shock, Pallor, Cyanosis, Apathy, Hypotonia, Slow response to stimuli, Somnolence, Hypotension, Syncope		Yes Resolved
[redacted] .33 Female [redacted]	22 Feb 13	Regulatory Authority, Physician	Current Condition: Heart disease congenital; Historical Condition: Surgery	[Infanrix hexa], [Synflorix]	3		Circulatory collapse, Death, Cardiovascular disorder, Infection, Diarrhoea	3 Days	Yes Fatal
[redacted] .67 Female [redacted]	22 Mar 13	Consumer		[Infanrix hexa]	2		Shock, Crying, Presyncope, Hypotonia, Pyrexia, Vomiting, Irritability		Yes Improved
[redacted] .5 Male [redacted]	12 Apr 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]			Anaphylactic shock, Loss of consciousness, Cardio-respiratory arrest, Cyanosis, Hypotonia, Hypertonia		Yes Resolved
[redacted] .25 Female [redacted]	29 May 13	Physician, Consumer	Historical Condition: Erythema	[Infanrix hexa]			Anaphylactic shock, Hypersensitivity	1 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .17 Female [redacted]	5 Jun 13	Regulatory Authority	Current Condition: Congenital musculoskeletal anomaly, Hypochondroplasia, Deformity thorax, Limb malformation, Gastroenteritis rotavirus; Historical Condition: Respiratory distress, Foetal growth restriction, Computerised tomogram, Echocardiogram, Ultrasound scan, No adverse event	[Infanrix hexa], [Prevenar 13]			Shock, Pyrexia, Tachycardia, Skin discolouration, Pallor, Feeling hot, Hypotension, Tachypnoea, Abdominal distension, Pharyngeal erythema, Hypotonia, Normochromic normocytic anaemia, Gastroenteritis rotavirus, Diarrhoea, Vomiting	1 Days	Yes Resolved
[redacted] .17 Male [redacted]	6 Jun 13	Physician		[Infanrix hexa]	1		Anaphylactic shock, Apnoea, Cyanosis		Yes Resolved
[redacted] .33 Female [redacted]	20 Aug 13	Other Health Professional, Consumer, Regulatory Authority	Current Condition: Dermatitis atopic	[Infanrix hexa], [Rotarix liquid formulation], [Prevenar 13]			Anaphylactoid reaction, Feeling hot, Urticaria, Rash erythematous, Crying, Irritability, Rash vesicular, Emotional distress		Yes Resolved
[redacted] UNK [redacted]	17 Sep 13	Physician		[Infanrix hexa]	2		Anaphylactic shock		Yes Unknown

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .5 Female [redacted]	14 Jan 14	Regulatory Authority, Physician, Consumer	Current Condition: Cough, Talipes, Cardiomyopathy	[Infanrix hexa]	3		Cardiopulmonary failure, Pneumonia, Circulatory collapse, Cough, Anxiety, Vomiting, Pyrexia, Diarrhoea, Decreased appetite, Throat irritation, Pallor, Condition aggravated	3 Days	Yes Fatal
[redacted] .13 Female [redacted]	10 Feb 14	Pharmacist, Physician, Regulatory Authority	Current Condition: Bronchiolitis; Historical Condition: No adverse event	[Infanrix hexa], [Prevenar 13]	1		Circulatory collapse, Loss of consciousness, Hypotonia, Respiratory disorder, Lividity, Feeling cold, Malaise, Drug administered to patient of inappropriate age	2 Days	Yes Resolved
[redacted] .42 UNK [redacted]	6 Mar 14	Regulatory Authority		[Infanrix hexa], [Prevenar 13]	2		Circulatory collapse, Loss of consciousness, Crying, Pallor, Hyperhidrosis, Cyanosis, Musculoskeletal stiffness		Yes Resolved
[redacted] .33 Male [redacted]	7 Apr 14	Consumer		[Infanrix hexa]	2		Anaphylactic reaction, Eyelid oedema, Crying, Pallor, Depressed mood, Vomiting, Diarrhoea, Milk allergy	4 Hours	Yes Unknown
[redacted] .17 Female [redacted]	5 Jun 14	Regulatory Authority, Physician, Other Health Professional	Historical Condition: Premature baby; Historical Drug: CPAP	[Infanrix hexa], [Synflorix]			Apnoea, Anaphylactic reaction, Bradycardia	2 Days	Yes Resolved
[redacted] .33 Male [redacted]	23 Sep 14	Regulatory Authority, Other Health Professional		[Infanrix hexa]			Anaphylactic reaction		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] 2 Female	30 Sep 14	Consumer		[Infanrix hexa], [Synflorix]			Crying, Respiratory arrest, Circulatory collapse, Pyrexia, Developmental delay		Yes Unknown
[redacted] .25 Male	24 Oct 11	Physician		[Infanrix hexa], [Prevenar 13], [RotaTeq]	2	[Infanrix hexa]	Convulsion, Circulatory collapse, Pallor, Hypotonic-hyporesponsive episode, Depressed level of consciousness		Yes Resolved
[redacted] .25 Female	19 Jan 12	Physician, Regulatory Authority		[Infanrix hexa], [Prevenar 13]	2	[Infanrix hexa], [Prevenar 13]	Loss of consciousness, Vomiting projectile, Diarrhoea, Pyrexia, Circulatory collapse, Hypotonia, Unresponsive to stimuli, Gaze palsy, Cardiovascular disorder, Gastroenteritis		Yes Resolved
[redacted] .92 UNK	25 Jan 12	Physician		[Infanrix hexa]			Circulatory collapse, Crying	1 Days	Yes Resolved
[redacted] .21 Male	20 Feb 12	Physician, Regulatory Authority	Historical Condition: Hyperbilirubinaemia neonatal, Phototherapy, Bronchitis, Vacuum extractor delivery; Current Condition: Congenital oral malformation	[Rotarix], [Infanrix hexa]	1	[Colecalciferol + sodium fluoride]	Gastroenteritis, Circulatory collapse, Pallor, Vomiting, Diarrhoea, Haematochezia, Mastication disorder, Salivary hypersecretion	13 Days	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .15 Male [redacted]	5 Mar 12	Regulatory Authority, Physician	Current Condition: Abdominal pain, Adjustment disorder; Historical Condition: Subarachnoid haemorrhage neonatal, Cerebral haemorrhage neonatal, Convulsion	[Rotarix liquid formulation], [Infanrix hexa], [Prevenar 13], [Neisvac-C]	1	[D-fluoretten], [Lefax liquid]	Hypotonic-hyporesponsive episode, Circulatory collapse, Hyporesponsive to stimuli, Hypotonia		Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .25 Female [redacted]	30 Jul 12	Regulatory Authority, Lawyer, Other Health Professional, Consumer, Physician	Historical Condition: Respiratory disorder, Neonatal infection, Neonatal behavioural syndrome; Current Condition: Positional plagiocephaly, Posture abnormal, Hypertonia, Umbilical hernia, obstructive, Diastasis recti abdominis, Congenital genital malformation female, Failure to thrive, Skull malformation, Dysmorphism, Physiotherapy, Restlessness, Hypotonia	[Infanrix hexa]	1		Clonus, Crying, Opisthotonus, Convulsion, Metabolic disorder, Restlessness, Motor dysfunction, Irritability, Asthenia, Vomiting, Gastrooesophageal reflux disease, Trismus, Salivary hypersecretion, Abnormal faeces, Constipation, Abdominal pain, Sleep disorder, Hyporeflexia, Choking, Hyperhidrosis, Injection site pain, Injection site erythema, Injection site swelling, Injection site induration, Circulatory collapse, Upper respiratory tract infection, Bronchitis, Cough, Rhinitis, Pharyngitis, Stridor, Extrapyramidal disorder, Coordination abnormal, Hypertonia, Gastrointestinal motility disorder, Flatulence, Ataxia, Developmental delay, Dystonia, Nervous system disorder, Gross motor delay		Yes Unresolved
[redacted] .21 Male [redacted]	26 Apr 13	Physician		[Infanrix hexa]	1		Hypotonic-hyporesponsive episode, Circulatory collapse, Depressed level of consciousness	12 Hours	Yes Resolved

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .23 Male [redacted]	2 May 13	Regulatory Authority, Physician		[Infanrix hexa], [Prevenar 13]	1		Acute hepatic failure, Pulmonary haemorrhage, Adenovirus infection, General physical health deterioration, Vomiting, Body temperature increased, Transaminases increased, Lactic acidosis, Hypoglycaemia, Hepatic function abnormal, Hyperammonaemia, Encephalopathy, Renal failure, Circulatory collapse	8 Days	Yes Fatal
[redacted] .33 Male [redacted]	11 Mar 14	Physician	Historical Condition: Pyelocaliectasis, Hypotension, Depressed level of consciousness	[Infanrix hexa]	2	[Infanrix hexa]	Shock, Hypotension, Depressed level of consciousness	24 Hours	Yes Unresolved
[redacted] .42 Male [redacted]	28 Apr 14	Physician, Consumer	Current Condition: Dermatitis atopic, Hypersensitivity	[Infanrix hexa], [Prevenar 13], [RotaTeq], [MMR vaccine]	3		Anaphylactoid reaction, Tongue oedema, Injection site erythema, Viral infection, Body temperature increased, Cough, Bronchitis, Restlessness		Yes Resolved
[redacted] .25 Female [redacted]	6 Oct 14	Physician, Regulatory Authority	Current Condition: Increased appetite, Peritoneal disorder, Mesenteritis; Historical Condition: Foetal heart rate abnormal	[Rotarix liquid formulation], [Infanrix hexa], [PREVENAR 13]	1	[BCG VACCINE]	Intussusception, Dehydration, Shock, Haematochezia, Loss of consciousness, Pyrexia, Fatigue, Vomiting, Hypotonia, Weight decreased, Diarrhoea, Drug administered to patient of inappropriate age		Yes Fatal

Case ID, Age (years), Gender and Country	Initial GSK Receipt Date	List of Reporter Types	List of Medical Conditions PT	List of Suspect Product Names	Dose Number	List of Concomitant Product Names	List of events PT	Onset from Last Dose	Case Level Seriousness and Outcome
[redacted] .33 Male [redacted]	7 Oct 14	Other Health Professional		[Infanrix hexa], [Prevenar 13]			Lip swelling, Dysphonia, Anaphylactic reaction		Yes Recovered/ Resolved