Original Article

Deaths Reported after Pentavalent Vaccine Compared with Death Reported after Diphtheria-Tetanus-Pertussis Vaccine: An Exploratory Analysis

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Abstract

Introduction: Immunization is one of the most effective public health tools available to prevent death and disease. Serious adverse events following immunization (AEFI) are rare. However, coincidental sudden-infant-death-syndrome (SIDS) deaths do occur temporally associated with vaccination. In 2010, the Government of India (GoI) introduced a new standard operating procedure (SOP) to report AEFI. There have been stray newspaper reports of deaths soon after the administration of the pentavalent vaccine (PV) which was introduced by the GoI in December 2011. This study was conducted to examine if there is an epidemiological signal from the data collected passively under the new SOP. **Materials and Methods:** We used data provided by the GoI on the number children who received three doses of diphtheria-tetanus-pertussis vaccine (DTP), the number receiving PV and the number of deaths in the vaccinated within 72 h. **Results:** After PV was introduced in the states, 45 million infants received DTP vaccination and 25 million received PV. There were 217 deaths within 72 h after DTP was administered and 237 following PV. There were 4.8 deaths per million vaccinated with DTP (95% confidence interval [CI]: 4.2–5.5) and 9.6 deaths (95% CI: 8.4–10.8) per million vaccinated with PV (odds ratio 1.98 (95% CI 1.65-2.38) There were 4.7 additional deaths (95% CI: 3.5–5.9), per million, vaccinated with PV instead of DTP ($P < 0.0001$). **Discussion:** Deaths following DTP vaccination would include the natural rate of deaths within that window period, plus deaths if any, caused by DTP. For purposes of this study, we assumed that all the deaths associated with DTP are coincidental SIDS deaths. Taking that as the base rate of SIDS, we look for any increase in the death rate after PV. This study demonstrated an increase in reports of sudden unexplained deaths within 72 h of administering PV compared to DTP vaccine. Whether improvements in AEFI surveillance system or other factors contributed to this increase cannot be ascertained from this study. **Conclusion:** These findings do not warrant deviation from current vaccination schedule, but the differential death rates between DTP and PV do call for further rigorous prospective population-based investigations.

Keywords: *Adverse events following immunization, pentavalent vaccine, TOKEN study*

Received: 17-09-2017
Accepted: 31-10-2017

Introduction

Pentavalent vaccine (PV) (combined Haemophilus influenzae type B (Hib), hepatitis B, whooping cough, tetanus, and diphtheria vaccine) was introduced in the national immunization programmes of Sri Lanka and

Access this article online

Quick Response Code:

Website: www.mjdrdypu.org

DOI: 10.4103/MJDRDYPU.MJDRDYPU_188_17

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How to cite this article: Puliyel J, Kaur J, Puliyel A, Sreenivas V. Deaths reported after pentavalent vaccine compared with death reported after diphtheria-tetanus-pertussis vaccine: An exploratory analysis. Med J DY Patil Vidyapeeth 0;0:0.

Bhutan before it was introduced in India. In both these countries, use of this vaccine was temporally associated with adverse events following immunization (AEFI) including unexplained deaths.[1] These were investigated by the WHO, and the deaths were declared as unlikely to be related to the vaccine. In India, starting 15 December 2011, PV was introduced into the country's immunization program to replace the diphtheria-tetanus-pertussis (DTP) vaccine (diphtheria, tetanus and whooping cough) in a staged manner with a view to add protection against Hib and hepatitis B without increasing the number of injections given to infants. In India also, there have been sporadic newspaper reports of deaths soon after administration of the new vaccine, including the unexplained death of twins, a day after vaccination.[2]

Serious adverse reactions following vaccination are very rare. Miller *et al*. note however that because a very large number are vaccinated, coincidental adverse events including deaths due to sudden-infant-death-syndrome (SIDS) that are temporally associated with vaccination, do occur.[3] It is said that the deaths associated with PV are merely coincidental SIDS deaths, associated temporally with immunization and they are unrelated to vaccination and the vaccine used.[4]

Another factor that should be borne in mind is that the Government of India (GoI) improved its systems for surveillance of AEFI and developed a detailed standard operating procedure (SOP) manual for AEFI in 2010.[5] Details of this time-bound reporting system are quoted below.

Reporting and investigation of adverse events following immunization

Serious AEFIs are defined as those that are life-threatening and those that result in hospitalization, disability (or have the potential to result in disability) or death.[5]

At the field level, auxiliary nurse midwives, health assistant and other field level health workers and medical officers (MO) of primary health centers (PHC) are expected enquire about and monitor the occurrence of AEFI. In case of a serious AEFI, the MO (PHC) is expected to be informed by telephone immediately. He/she has then to initiate an investigation personally to verify the facts, fill the first information report (FIR) and have it sent to the district immunization officer (DIO) within 24 h and also inform the DIO by telephone or fax immediately. The incriminated vial of vaccine and syringe used to administer the vaccine are collected and sent under cold chain requirements to DIO and finally to Central Research Institute, Kasauli for laboratory investigation.[5]

The DIO initiates an investigation and files a preliminary investigation report (PIR) and detailed investigation report (DIR). The FIR is sent to the Assistant Commissioner Universal Immunization Programme within 24 h, the PIR within 7 days and the DIR within 90 days. Deaths are investigated by the regional investigation team (RIT) which team is informed through the State Expanded Programme of Immunization Officer (SEPIO) by telephone or fax.[5]

In the event of death, the RIT is expected to make an onsite investigation and then file a preliminary report available to the SEPIO within 72 h. The final report is readied within a reasonable time (3 months) period after completing necessary tests and detailed investigations.[5]

The State Expert Committee recommends cases for expert review and causality assessment. The expert review and causality assessment team review individual serious and unusual AEFIs to assess a potential causal link between the event and the vaccine. The committee meets at least twice a year to review the serious and unusual AEFI.[5]

Better reporting of AEFI through implementation of this new SOP could have contributed to the perception that there is an increased incidence of deaths after the introduction of PV. The SIDS rate in India is not known. For this study, we assumed that all deaths within 72 h of receiving DPT are naturally occurring SIDS deaths. We hypothesize that if there is a significantly higher rate of deaths after PV compared to DPT administered to other children contemporaneously in the same state, the increased rate of deaths cannot be attributed to the natural rate of SIDS but may be caused by PV. In each state, we looked at the deaths associated with DPT after PV was introduced in the state, to ensure that all the AEFI deaths were being reported using the same SOP.

Materials And Methods

Data on AEFI deaths occurring within 72 h after vaccine administration, reported to the government surveillance system from April 2012 to May 14, 2016, and the numbers of infants (0–11 months old) vaccinated from April 2012 to March 29, 2016 (as on April 9, 2016) were obtained from the Ministry of Health and Family Welfare (MoH and FW) of the GoI under the Right to Information Act (RTI) 2005. The RTI reply is posted online.[6] Data from the health information management system of the MoH and FW[7] on a number of children vaccinated with DPT and PV were extracted to Microsoft Excel spreadsheets, and the raw data used for the analysis is posted online.[8] We utilized data on DPT and PV from states after PV was introduced and as it was being phased-in, so some children in the state were receiving the DPT and others were getting PV. If a state introduced PV in 2014, then data on DPT doses and

deaths following vaccination were noted from that year on. We assume that within the state, the areas selected by the Government for early introduction of the vaccine was a matter of convenience and the underlying SIDS rate was the same in all areas of the state. There is no evidence to suggest that areas within the state with higher SIDS reporting, were selected for early introduction of PV.

Statistical analysis was performed with MedCalc 14 v14.8.1 (MedCalc Software bvba, Acacialaan 22, 8400, Ostend, Belgium). The 95% confidence interval (CI) was determined for rates. Comparison between groups of categorical data was carried out using the Chi-square test. Correlation coefficient "*r*" was examined for correlations and its *P* value was determined for significance. A value of $P < 0.05$ was considered as statistically significant.

Results

Approximately 45 million infants (the actual figure 44936653 infants, was used in the analysis) received DTP vaccination, and approximately 25 million (actual figures 24803770) were administered three doses of PV. Two hundred and seventeen infants died after DTP and 237 died following PV [Table 1]. There were 4.8 deaths per million vaccinated with DTP (95% CI: 4.2–5.5) and 9.6 deaths (95% CI: 8.4–10.8) per million vaccinated with PV (odds ratio 1.98 (95% CI: 1.65–2.38). There were 4.7 additional deaths (95% CI: 3.5–5.9) within 72 h, per million vaccinated with PV instead of DPT ($P < 0.0001$).

There were wide differences between states in the AEFI death rates reported. States reporting higher rates of death with DPT were also the ones reporting more deaths with PV (Spearman's $\rho = 0.142$, $P = 0.146$). AEFI death rates with PV in the different states ranged from 0 going up to 430 deaths per million vaccinated [Table 2].

Table 1: Adverse events following immunization death rates for diphtheria-tetanus-pertussis and pentavalent vaccine

	DTP vaccine	PV
Total vaccinated	44,936,653	24,803,770
Total deaths	217	237
Death rate per million vaccinated*	4.8	9.6

*$P<0.0001$. DTP: Diphtheria-tetanus-pertussis, PV: Pentavalent vaccine

Table 2: Adverse events following immunization death rate per million vaccinated for diphtheria-tetanus-pertussis and pentavalent vaccine in different states

State	Total number of deaths	
	DTP death rate	PV death rate
Andhra Pradesh old	3.1 (8)	23.0 (13)
Arunachal Pradesh	36.2 (2)	0
Assam	15.7 (11)	13.3 (7)
Bihar	4.8 (24)	5.8 (14)
Chandigarh	0	319.4 (4)
Chhattisgarh	5.1 (6)	14.0 (6)
Dadra and Nagar Haveli	0	0
Daman and Diu	0	0
Delhi	0	15.9 (9)
Goa	0	48.8 (3)
Gujarat	0.7 (1)	2.7 (9)
Haryana	3.6 (2)	18.4 (26)
Himachal Pradesh	3.5 (1)	24.5 (1)
Jammu and Kashmir	0	13.9 (7)
Jharkhand	1.2 (1)	7.1 (4)
Karnataka	5.5 (8)	10.5 (32)
Kerala	0	10.9 (16)
Lakshadweep	0	0
Madhya Pradesh	3.4 (14)	12.4 (21)
Maharashtra	3.8 (21)	13.9 (4)
Manipur	0	223.0 (1)
Meghalaya	28.0 (4)	0
Mizoram	160.3 (9)	430.1 (2)
Nagaland	0	0
Odisha	2.1 (1)	27.3 (6)
Puducherry	0	0
Punjab	0	10.1 (4)
Rajasthan	1.8 (2)	3.6 (6)
Sikkim	0	0
Tamil Nadu	50.7 (1)	2.6 (9)
Telangana	4.5 (4)	11.1 (4)
Tripura	85.4 (13)	158.8 (1)
Uttar Pradesh	4.0 (55)	48.2 (11)
Uttarakhand	5.6 (1)	5.1 (1)
West Bengal	9.2 (28)	12.0 (16)

DTP: Diphtheria-tetanus-pertussis, PV: Pentavalent vaccine

Discussion

It is often difficult to say whether a death soon after immunization is caused by the vaccine or is a coincidental event. To overcome this problem we have compared deaths following immunization with one or the other of the two vaccines given at the same age, in a large cohort of babies. The rate of coincidental deaths will be similar no matter what vaccine is given. The study assumes that all deaths following DTP are coincidental SIDS deaths and that even if no vaccine was given on that day; these children would have died anyway. We hypothesis further, that if PV does not result in deaths, there would be no increase in the death rates in children given this vaccine.

We have, in this analysis, looked at AEFI deaths within 72 h of vaccination. Not all AEFI deaths occur within 72 h and our calculations underestimate the total deaths from AEFI. However, if the window period is enlarged, there is an increased chance that more deaths unrelated

to vaccination would be included. We took the cue from the TOKEN study[9] looking at sudden infant deaths following PV which found significantly more deaths within the first 72 h. It is a weakness of this analysis that we are not able to capture all AEFI deaths from the vaccine. It merely examines if there a significant increase in deaths following vaccination with one of the vaccines within a small window period.

Extrapolating the data, using the mean values for the excess deaths with PV, we estimate that if the birth cohort of 26 million in India is vaccinated each year, there is would be 122 additional deaths (95% CI: 101–145) within 72 h, due to the switch from DTP to PV.

There was great variation in the death rates reported from different states. This could reflect a real difference in susceptibility to AEFI in different states, or it could be that some states record these deaths more meticulously. If we reject the conclusion that the large differences seen in the AEFI rate are related to differences in local susceptibility, we have to accept the possibility that it relates to poor recording of AEFI in some states. It follows that nation-wide projections should be made based on figures available from states with the best reporting. The analysis shows there is likely to be 7020–8190 deaths from the vaccine each year if data from states with the better reporting, namely Manipur and Chandigarh, are projected nationwide.

Most of these deaths have been reviewed by the expert review and causality assessment team and none of the deaths were deemed to be "Consistent causal association to immunization: A1 Vaccine product-related reaction." According to the revised WHO causality assessment manual of AEFI,[10] only reactions for which their "evidence in the literature that the vaccine(s) may cause the reported event" even if administered correctly are classified as "Consistent causal association to immunization: A1 vaccine product-related reaction" [Figure 1 for the algorithm and Figure 2 for the AEFI causality assessment classification for a single case] The product insert for DTP[11] and PV[12] do not report death as one of the adverse reactions and so it is not surprising that none of these deaths investigated are recorded as "A1 Vaccine product-related reaction" (for want of prior evidence in published literature).

Previous reports of pentavalent adverse events following immunization deaths

A PV Quinvaxem (Crucell), was introduced in Sri Lanka on January 1, 2008.[1] This was followed by 3 deaths which were "probably" caused by the vaccine given that WHO team of experts investigating the death reported that there was no alternate explanation for the events. The team however classified the deaths as "unlikely" to be related to the vaccine.[13]

The adverse events following immunization manual revised

Following this, in March 2013 the "User Manual for AEFI" was revised,[10] acknowledging that most of its concepts and definitions were adapted from "Definitions and Application of Terms for Vaccine Pharmacovigilance Report of CIOMS/WHO Working Group on Pharmacovigilance."[14] The CIOMS/WHO document on page 170, "Notes for Guidelines," states: "If there is adequate evidence that an event does not meet a case definition, such an event should be rejected and should be reported as "Not a case of (AEFI)."[14]

Soon after the revised WHO AEFI causality assessment scheme was published, on May 4, 2013,[10] the Ministry of Health of Viet Nam suspended the use of Quinvaxem (Crucell) when it had caused 9 deaths.[15] WHO experts investigated the Viet Nam deaths. This time they reported "Quinvaxem was prequalified by WHO. No fatal AEFI has ever been associated with this vaccine."[16] This is the same brand of PV which was used in Sri Lanka where three death had occurred.[13] Using the revised AEFI causality assessment, the Sri Lankan deaths had been re-classified as "Not a case of (AEFI)." After that, the WHO "Safety of Quinvaxem report" could state "no fatal AEFI has ever been associated with this vaccine". The memory of the Sri Lanka deaths had been erased by this change.

TOKEN study of deaths with pentavalent vaccine

An epidemiological study investigating PV link to unexplained sudden unexpected death (uSUD) of children between their 2 months and 2 years is available in the TOKEN report.[9] vonKries had previously found a statistically significantly increased standardized mortality ratio (SMR) within 2 days after vaccination with hexavalent vaccines (Hexavac®)[17] and the TOKEN study was done to confirm or refute the association of uSUD with PV and Hexavalent vaccines. This study, using exploratory analyses, indicated an elevated uSUD risk after PV vaccination but not after Hexavalent vaccination. However, despite its rigorous methodology, the TOKEN study suffered from serious statistical and methodological limitations according to the authors and hence, its findings should be interpreted with caution.[9]

Precautionary principle

In spite of the data presented in this paper from a large cohort, it should be pointed out that the evidence is merely circumstantial and not conclusive. The precautionary principle states that "if an action or policy has a suspected risk of causing harm to the public,

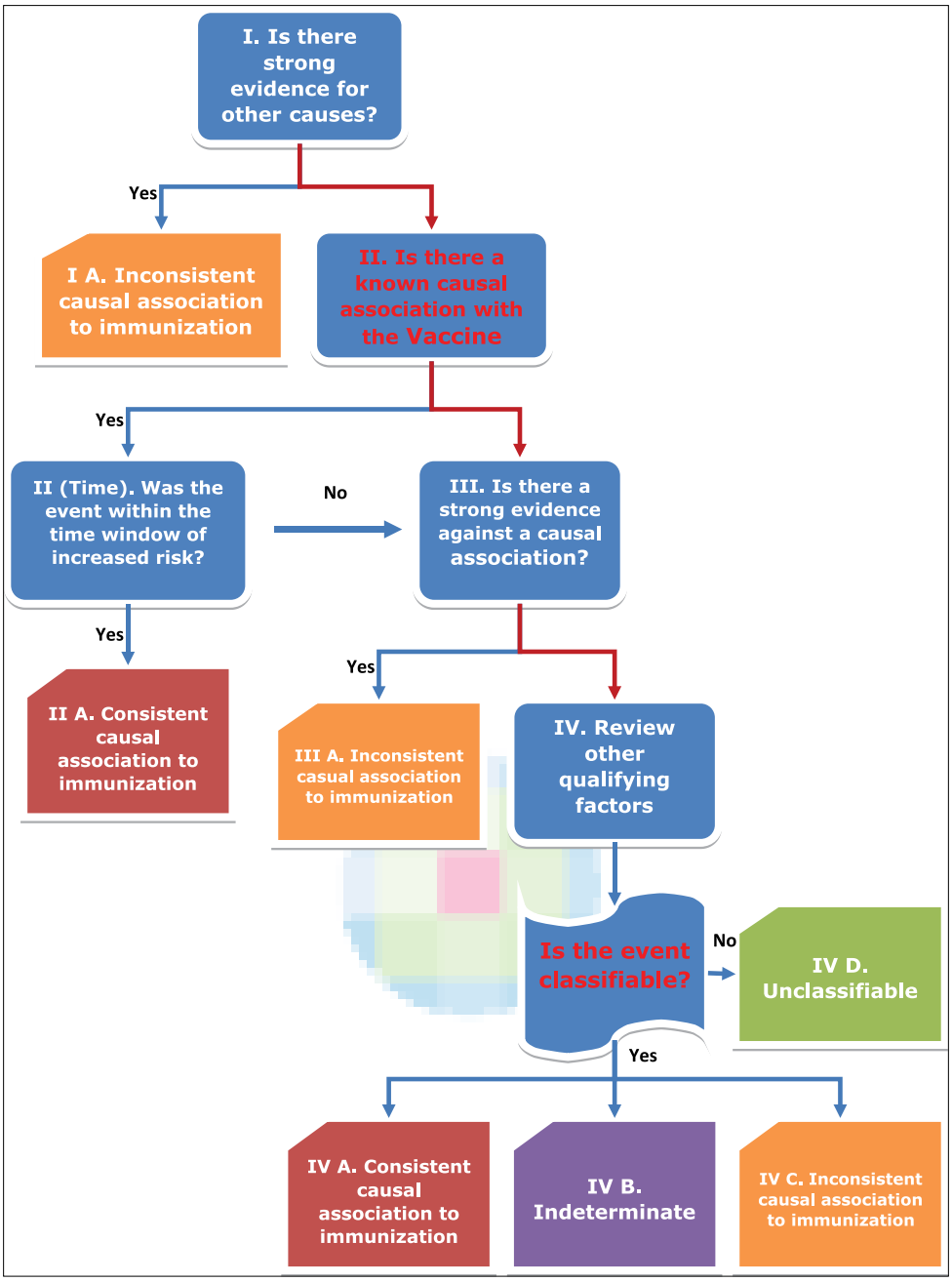

Figure 1: The Revised AEFI Causality Assessment Algorithm. (Adapted from the WHO AEFI Manual (9))

even if there is no scientific consensus, there is a social responsibility to protect the public from exposure to harm".[18] There are statutory obligations, for example under Article 2 European Convention on Human Rights (Art 2 ECHR), "to establish framework of laws, precautions, and means of enforcement which will, to the greatest extend reasonably practicable, protect life." A prospective rigorous review of the deaths following PV is called for to protect the public.

Strengths and limitation of the study

The strength of our study is that it is based on a large, population-based cohort. Such an analysis has the potential to provide an accurate picture of AEFI. However, using this dataset also contributed to the limitations of the study. One important limitation of our data is that it is dependent on the reporting by health workers, many of whom have very limited education and literacy.

Also the government database does not provide the exact ages when the infants were administered the vaccinations. It is known that the SIDS rate is lower as the children become older. It is recommended that three doses of the vaccine are given at monthly intervals after 6 weeks of age. It is not known if there is any variation between

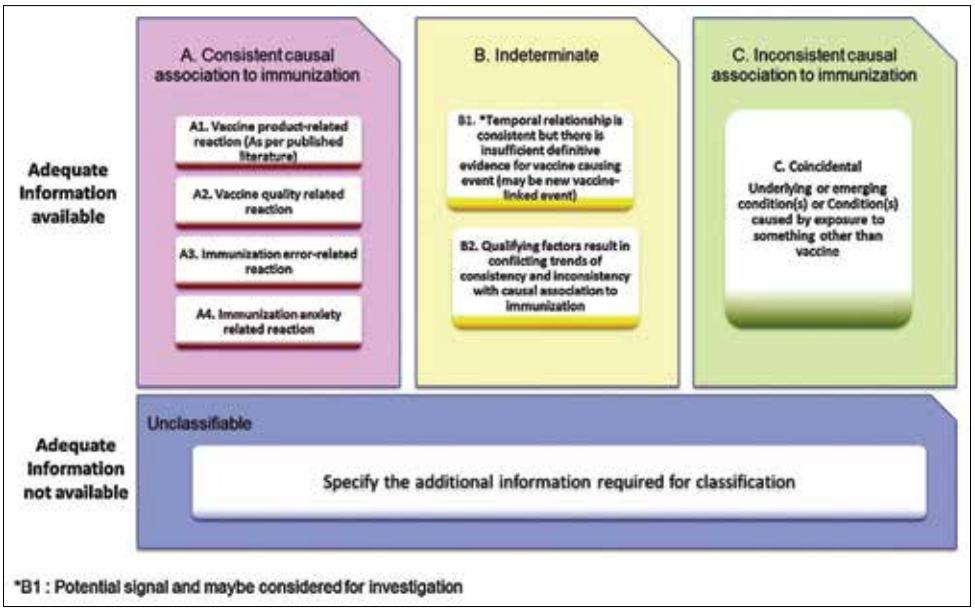

Figure 2: AEFI causality assessment classification of a single case. (As published in WHO AEFI Manual (10))

states in compliance with this schedule and whether that is responsible for the differences seen, but this seems unlikely. Further, the study looks only at a short-term increase in deaths (within 3 days of vaccination), but it does not calculate the potential benefits on infant mortality, for example by protection against lethal diseases like hemophilus influenza.

In this study, we consider PV as a single entity and it is not possible in this analysis to ascertain what component, whether vaccine antigen or additives or combination of these agents are responsible for the deaths.

Vaccination practices in developed countries

Most developed countries use the acellular pertusis vaccine in the DTP (DTaP) and in other combination vaccines. A Cochrane review of combined DTP-Hepatitis B-Hib vaccine found less immunological response to the combined vaccine than when they were administered separately and there were more local reactions to the combined vaccine.[19] Therefore, this combination vaccine is not used in the USA. The Vaccine Adverse Event Reporting System (VAERS) data in the USA suggests there have not been any serious adverse events with these vaccines given separately.[20]

For developing countries too, it can be argued that the same benefit against lethal diseases can be achieved if the vaccines DTP, Hib, and hepatitis B are given separately as it is done in the USA, and it may be safer.

Conclusion

This study has demonstrated a probable increase in sudden unexplained deaths within 72 h of administering PV compared to DTP vaccine. Whether improvement in AEFI surveillance systems or other hitherto unstudied/unrecognized factors contributed to this increase cannot be ascertained from this study. These findings do not warrant deviation from the current vaccination schedule but the differential death rates with DTP and PV does call for further rigorous prospective population-based investigations.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Global Advisory Committee on Vaccine Safety Review of Pentavalent Vaccine Safety Concerns in Four Asian Countries. Report from the Meeting; 12 June, 2013. Available from: http://www.who.int/vaccine_safety/committee/topics/hpv/GACVSstatement_pentavalent_June2013.pdf. [Last accessed on 2016 May 20].
2. Special Correspondent. Infant Twins Die a Day After Vaccination. The Hindu; 5 December, 2015. Available from: http://www.thehindu.com/news/cities/bangalore/infant-twins-die-a-day-after-vaccination/article7950650.ece. [Last accessed on 2016 Aug 01].
3. Miller ER, Moro PL, Cano M, Shimabukuro TT. Deaths following vaccination: What does the evidence show? Vaccine 2015;33:3288-92.
4. Deshmukh V, Lahariya C, Krishnamurthy S, Das MK, Pandey RM, Arora NK, *et al.* Taken to health care provider or not, under-five children die of preventable causes: Findings from cross-sectional survey and social autopsy in rural India. Indian J Community Med 2016;41:108-19.
5. Government of India. Standard Operating Procedure (SOP) for Investigation of Adverse Events Following Immunization (AEFI);

2010. Available from: http://www.searo.who.int/india/topics/routine_immunization/AEFI_standard_operating_procedures_SOPs_2010.pdf. [Last accessed on 2016 Sep 01].

6. Ministry of Health and Family Welfare Government of India. RTI Reply Z33013/01/2016-Imm (Pt); 3 May, 2016. Available from: http://bit.ly/RTIReply. [Last accessed on 2016 Aug 05].
7. Ministry of Health and Family Welfare Government of India. Health Management Information System Reports. Available from: https://www.nrhm-mis.nic.in/hmisreports/frmstandard_reports.aspx. [Last accessed on 2016 Aug 01].
8. Kaur J, Puliyel A, Puliyel J. Data Extracted in Excel Sheets used for Analysis. Available from: http://www.bit.ly/DPTPentaData. [Last accessed on 2016 Aug 05].
9. Schlaud M, Poethko-Müller C, Kuhnert R, Hecker H. TOKEN Study on Deaths in Young Children (2nd to 24th month of Life) Study Report. Available from: http://www.rki.de/EN/Content/Health_Monitoring/Projects/TOKEN_Study/Studyreport.pdf?__blob=publicationFile. [Last accessed on 2016 Aug 01].
10. WHO. The Causality Assessment of Adverse event Following Immunization User Manual for the Revised WHO Classification WHO/HIS/EMP/QSS; March, 2013. Available from: http://www.who.int/vaccine_safety/publications/aevi_manual.pdf?ua=1. [Last accessed on 2017 Nov 25].
11. Serum Institute of India. Triple Antigen. Available from: http://www.vaxinpoint.in/wp-content/uploads/2014/02/Triple-antigen.pdf. [Last accessed on 2017 May 14].
12. Pentaxim Summary of Product Characteristic. Sanofi Pasteur Ltd. Available from: http://www.sfda.moph.go.th/zone_search/files/2C_22_47_N.pdf. [Last accessed on 2017 May 14].
13. Saxena KB, Banerji D, Qadeer I, Kurian NJ, Priya R, Shiva M, *et al.* "Antivaccine lobby" replies to the BMJ. BMJ 2010;341:c4001.
14. CIOMS/WHO Definitions and Application of Terms for Vaccine Pharmacovigilance Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance Available from: http://www.who.int/vaccine_safety/initiative/tools/CIOMS_report_WG_vaccine.pdf. [Last accessed on 2017 Nov 25].
15. TuoiTre News. Vietnam Suspends Quinvaxem Vaccine Following 9 Deaths. TuoiTre News; 5 May, 2013. Available from: http://www.tuoitrenews.vn/society/9330/vietnam-suspends-quinvaxem-vaccine-following-9-deaths. [Last accessed on 2015 Dec 01].
16. WHO. Safety of Quinvaxem (DTwP-HepB-Hib) Pentavalent Vaccine; 10 May, 2013. Available from: http://www.who.int/immunization_standards/vaccine_quality/quinvaxem_pqnote_may2013/en/. [Last accessed on 2017 Feb 23].
17. von Kries R, Toschke AM, Strassburger K, Kundi M, Kalies H, Nennstiel U, *et al.* Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, haemophilius influenzae type b): Is there a signal? Eur J Pediatr 2005;164:61-9.
18. Science and Environmental Health Network. Precautionary Principle Wingspread Conference on the Precautionary Principle; 26 January, 1998. Available from: http://www.sehn.org/wing.html. [Last accessed on 2016 May 23].
19. Bar-On ES, Goldberg E, Leibovici L. Combined DTP-HBV-HIB vaccine versus separately administered DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and haemophilus influenzae B (HIB). Cochrane Database Syst Rev 2012;4:CD005530.
20. CDC. Safety Information about Specific Vaccines. Available from: https://www.cdc.gov/vaccinesafety/vaccines/. [Last accessed on 2017 May 25].