COMMENT

Infanrix hexa and sudden death: a review of the periodic safety update reports submitted to the European Medicines Agency

JACOB PULIYEL, C SATHYAMALA

Abstract

There have been a number of spontaneous reports of sudden unexpected death soon after the administration of Infanrix hexa (combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenza type B vaccine). The manufacturer, GlaxoSmithKline (GSK), submits confidential periodic safety update reports (PSURs) on Infanrix hexa to the European Medicines Agency (EMA). The latest is the PSUR 19. Each PSUR contains an analysis of observed/expected sudden deaths, which shows that the number of observed deaths soon after immunisation is lower than that expected by chance.

This commentary focuses on that aspect of the PSUR which has a bearing on policy decisions. We analysed the data provided in the PSURs. It is apparent that the deaths acknowledged in the PSUR 16 were deleted from the PSUR 19. The number of observed deaths soon after vaccination among children older than one year was significantly higher than that expected by chance once the deleted deaths were restored and included in the analysis.

The manufacturer must explain the figures that have been submitted to the regulatory authorities. The procedures undertaken by the EMA to evaluate the manufacturer's claims in the PSUR need to be reviewed. The Drugs Controller General of India nearly automatically accepts drugs and vaccines approved by the EMA. There is a need to reappraise the reliance on due diligence by the EMA.

Introduction

On October 23, 2000, the marketing of two hexavalent vaccines, Infanrix hexa® (GlaxoSmithKline plc-GSK) and Hexavac® (Sanofi Pasteur MSD, SNC), which combine diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenza type B, was authorised in the European Union. Following authorisation, there were several spontaneous reports of sudden unexpected death soon after the administration of these hexavalent vaccines. In 2005, von Kries and colleagues (1) performed a detailed analysis in which they compared the observed deaths soon after vaccination with the deaths expected by chance. They found that the standardised mortality ratio (SMR) within two days of the Hexavac vaccination was significantly increased among children vaccinated in the second year of life. This was not the case with Infanrix hexa™. At the request of the marketing authorisation holder, Hexavac was withdrawn in 2005 and Infanrix hexa continued to be marketed in Europe (2).

According to European law, the European Medicines Agency (EMA) is accountable for the protection of public health through the evaluation of the medicines approved by it as the regulatory authority. The manufacturers are responsible for the efficacy, quality and safety of their drugs (3).

The Italian Court of Judge Nicola Di Leo made GlaxoSmithKline's confidential 15th and 16th periodic safety update reports (PSURs) from 2009 to 2011 available to the public (4). The PSUR 19 (incorporating PSURs 17, 18 and 19, dated January 15, 2015) was obtained by Dr Loretta Bolgan from the EMA under Article 3 of the EMA rules (EMA 110196/2006 of November 30, 2010) (5). Dr Bolgan sent this PSUR to the first author (JP), requesting him to write a report to be presented to the European Parliament. This commentary is based on all these PSURs. In the context of the safety aspect previously highlighted by von Kries (1), this commentary examines sudden deaths following the use of the Infanrix hexa vaccine. Other aspects dealt with in the PSURs are not examined.

PSUR 15 – clustering of deaths after vaccination

Most deaths occurring in the post-neonatal period are due to infections, congenital defects, malignancies or accidents. Seldom do babies die without any evident cause and such deaths are classified as (i) sudden infant death syndrome (SIDS), defined in the PSUR as death that occurs in the first year of life and remains unexplained after autopsy, or (ii) sudden unexpected death (SUD), defined as death which occurs in the first two years of life, and which remains unexplained after clinical and final event history, but without autopsy. Together, these two are considered sudden death (SD) in the PSUR 15.

Authors: **Jacob Puliyel** (corresponding author – puliyel@gmail.com), Head, Department of Pediatrics, St Stephens Hospital, Delhi 110054, INDIA; **C Sathyamala** (csathyamala@gmail.com), Public Health Physician and Epidemiologist, 121, Pocket-B, SFS Flats, Sukhdev Vihar, New Delhi 110 025, INDIA.

To cite: Puliyel J, Sathyamala C. Infanrix hexa and sudden death: a review of the periodic safety update reports submitted to the European Medicines Agency. *Indian J Med Ethics*. Published online on September 5, 2017. Corrected on September 9, 2017*. DOI: 10.20529/IJME.2017.079

Manuscript Editor: Mala Ramanathan

A number of vaccines are administered on any given day to children under the age of 2 years; the number of children vaccinated all over the world is very large. It is possible that by chance, some vaccinated children might die of coincidental SIDS/SUD, events which might have occurred even if these children had not been vaccinated on that day. To ascertain if such a death was caused by vaccination or was a coincidental event, an observed/expected analysis of SD is performed. The analysis estimates if the number of deaths observed after vaccination exceeds that which can be expected by chance.

Sudden deaths: observed vs expected

The PSUR 15 explains how this analysis is performed (4:p 782): "The Company evaluated whether the number of sudden deaths reported in this age group exceeded the number one could expect to occur by coincidence. Since the distribution of the age at which subjects are vaccinated is unknown, the Company assumed that the proportion of adverse events by age is representative for the actual age distribution at vaccination. It can thus be estimated that 90.6% of all recipients of Infanrix hexa™ were in their first year of life, and 9.4% were in their second year of life. Therefore, the number of doses (since launch) was estimated to be 54,927,729 and 5,698,904, respectively. Given that Germany is the main country where Infanrix hexa doses are distributed (close to 30% only in Germany), it was assumed that the incidence of sudden death observed in Germany is representative of the entire population of Infanrix hexa™ recipients (German Federal Bureau of Statistics, Statistisches Bundesamt; incidence rate in first year of life: 0.454/1000 live births; second year: 0.062/1000 live births, data 2008)."

The PSUR documents the deaths reported within 20 days of vaccination.

The number of observed deaths was less than what was expected (Table 1). However, among the infants, there was a clustering of deaths immediately following vaccination, with 42 deaths taking place in the first three days after vaccination, and only 8 in the next 3 days. Among those below one year of age, 54 deaths (93%) occurred in the first 10 days, and 4 (7%) in the next 10 days. Had the deaths been "coincidental SIDS deaths", this disparity in the number of deaths in the two time periods would not have been observed. SIDS deaths would have been spread uniformly over the 20-day period. The fact that the rate of death decreases rapidly with the passage of time following immunisation suggests that the deaths could be related to vaccination.

Similarly, among children older than one year, 5 deaths (83.3%) occurred in the first 10 days and 1 death (17%) occurred in the next 10 days. The clustering of deaths reported in the PSUR 15 was noticed in the PSUR 16 as well, and this has been commented upon previously (6).

GlaxoSmithKline response

Responding to this criticism (7), the Chief Executive Officer (CEO) of GlaxoSmithKline (GSK), Sir Andrew Witty, through the company's Chief Medical Officer, Dr Norman Begg, suggested in a letter that reporters are much more likely to think about a potential causal association and thus, report an event to GSK if it occurs shortly after vaccination rather than if it occurs weeks later. He further wrote, "In light of the above, we remain confident in the conclusions previously reached by GSK and shared with regulatory agencies and public health authorities worldwide that the currently available data do not suggest an increased risk of sudden infant death following vaccination with Infanrix hexa. Should the available data and information change to suggest that there is such an increased risk, we

Table 1 (*Corrected)
PSUR 15: analysis of observed/expected sudden deaths

Time since vaccination	1st year			2nd year		
	Observed deaths	Cumulative observed deaths	Cumulative expected deaths	Observed deaths	Cumulative observed deaths	Cumulative expected deaths
Less than 1 day	10	10	54.7	1	1	0.8
1 day	10	20	109.3	1	2	1.5
2 days	13	33	164.0	1	3	2.3
3 days	9	42	218.6	0	3	3.1
4 days	7	49	273.3	0	3	3.9
5 days	1	50	327.9	0	3	4.6
6 days	0	50	382.6	0	3	5.4
7 days	1	51	437.3	1	4	6.2
8 days	1	52	491.9	1	5	7.0
9 days	2	54	546.6	0	5	7.7
13 days	0	54	765.2	1	6	10.8
15 days	1	55	874.5	0	6	12.4
16 days	1	56	929.2	0	6	13.2
18 days	1	57	1038.5	0	6	14.7
19 days	1	58	1093.1	0	6	15.5

(***Source:*** *Adapted from Table 24, The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance Report to Regulatory Authority, PSUR 15, p.783*)

remain committed to promptly notify the authorities and to take the necessary actions to communicate such data and information to healthcare professionals."

This response contains a tacit admission that there was no active surveillance during the post-vaccination period and only deaths spontaneously reported to GSK were included under the heading of "observed deaths". This was likely to result in an underestimation of the deaths following vaccination. It is to be noted that for "expected deaths" the number of doses of vaccine distributed is utilised. The report acknowledges that all the doses of the vaccine distributed need not have been utilised. In this way, the figure for "expected deaths" may have been inflated.

However, in view of the CEO's explanation and assurance that GSK was committed to promptly notify the authorities and healthcare professionals of any increased risk with Infanrix hexa, the matter of the clustering of deaths was not pursued further.

PSUR 16: doubling of expected deaths

If all children who received the first dose of the vaccine go on to receive four doses and the last dose is in the second year of life, then it can be estimated that one-fourth (25%) of the doses are administered to children over the age of one year. This is the vaccine schedule recommended in Germany. However, some countries, such as Italy, advise only three doses, all in the first year and none in the second. Also, not all children receive all the doses recommended. So it is unlikely that 20%–25% of doses are used in the second year. In the PSUR 15, it was estimated that 90.6% of the doses sold were used for infants under one year of age and 9.4% for those above one year of age. In the PSUR 16, the estimate of doses received in the second year more than doubled (from 9.4% to 20%), and thus the estimate of expected deaths doubled. In spite of the doubling of expected deaths, the number of observed deaths in the second year was higher than expected in the first 3 days after vaccination (Table 36, p249). If the PSUR 15 estimate that 9.4 % of the doses are used in the second year is correct and holds true for the PSUR 16, observed deaths are higher than expected deaths in the first 7 days.

Table 2
PSUR 16: observed/expected deaths in 2nd year

Time since vaccination (days)	Cumulative observed (2nd year) PSUR 16	Cumulative expected deaths reported in PSUR 16 after doubling recipient numbers (20% doses in 2nd year)	Cumulative expected deaths if 9.4% doses were used in the 2nd year (as in PSUR 15)*
0	2	1.98	0.93
1	5	3.96	1.86
2	6	5.94	2.79
3	6	7.92	3.72
4	6	9.9	4.65
5	7	11.88	5.58
6	7	13.86	6.51
7	7	15.84	7.44

*Source: Adapted from PSUR 16, Table 36, p249 *Calculated by the authors*

PSUR 19: expected deaths weighted by country and yearly proportion of doses

In the PSUR 19, a weighted average of sudden deaths by calendar time of the German, French and Dutch incidence rates was calculated to arrive at the expected incidence of sudden deaths. In very simple terms, this means that if 60% of the doses were distributed in Germany in a given year, the SD rate in Germany was given a weightage of 60% when calculating the overall SD rate for that year; if 30% were distributed in France, the SD rate in France was given a weightage of 30% and 10% weightage was given to the Dutch SD rate. Finally, the overall SD rate was calculated for all the years together. The overall SD rate was calculated as 0.0102/1000 live births for the second year. This figure is one-sixth of the expected rate used in the PSURs 15 and 16 (which calculated expected sudden deaths at 0.062/1000 live births, using German data).

The Poisson 95% CI of the observed deaths in the second year is reported in Table 8 on p 447 of the PSUR 19. It is reported that for the second year of life, the number of observed deaths was higher, though not significantly, than that of expected deaths within a risk period of 1–4 days after vaccination.

Missing deaths in the PSUR 19

From the PSUR 16 to the PSUR 19, the total doses of the vaccine went up from 69 million to 112 million. According to the PSUR 19, 20.2% of the doses distributed were presumed to have been given to children in the second year of life (PSUR 19, pp 436–448). Cases of death in which the age of vaccination was not known, the time to death was not recorded, or the time to death exceeded 19 days, were excluded.

The PSUR 19 (deaths up to October 22, 2014) does not report the sudden deaths mentioned in the PSUR 16 (cases of death occurring up to October 22, 2011). It is of note that in the PSUR 16 the age of the child who died after vaccination and the time to death (within 14 days of vaccination) were both recorded. The cumulative deaths reported are lower in the PSUR 19 than in the PSUR 16. As for children over one year of age, the PSUR 19 records the occurrence of only 5 deaths in the first 19 days after vaccination, whereas the PSUR 16 reports 8. The numbers are not consistent with each other. We wonder why this is so.

Ten years after the publication of a Center for Disease Control paper examining the relationship between the measles, mumps and rubella (MMR) vaccine and autism (8), one of the authors, William Thompson, admitted that he and his co-authors omitted statistically significant information showing that African American males who received MMR before the age of 36 months were at increased risk of autism (9). The authors deleted the data of children who did not have Georgia birth certificates (10), thus disqualifying a disproportionate number of black children, and presented their data so that it

showed that there was no increased risk. It is not clear whether the authors of the PSUR 19 similarly disqualified children documented to have died in the PSUR 16.

Table 3 presents the observed and expected deaths reported in the PSUR 19 and the observed deaths after restoring the deaths reported in the PSUR 16.

When the observed death figures from the PSUR 16 are used, the number of observed deaths is significantly higher than expected for the first four days after vaccination. It must be borne in mind, as explained earlier, that since the number of observed deaths is collected passively, it is likely to be underestimated. Expected deaths, on the other hand, are likely to be overestimated as they are calculated with the assumption that all the doses distributed have been used without any wastage and no vaccine has been discarded on account of exceeding its shelf life. GSK should have reported the statistically significant increased risk of death in the four-day period after vaccination to the regulatory authority and medical practitioners.

Table 3:
PSUR 19: Observed and expected deaths in the 2nd year

Time since vaccination (days)	Cumulative observed deaths according to PSUR 19	Cumulative observed deaths in PSUR 16* (Poisson 95% CI)	Cumulative expected deaths according to PSUR 19
0	0	2 (0.24-7.22)	0.54
1	2	5 (1.62-11.67)	1.08
2	3	6 (2.20-13.05)	1.62
3	3	6 (2.20-13.05)	2.16
4	3	6 (2.20-13.05)	2.70
5	3	7 (2.81-14.42)	3.24
6	3	7 (2.81-14.42)	3.77
7	3	7 (2.81-14.42)	4.31
8	4	7 (2.81-14.42)	4.85
9	4	7 (2.81-14.42)	5.39
10	4	7 (2.81-14.42)	5.93
11	4	7 (2.81-14.42)	6.47
12	4	7 (2.81-14.42)	7.01
13	5	8 (3.45-15.76)	7.55
14	5	8 (3.45-15.76)	8.09
15	5	8 (3.45-15.76)	8.63
16	5	8 (3.45-15.76)	9.17
17	5	8 (3.45-15.76)	9.71
18	5	8 (3.45-15.76)	10.24
19	5	8 (3.45-15.76)	10.78

Source: Data adapted from Table 8, PSUR 19, p 447
(**Data on deaths from the PSUR 16 from Table 36, p 249, with Poisson 95% CI added in*)

Doses used in the second year

The PSUR 19 assumes that 20.2% doses have been used in the second year. It states that since the distribution of the age at which subjects are vaccinated is unknown, the company assumed that the proportion of adverse events (including death) by age is representative of the actual age distribution at vaccination. Thus, as 20.2% of adverse events occurred among children above one year of age, the company assumed that 20.2% doses were used for this age group.

It is facile to estimate the number of doses used in the second year on the basis of the observed adverse events (including death), and then use this estimate of doses to calculate the number of expected deaths, and finally, to compare this number with that of observed deaths – given that the estimate of expected deaths is calculated from the observed adverse events (including death) in the first place.

Assuming that all deaths following vaccination are coincidental SIDS/SUD deaths and not causally related to the vaccine, and given that (according to the PSUR 19) the natural frequency of sudden deaths in the first year is 44 times higher than that in the second year (0.441/1000 in the first year and 0.0102/1000 in the second year), 44 times as many children have to be vaccinated in the second year to reach the same number of deaths as in the first year. In a cohort of 100 deaths, if 20% of sudden deaths occur in the second year and 80% in the first year, 880 children have to be vaccinated in the second year for every 80 vaccinated in the first year. In that case, it must be assumed that 91% of all doses of Infanrix hexa are used in the second year and only 9% are used in the first year (instead of it being the other way around). This reflects the absurdity of calculating dose distribution by age, on the basis of the age distribution of adverse events, as done in the GSK document.

The only way to estimate the number of doses used in the second year is to examine the vaccination schedules in different countries – looking at countries that advise the fourth dose in the second year and those that do not advise any doses in the second year. A weightage can be given for the number of doses distributed in these countries. The dropout rate (children dropping out of the vaccination programme after receiving the first doses) must also be factored into the final calculation of the proportion of doses used in the second year. It would seem that a reasonable estimate of doses used in the second year is probably 9.4% of the total doses, and this is the figure used in the PSUR 15.

The ethical dilemma – the trolley problem

This commentary does not attempt to examine if these excess deaths after vaccination (presumed to be caused by the vaccine) can be offset by the lives saved through disease prevention owing to the vaccine. In her classical thought experiment, called the "Trolley dilemma", Philippa Foot asks if it is ethical to redirect a runaway trolley from a track on which it would kill five persons to another track where only one would die (11). In a variation of the trolley dilemma, the single person on the alternative track is the child of the person who can switch the tracks. Judith Thomson assumes that five lives can be saved with organ transplants from one healthy

donor, and asks if it would be ethical to surreptitiously kill one person to save the other five (12). Ethicists argue that the end cannot justify the means. If one glosses over the deaths after vaccination, one can prevent/delay the evaluation of the vaccine's safety profile and this has the potential to result in more, unnecessary deaths, which is difficult to justify ethically.

Relevance to India

The regulatory authority of the Government of India is the Drug Controller General of India (DCGI). According to the DCGI's rules, drugs approved in one or more countries, such as the USA, the UK, Canada, Japan, Australia and the countries of the European Union, will be considered for approval in India (13). Only bridging studies for the evaluation of the impact of ethnic factors on the efficacy, safety, dosage and dose regimens of the drugs are required (14).

Recently, studies examining the immunogenicity and safety of the hexavalent combination in small trials have been published from India (15, 16). Also, *Indian Pediatrics* published an editorial entitled "Hexavalent vaccinations: The future of routine immunization?"(17), which suggested that this combined vaccine was being promoted for India. It is crucial that the regulatory authority in India is aware of the concerns raised in this commentary on the PSUR reports. This is especially so because surveillance systems in India are weak.

Summary and conclusion

von Kries (1) reported a statistically significant increase in the SMR in children in their second year of life, within two days of vaccination with Hexavac® (one of the two licensed hexavalent vaccines, now withdrawn).

In its periodic safety update reports, GSK, the company manufacturing Infanrix hexa, evaluates whether the number of sudden deaths reported after vaccination with their product exceeded the number that could be expected by chance. The clustering of deaths soon after immunisation suggests that the deaths could have been caused by the vaccine.

Furthermore, our analysis shows that the deaths acknowledged in the PSUR 16 have been deleted from the PSUR 19. The observed deaths are spontaneously reported to GSK and are likely to be underestimated. Adding in the deaths deleted from the PSUR 16, there is a statistically significant increased risk of death in the first four days after vaccination, compared to the expected deaths. The manufacturers will need to explain why these deaths were not included in the PSUR 19. The increased risk of death was not communicated to the regulatory authorities or to the health personnel administering this vaccine.

Given the above, it is difficult to understand how the EMA accepted the PSUR 19 at face value. It may be argued that due diligence was not exercised, as a result of which numerous children were unnecessarily exposed to the risk of death.

The DCGI must be made aware of these infirmities in the PSUR on Infanrix hexa™.

**Corrections:* *This paper was published online on September 5, 2017 and taken off the website for corrections by the authors on September 6, 2017. These corrections were:*

1) Table 1, Column 7: the entire column was replaced as figures had been taken from the wrong document. Corresponding changes were made in Column 1.

2) On the subsequent pages, corrections were made with regard to two numbers, column heads in both Tables 2 and 3; and References 8 to 14 which have been re-numbered.

References

1. von Kries R, Toschke AM, Strassburger K, Kundi M, Kalies H, Nennstiel U, Jorch G, Rosenbauer J, Giani G. Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, Haemophilus influenzae type b): is there a signal? *Eur J Pediatr.* 2005 Feb;164(2):61–9. Epub 2004 Dec 16.
2. European Medicines Agency (EMEA). Press Release. EMEA recommends suspension of Hexavac. London, September 20, 2005. Doc. Ref. EMEA/297369/2005 [cited 2017 May 12]. Available from: https://lakemedelsverket.se/upload/nyheter/2005/PressmedEMEA%5B1%5D.pdf
3. Directive 2001/83/EC of the European Parliament and of the Council of November 6, 2001 on the community code relating to medicinal products for human use. Official Journal L–311, 28/11/2004, p. 67–128 [cited 2017 May 3]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004481.pdf
4. GlaxoSmithKline Biological clinical safety and pharmacovigilance's confidential report to the EMA: PSUR 15 and PSUR 16 [cited 2017 Aug 1]. Available from:http://autismoevaccini.files.wordpress.com/2012/12/vaccin-dc3a9cc3a8s.pdf
5. GlaxoSmithKline Biological clinical safety and pharmacovigilance's confidential report to the EMA: PSUR 19 [cited 2017 Aug 1]. Available from: http://ijme.in/wp-content/uploads/2017/09/infanrix-pusr.pdf
6. Puliyel J. PubMed Commons comment on Baldo V, Bonanni P, Castro M, Gabutti G, Franco E, Marchetti F, Prato R, Vitale F. Combined hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus-Haemophilus influenzae type B vaccine; Infanrix™ hexa: twelve years of experience in Italy. *Hum Vaccin Immunother.* 2014 [cited 2017 Aug 1];10(1):129–37. doi: 10.4161/hv.26269. Epub 2013 Sep 4. Available from:http://www.ncbi.nlm.nih.gov/pubmed/24004825#cm24004825_8656.
7. Sir Andrew Witty, CEO GlaxoSmithKline, responds through Norman Begg, Chief Medical Officer, GSK Vaccines, to Infanrix controversy related to PSUR 16 [cited 2017 Aug 1]. Available from: http://ijme.in/wp-content/uploads/2017/09/infanrix-gsk-cmo-response.pdf
8. De Stefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C. Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. Pediatrics. 2004 Feb;113(2):259–66.
9. Morgan FM. Statement of William W Thompson, PhD, regarding the 2004 article examining the possibility of a relationship between MMR and autism dated August 27, 2015 [cited 2017 Aug 3]. Available from: https://leftbrainrightbrain.co.uk/2014/08/28/statement-of-william-w-thompson-ph-d-regarding-the-2004-article-examining-the-possibility-of-a-relationship-between-mmr-vaccine-and-autism/
10. Center for Disease Control and Prevention. CDC Statement Regarding 2004 Pediatrics Article,"Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta"[cited 2017 Aug 2]. Available from: https://www.cdc.gov/vaccinesafety/concerns/autism/cdc2004pediatrics.html
11. Foot PR. The problem of abortion and the doctrine of the double effect. In: *Virtues and vices*. Oxford: Basil Blackwell; 1978.
12. Thomson JJ. The trolley problem. *The Yale Law Journal*. 1985 May;94(6):1395–415.
13. Central Drugs Standard Control Organisation Delhi. Guidelines on approval of clinical trial and new drugs. Available at http://www.cdsco.

nic.in/writereaddata/Guidance_for_New_Drug_Approval-23.07.2011.pdf Accessed on 2 August 2017
14. Liu JP, Chow SC. Bridging studies in clinical development. *J Biopharm Stat*. 2002;12:359-67.
15. Chhatwal J, Lalwani S, Vidor E. Immunogenicity and safety of a liquid hexavalent vaccine in Indian infants. *Indian Pediatr*. 2017 Jan 15;54(1):15–20. Epub 2016 Nov 5.
16. Lalwani SK, Agarkhedkar S, Sundaram B, Mahantashetti NS, Malshe N, Agarkhedkar S, Van Der Meeren O, Mehta S, Karkada N, Han HH, Mesaros N. Immunogenicity and safety of 3-dose primary vaccination with combined DTPa-HBV-IPV/Hib in Indian infants. *Hum Vaccin Immunother.* 2017 Jan 2;13(1):120–7. doi: 10.1080/21645515.2016.1225639. Epub 2016 Sep 15.
17. Shashidhar A. Hexavalent vaccinations: the future of routine immunization? *Indian Pediatr.* 2017 Jan 15;54(1):11–13.