Puliyel Sathyamala Infanrix hexa deaths: Review comments:

Comments of Reviewer 1:

1. This paper is relevant to the journal and the discussion includes the Indian perspective adequately.

Response: We thank the reviewer for saying so

2. Much of it has appeared elsewhere in the public domain, as informed by the authors themselves. There is some new contribution in terms of information, but the ethical debate is limited and the article merely resonates the stand of the authors in the earlier mentioned works.

Response: We thank the reviewer for saying so. Regarding the ethical debate, this comes up again in 5 below and is answered there.

3. The conclusions are warranted, but not well developed. Only one perspective is.

Response: Thanks for saying the conclusions are warranted.

With reference to there being only one perspective: This comment is a critique of the PSUR report submitted to EMA. As such it has only one perspective – that of the critique. It is not a critique of the vaccine but merely the PSUR.

4. There are no loose generalizations but it does have assumptions on the part of the authors, and these are not critiqued adequately, while assumptions made by others referred to in the paper are acutely critiqued.

Response: Thanks for saying there are no loose generalizations. As stated above the article is merely a critique of one assertion made in the PSUR

5. The approach to the risk of death is unidirectional – "thereby it exposed numerous children unnecessarily to the risk of death" – only deaths due to vaccines (assumed) is considered. The risk of death due to infectious diseases is inadequately discussed.

Response: As stated in 3 above

"This comment is a critique of one assertion made in the PSUR report submitted to EMA. It is not a critique of the vaccine but merely the PSUR."

If deaths have been covered up in a PSUR made confidentially to the regulatory authority, that can casr a shadow on the trust we place on regulatory decisions.

The benefits from vaccination are not disputed. Even for the most life-saving vaccine – a cover-up of deaths cannot be justified.

The article only deals with the issue of the ‘missing deaths'.

6. Ethical discussions generally try to address multiple angles of the issue and to help with the dilemmas arising in decision making. Customary examples such as the "trolley" and ‘transplant" discuss one situation vis-a-vis the other and even try to unravel layers in each situation. This paper does not reach that level, and remains a propaganda piece, albeit with important questions asked.

Response: The paper only raises one issue that the reviewer says is an important question.

We thank the reviewer for bringing up the trolley and transplant dilemma. We have incorporated a paragraph about this in the revised manuscript. Just as in the transplant dilemma it is not justified to kill one healthy person to harvest his organs to save 5 others, a covering up deaths in the PSUR cannot be justified assuming that overlooking this may help keep the vaccine in the market and the vaccine may save lives by preventing disease.

7. While there are two authors – the phrase "I have previously commented", suggests otherwise.

Response: This has been corrected. The original draft was written, as always, by one person and modified by the coauthor

Reviewer 2

We thank the reviewer for painstakingly correcting this manuscript.

The responses to his queries are written alongside his comments.

A final clean version is being submitted.

The track changes version has become messy to read and edit even for the authors. So there are a few revisions done after we switched off the track changes mode. We hope this may be condoned and the reviewer will evaluate the clean version.

Infanrix hexa (combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and haemophilus influenza type B vaccine) and Sudden Death – a review of the regulatory evidence from the European Medicines Agency

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**Abstract**

There have been a number of spontaneous reports of sudden unexpected deaths soon after administration of Infanrix hexa (combined diphtheria, tetanus, acellularpertussis, hepatitis B, inactivated poliomyelitis and haemophilus influenza type B vaccine).

The manufacturer GlaxoSmithKline (GSK) provides the European Medicines Agency (EMA) confidential periodic safety update reports (PSUR) about Infanrix hexa. The latest is the PSUR 19. Each PSUR contains an observed/expected analysis of sudden deaths, which show that the observed deaths soon after immunization, are lower than that expected by chance.

We analyzed the data provided in the PSUR. It is apparent that the deaths that were acknowledged in the PSUR 16 were deleted in the 19th PSUR. IThe observed deaths soon after vaccination in the children older than one year was significantly higher than would be expected by chance once these deleted deaths were included in the analysis.

The manufacturermust explain the faulty figures that they submitted to the regulatory authorities. The procedure undertaken by the EMA to evaluate themanufacturer’s claims in the PSURneed to be reviewed.

The Drug Controller General of India nearly automatically accepts drugs and vaccines approved by the EMA . Thereliance on due diligence by the EMA needs to be re-evaluated.

**Introduction**

Two hexavalent vaccines Infanrix hexa® (GlaxoSmithKline plc- GSK) and Hexavac® (Sanofi Pasteur MSD, SNC), which combine diphtheria, tetanus, acellular pertusis, hepatitis B, inactivated poliomyelitis and haemophilus influenza type B wereauthorized to be marketed in the European Union on 23 October 2000. Following authorization there were a number of spontaneous reports of sudden unexpected deaths soon after administration of the vaccine. In 2005, vonKries and colleagues(1) performed a detailed analysis in which the observed deaths soon after vaccination were compared with the deaths expected by chance. They found a significantly increased standardized mortality ratio (SMR) within two days after vaccination of Hexavac® in children vaccinated in the 2nd year of life. The same was not seen with Infanrix hexa. After the withdrawal of Hexavac in 2005 at the request of the marketing authorization holder, 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 evaluation of the medicines it approves as the regulatory authority. The manufacturers are responsible for the efficacy, quality and safety of their drugs (3).

The Italian Court of Justice, Nicola Di Leo, made GlaxoSmithKline’s confidential 15th and 16th Periodic Safety Update Reports (PSURs, from 2009 to 2011) available to the public (4).to write a reportto the European Parliament.

The PSUR 19 (incorporating PSUR 17, 18 and 19 dated 15 January 2015 was obtained by Dr Loretta Bolgan from the EMA under Article 3 of the EMA rules (EMA 110196/2006 of 30 November 2010) (5). Dr Bolgan sent this PSUR to the first author (JP) to write a report to be presented to the European Parliament. Our commentary is based on these PSURs.

In the context of the safety signal previously highlighted by von Kries (1) this commentary examines sudden deaths following use of this vaccine. Other aspects of the PSUR 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 and accidents. Seldom do babies die without any evident cause and such deaths are classified as SIDS (Sudden Infant Death Syndrome) or otherwise SUDs (Sudden Unexpected Deaths) beyond infancy. Diagnosis requires that the death remains unexplained even after a thorough autopsy and detailed death scene investigation.

A number of vaccines are administered to children under the age of 2 years and on any given day; there are a very large number of children vaccinated all over the world. It is possible that by chance vaccinated children would die of coincidental SIDS/SUD which would have occurred in those children even if they had not been vaccinated on that day. To ascertain if SIDS/SUD are caused by vaccination an observed/expected analysis of sudden deaths (SD) is performed to estimate if the deaths observed after vaccination exceeds that which can be expected by chance.

**Sudden Deaths: Observed vs. Expected**

**The 15th PSUR explains how this analysis is performed (page 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 for the entire population of Infanrix hexa™ recipients (German Federal Bureau of Statistics, Statistisches Bundesamt; incidence rate in 1st year of life: 0.454/1,000 live births; second year: 0.062/1,000 live births, data 2008).

The PSUR documentsthe deaths that have happened within 20 days of vaccination.

**Table 1**

**Observed/Expected Analysis of Sudden Deaths in PSUR 15**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Time since Vaccination  (days) | Observed  (1styear) | Expected | Observed(2nd  year) | Expected |
| Less than 1 day | 10 | 54.7 | 1 | 1.98 |
| 1 day | 20 | 109.3 | 2 | 3.96 |
| 2 days | 33 | 164 | 3 | 5.94 |
| 3 days | 42 | 218.6 | 3 | 7.92 |
| 4 days | 49 | 273.3 | 3 | 9.9 |
| 5 days | 50 | 327.9 | 3 | 11.88 |
| 6 days | 50 | 382.6 | 3 | 13.86 |
| 7 days | 51 | 437.3 | 4 | 15.84 |
| 8 days | 52 | 491.9 | 5 | 17.82 |
| 9 days | 54 | 546.6 | 5 | 19.8 |
| 13 days | 54 | 765.2 | 6 | 27.72 |
| 15 days | 55 | 874.5 | 6 | 31.68 |
| 16 days | 56 | 929.2 | 6 | 33.66 |
| 18 days | 57 | 1038.5 | 6 | 37.62 |
| 19 days | 58 | 1093.1 | 6 | 39.6 |

(Source: Table24 The GlaxoSmithKline Biological Clinical Safety and Pharmacovigilance report to Regulatory Authority PSUR 15)

The observed deaths are 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 deaths in the next 3 days. 54deaths (93%) below 1 year, occur in the first 10 days and 3 deaths 7%) occur in the next 10 days. Had the deaths been ‘coincidental SIDS deaths’ this disparity in 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 deaths decreases rapidly as time elapses after immunization suggests that the deaths could be related to vaccination.

In the same way, in children older than oneyear, 5 deaths (83.3%) occur in the first 10 days and1 death(17%) occurs in the next 10 days. The clustering of deaths seen in PSUR 15 was also noticed in the PSUR 16 and this has been commented on previously (6).

**GSK Response**

The CEO of GlaxoSmithKline, Sir Andrew Witty, responded to this criticism (7).

In the letter he suggeststhat reporters are more likely to think about a potential causal association and thus report an event to GSK when the event occurs shortly after vaccination than when it occurs weeks 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. Nevertheless, as part of our ongoing monitoring and evaluation of the safety of all of medicines and vaccines, we will continue to monitor and evaluate all cases of Sudden Infant Death reported and share the results of those analyses with authorities in those countries where Infanrixhexa is licensed. Should the available data and information change to suggest that there is such an increased risk, we remain committed to promptly notifying the authorities and to taking the necessary actions to communicate such data and information to healthcare professionals.”

This response tacitly admitted that there was no active surveillance during the post vaccination period and only deaths spontaneously reported to GSK were included under the heading ‘observed deaths’. This is likely to underestimate the deaths following vaccination. However in view of the explanation and the assurance by the CEO that GSK was committed to promptly notify the authorities and health care professionals of any increased risk with Infanrix hexa observed, this matter of the clustering of deaths in the PSUR was put aside.

**PSUR 16 –Doubling of Expected Deaths**

If all children who received the first dose of the vaccine went on to receive four doses and the last dose was in the second year of life, then it can be estimated that one fourth (25%) of the doses were used in children over the age of one year. This is the vaccine-schedule recommended in Germany. However not all children receive all the doses recommended. However some countries like Italy advise three doses in the first year and no doses in the second year. Also not all children receive all the doses recommended. In PSUR 15 it was estimated that 91% doses sold were used in infants and 9% of the doses were used in the second year. In PSUR 16 the estimate of doses received in the second year was more than doubled from 9.4% to 20% and so the estimate of expected deaths was doubled. In spite of this doubling of expected deaths, the number of observed deaths in the 2nd year was higher than expected in the first 4 days after vaccination (Table 36 on page 249). If the PSUR 15 criteria of 9% were used, observed deaths would have exceeded expected deaths for 7 days.

**Table 2**

**PSUR 16: Observed/Expected death in 2nd year**

|  |  |  |  |
| --- | --- | --- | --- |
| Time since  Vaccination  (days) | Observed  (2nd year)  PSUR 16 | Expected death reported in 16 PSUR after  doubling  recipient numbers  (20% doses in 2nd year) | Expected deaths  if 9.4% children  vaccinated were in  their second  year of life  ( as in the 15th  PSUR)\* |
| 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 (Table 36 on page 249)

\*Calculated by the author

**PSUR 19: Expected Deaths Weighted by Country and Yearly Proportion of Doses**

In PSUR 19, a weighted average of sudden deathsby calendar time of the German, French and Dutch incidence rate was calculated to arrive at the expected incidence of sudden deaths. This was calculated as 0.0102/1000 live births for the second year. This figure is one sixth of the expected rate used in PSUR 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 Page 447 of the 19th PSUR. It is reported that for the second year of life the observed SDs was higher than expected within a risk period 1 to 4 days post vaccination, though not significantly.

**Missing Deaths in the 19th PSUR**

The total doses of the vaccine went up from 69 million in PSUR 16 to 112 million doses in the PSUR 19.20% of doses distributed were presumed to have been given to children in the second year of life (Page 436 to 448). Deaths where age of vaccination was not known and where time to death was not recorded or the time to death exceeded 19 days were excluded.

The sudden deaths reported in the PSUR 16 (up to 22 October 2011) are missing from the PSUR 19 (deaths up to 22 October 2014). The and cumulative deaths reported are lower in the PSUR 19 than in the PSUR 16. There are 5 deaths in the 20 days after vaccination in children over one year, reported in the PSUR where the PSUR 16 records 8 deathsby . All the 8 deaths reported in the PSUR 16 were in children in the second year and within 14 days of vaccination. We wonderwhy the three deaths were erased.

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

**Table 3 Observed and Expected deaths in the second year 19th PSUR**

|  |  |  |  |
| --- | --- | --- | --- |
| Time since  Vaccination (days) | Observed deaths  according to PSUR 19 | Observed deaths  In PSUR 16\*  (Poisson 95% CI ) | 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 from Table 8 PSUR 19

(\*Data on deaths from the 16th PSUR from Table 36 on page 249)

It must be borne in mind that the observed deaths are passively collected and so is likely to be an underestimation. Expected deaths on the other hand are derived assuming that all the doses sold have been used without any wastage or any vaccine being discarded as having crossed their expiry date, are likely to overestimation. When the observed death figures from the PSUR 16 are used, observed deaths are significantly higher than expected for the first four days after vaccination in spite the infirmities of the estimation techniques described. GSK should have reported that there was a statistically significant increased risk of death in the 4 day period after vaccination with Infanrix hexa.

**Doses are Used in the Second Year**

In the PSUR 19, it is assumed that 20.2% doses have been used in the second year:The PSUR 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 deaths) by age is representative for the actual age distribution at vaccination. Thus as 20.2% of adverse events occurred in children above 1 year the company assumed that 20.2% doses were used in this age group.

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

Assuming that all deaths following vaccination are coincidental SIDS/SUD and not causally related to the vaccine, and given that (according to the PSUR 19) sudden deaths in the first year are 44 times more frequent than 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 happen in the second year and 80% 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% is used in the first year. This reflects the absurdity that one must confront if we calculate dose distribution by age, from the age distribution of adverse events that include sudden deaths, as done in the GSK document. The EMA seems to have accepted this unquestioningly.

The onlyway to estimate the number of doses used in the second year, is to look at the vaccination schedules in different countries – looking at countries that advise a forth dose in the second year, and from the distribution of doses in those countries calculate after factoring inthe dropout rate (children dropping out of the vaccination programme after receiving the first dose) estimate the proportion of doses used in the children over the age of one year . By this estimation it would seem that 9.4% as employed in the 15 PSUR is probably a reasonable estimate of doses in the second year.

**The Ethical Dilemma – The Trolley Problem**

This commentary does not attempt to examine if these excess death after vaccination, (presumed to be caused by the vaccine) can be offset against the lives saved through disease prevention by the vaccine.In her classical thought experiment called the ‘Trolley dilemma’ Philippa Foot asks if it is ethical to redirect a runaway trolley on a track that would kill 5 persons, to another track where only one would die (13). In a variation of the trolley dilemma the single person on the alternate 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 health donor, asks if it would be ethical to surreptitiously kill one person to save the other five (14). Ethicists argue that one is not allowed to directly bring about harm, even if it is for a greater good. A glossing over of the deaths after vaccination can prevent/delay evaluation of the vaccine’s safety profile and this has potential to result in more deaths.



**Relevance to India**

The regulatory authority of the Government of India is the Drug Controller General of India (DCGI). According to the DCGI rules, a drugapproved in one or more countries like USA, UK, Canda, European Union Japan and Australia will be considered for approval in Indiain India (8). Bridging studies are all that is required for evaluation of the impact of ethnic factors on the efficacy, safety, dosage, and dose regimen (9).

Recently there have been studies published from India looking at immunogenicity and safety of the Hexavalent combination in small trials (10,11).There have also been editorials published, entitled “Hexavalent Vaccinations: The Future of Routine Immunization?”(12) suggesting that thiscombined vaccine is being promoted in India. It is crucial that the regulatory authority in India is aware of the concerns raised through this commentary on the PSUR reports.

**Summary and Conclusion**

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1. Von Kries (1) reported a statistically significant increased standardised mortality ratio (SMR) in children in their 2nd year of life, within two days after vaccination with Hexavac® (one of the two licensed hexavalent vaccines, now withdrawn).
2. 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 immunization suggests the deaths could be caused by the vaccine.
3. This analysis shows that deaths acknowledged in the PSUR 16 have been deleted from PSUR 19. There seems to be statistically significant increased in risk of death in the first 4 days after vaccination. The manufacturers will need to explain why these deaths were deleted from the PSUR. The increased risk was not communicated to the regulatory authorities or to the health personnel administering this vaccine.
4. Given the above, it is difficult to understand how the EMA accepted PSUR 19 at face value. As the regulator, it may be argued that due diligence was not performed and thereby it exposed numerous children unnecessarily to the risk of death.
5. The DCGI must be made aware of these infirmities in the PSUR on Infanrix hexa submitted to the EMA

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