**Infanrix hexa (combined diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis and Haemophilus influenza type B vaccine) and Sudden Death:**

**A review of the periodic safety update reports submitted to the regulatory authority - 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, acellular pertussis, 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.

This commentary focuses on one aspect of the PSUR that has a bearing on policy decisions. We analysed the data provided in the PSURs. It is apparent that the deaths that were acknowledged in the PSUR 16 were deleted from the PSUR 19. The observed deaths soon after vaccination in the 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 these figures that they 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 Drug Controller General of India nearly automatically accepts drugs and vaccines approved by the EMA. The reliance on due diligence by the EMA needs to be reappraised.

**Introduction**

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 were authorized 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, von Kries 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). 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. This commentary is based on those 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 or accidents. Seldom do babies die without any evident cause and such deaths are classified as SIDS (sudden infant death syndrome) defined in the PSUR as death occurring in the first year of life which remains unexplained after autopsy or SUD (sudden unexpected deaths) defined as death occurring in the first two years of life which remain unexplained after clinical and final event history but without autopsy. Both these are together considered as sudden death (SD) in the PSUR.

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 some vaccinated children would die of coincidental SIDS/SUD which would have occurred in those children even if he/she had not been vaccinated on that day. To ascertain if the death was caused by vaccination or if it was a coincidental event, 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 PSUR 15 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 of 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 documents the deaths reported within 20 days of vaccination.

Table 1

PSUR 15: Observed/Expected Analysis of Sudden Deaths

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Time since |  | 1st Year |  |  | 2nd Year |  |
| Vaccination (days) | Observed deaths | Cumulative Observed  deaths | Cumulative Expected  Deaths | Observed deaths | Cumulative  Observed  deaths | Cumulative  Expected  Deaths |
| Day 1 | 10 | 10 | 54.7 | 1 | 1 | 1.98 |
| Day 2 | 10 | 20 | 109.3 | 1 | 2 | 3.96 |
| Day 3 | 13 | 33 | 164 | 1 | 3 | 5.94 |
| Day 4 | 9 | 42 | 218.6 | 0 | 3 | 7.92 |
| Day 5 | 7 | 49 | 273.3 | 0 | 3 | 9.9 |
| Day 6 | 1 | 50 | 327.9 | 0 | 3 | 11.88 |
| Day 7 | 0 | 50 | 382.6 | 0 | 3 | 13.86 |
| Day 8 | 1 | 51 | 437.3 | 1 | 4 | 15.84 |
| Day 9 | 1 | 52 | 491.9 | 1 | 5 | 17.82 |
| Day 10 | 2 | 54 | 546.6 | 0 | 5 | 19.8 |
| Days 11 to 14 | 0 | 54 | 765.2 | 1 | 6 | 27.72 |
| Days 15 to 16 | 1 | 55 | 874.5 | 0 | 6 | 31.68 |
| Day 17 | 1 | 56 | 929.2 | 0 | 6 | 33.66 |
| Days 18 to 19 | 1 | 57 | 1038.5 | 0 | 6 | 37.62 |
| Day 20 | 1 | 58 | 1093.1 | 0 | 6 | 39.6 |

(Source: Adapted from Table 24 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. 54 deaths (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 a 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 one year, 5 deaths (83.3%) occur in the first 10 days and 1 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 a letter he suggested that reporters are much 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 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 remain committed to promptly notify the authorities and to take the necessary actions to communicate such data and information to healthcare professionals."

This response tacitly admits 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. It will be noted that for ‘expected deaths’ the number of doses of vaccine distributed is utilized. The report acknowledges that all the doses of the vaccine distributed, need not have been utilized. In this way the figure for ‘expected deaths’ may be inflated.

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, this matter of the clustering of deaths in the PSUR was not perused further.

**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 are used in children over the age of one year. This is the vaccine-schedule recommended in Germany. However some countries like Italy advise only three doses, all in the first year and no doses in the second year. Also not all children receive all the doses recommended. So it is unlikely that 20 to 25% of doses are used in the 2nd year. In the PSUR 15, it was estimated that 90.6% doses sold were used in infants under one year and 9.4% of the doses were used after the age of one 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 estimate that 9.4 % of the doses were used in the second year, 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 PSUR 16  after doubling  recipient numbers  (20% doses in 2nd year) | Expected deaths  if 9.4% doses were used in in  in the 2nd year  (as in the 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 (Table 36 on page 249) \*Calculated by the authors

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

In PSUR 19, a weighted average of sudden deaths by calendar time of the German, French and Dutch incidence rate 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% was distributed in France the SD rate in France was given a weightage of 30% and 10% weightage was given for 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 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 PSUR 19. It is reported that for the second year of life the observed deaths were higher than expected within a risk period 1 to 4 days post vaccination, though not significantly.

**Missing Deaths in the PSUR 19**

The total doses of the vaccine went up from 69 million in PSUR 16 to 112 million doses in the PSUR 19. 20.2% of doses distributed were presumed to have been given to children in the second year of life (PSUR 19, 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.

Sudden deaths reported in the PSUR 16 (deaths up to 22 October 2011 where age at vaccination, and time to death was recorded to be less than 14 days) are missing from the PSUR 19 (deaths up to 22 October 2014). The cumulative deaths reported are lower in the PSUR 19 than in the PSUR 16. In children over one year of age, there are only 5 deaths recorded in the PSUR 19 in the first 19 days after vaccination, where the PSUR 16 reports 8 deaths. 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 a relationship between MMR and autism (10), one of the authors William Thompson admitted that he and his co-authors omitted statistically significant information that African American males who received MMR before the age of 36 months were at increased risk of autism (11). The authors deleted data of children without Georgia birth certificates (12) and so disqualified a disproportionate number of black children and presented their data that there was no increased risk. It is not clear whether the authors of the PSUR 19 performed some similar retroactive disqualification of children documented to have died in the PSUR 16.

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

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

Source: Data adapted from Table 8 PSUR 19 on page 447

(\*Data on deaths from the PSUR 16 from Table 36 on page 249 with Poisson 95% CI added-in)

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. It must be borne in mind as explained previously that the observed deaths are passively collected and so is likely to be an underestimation. Expected deaths on the other hand are likely to be an overestimation as it is calculated assuming that all the doses distributed have been used without any wastage or any vaccine being discarded beyond their shelf life. GSK should have reported to the regulatory authority and medical practitioners of the statistically significant increased risk of death in the 4 day period after vaccination with Infanrix hexa.

**Doses 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 estimate of expected deaths is calculated from the 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) 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 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 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 the countries that do not advise any doses in the second year. A weightage can be given for the number of doses distributed in these countries and the final calculation of proportion of doses used in the second year must factor in the dropout rate (children dropping out of the vaccination programme after receiving the first doses). It would seem that 9.4% of total doses are probably a reasonable estimate of doses used in the second year 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 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 the end cannot justify the means. 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, 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 rules, drugs approved in one or more countries like USA, UK, Canada, European Union, Japan and Australia will be considered for approval in India (8). Only bridging studies for evaluation of the impact of ethnic factors on the efficacy, safety, dosage, and dose regimen are required (9).

Recently there have been studies published from India looking at immunogenicity and safety of the Hexavalent combination in small trials (15, 16).There has also been an editorial published, entitled "Hexavalent Vaccinations: The Future of Routine Immunization?"(17) suggesting that this combined vaccine is 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**

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. The observed deaths are spontaneously reported to GSK and this is 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 4 days after vaccination compared to the expected deaths. The manufacturers will need to explain why these deaths were deleted from the PSUR 19. The increased risk of death 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. 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

**References**

1. 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, Haemophiliusinfluenzae type b): is there a signal? European journal of Pediatrics. 2005;164:61-9.
2. EMEA. Press Release European Medicines Agency recommends suspension of Hexavac. Reactions. London, 20 September 2005. Doc. Ref. EMEA/297369/2005 Available at https://lakemedelsverket.se/upload/nyheter/2005/PressmedEMEA%5B1%5D.pdf Accessed on 12 May 2017
3. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use. Official Journal L – 311, 28/11/2004, p. 67 – 128. Available at http://www.ema.europa.eu/docs/en\_GB/document\_library/Regulatory\_and\_procedural\_guideline/2009/10/WC500004481.pdf Accessed on 3 May 2017
4. GlaxoSmithKline Biological clinical safety and pharmacovigilance’s confidential report to the EMA: PSUR 15 and PSUR 16 Available at <http://autismoevaccini.files.wordpress.com/2012/12/vaccin-dc3a9cc3a8s.pdf> Accessed on 1 August 2017
5. GlaxoSmithKline Biological clinical safety and pharmacovigilance’s confidential report to the EMA: PSUR 19 Available at <http://jacob.puliyel.com/paper.php?id=395> Accessed on 1 August 2017
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;10(1):129-37. PubMed Commons posting of 13 January 2015. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24004825#cm24004825_8656>. Accessed on 1 August 2017
7. Sir Andrew Witty CEO GlaxoSmithKline responds through Norman Begg to Infanrix controversy related to PSUR 16 Available at <http://jacob.puliyel.com/paper.php?id=394>. Accessed on 1 August 2017
8. 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
9. Liu JP, Chow SC. Bridging studies in clinical development. J Biopharm Stat. 2002;12:359-67.
10. DeStefano 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.](https://www.ncbi.nlm.nih.gov/pubmed/?term=Age+at+First+Measles-Mumps-Rubella+Vaccination+in+Children+With+Autism+and+School-Matched+Control+Subjects%3A+A+Population-Based+Study+in+Metropolitan+Atlanta) 2004;113:259-66.
11. 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. Available at 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/ Accessed on 3 August 2017
12. CDC. 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" Available at <https://www.cdc.gov/vaccinesafety/concerns/autism/cdc2004pediatrics.html> Accessed on 2August 2017
13. Foot PR. The Problem of Abortion and the Doctrine of the Double Effect in *Virtues and Vices*. Oxford, Basil Blackwell, 1978.
14. Thomson JJ, [*The Trolley Problem*](http://philosophyfaculty.ucsd.edu/faculty/rarneson/Courses/thomsonTROLLEY.pdf), The Yale Law Journal. 1985;94:1395-1415.
15. Chhatwal J, Lalwani S, Vidor E. Immunogenicity and Safety of a Liquid HexavalentVaccine in Indian Infants. Indian Pediatr. 2017;54:15-20
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 VaccinImmunother. 2017;13:120-127.
17. Shashidhar A. Hexavalent Vaccinations: The Future of Routine Immunization? Indian Pediatr. 2017;54:11-13.