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ORIGINAL PAPER

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Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, *Haemophilius influenzae* type b): is there a signal?

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Abstract Deaths in temporal association with vaccination of hexavalent vaccines have been recently reported. The objective of this paper is to assess whether these temporal associations can be attributed to chance. Standardised mortality ratios (SMR) for deaths within 1 to 28 days after administration of either of the two hexavalent vaccines in the 1st and 2nd year of life were determined using the respective annual rates for sudden unexpected deaths (SUDs) from the national vital statistics. The distribution of SUD cases and the vaccination uptake by month were estimated from surveys and sales figures for the individual vaccines. Sensitivity analyses were performed to account for limitations in the data sources. For one of the vaccines, Vaccine B, all SMRs were well below one. For the other, Vaccine A, SMRs exceeded one insignificantly on the 1st day after vaccination in the 1st year of life. In the 2nd year of life, however, the SMRs for SUD cases within 1 day of vaccination with vaccine A were 31.3 (95% CI 3.8–113.1; two cases observed; 0.06 cases expected) and 23.5 (95% CI 4.8–68,6) for within 2 days after vaccination (three cases observed; 0.13 cases expected). Extensive sensitivity analyses could not attribute these findings to limitations of the data sources. *Conclusion*: These findings based on spontaneous reporting do not prove a causal relationship between vaccination and sudden unexpected deaths. However, they constitute a signal for one of the two hexavalent vaccines which should prompt intensified surveillance for unexpected deaths after vaccination.

Keywords Safety · Standardised mortality ratios · Sudden unexpected death · Vaccines

Abbreviations DTPa-IPV-HBV-Hib: diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, *Haemophilius influenzae* type b · PEI: Paul Ehrlich Institute · SMR: standardised mortality ratio · SUD: sudden unexplained death

In this paper the two vaccines have been labelled Vaccine A and Vaccine B. The brand names are not conveyed since the European licensing agency has not recommended regulatory action against either vaccine. http://www.emea.eu.int/pdfs/human/press/pus/588903en.pdf

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Introduction

Hexavalent vaccines protect children from six infectious diseases: poliomyelitis, diphtheria, tetanus, pertussis, *Haemophilius influenzae* type b infections and hepatitis B. The rationale to combine these vaccines into one syringe was to reduce the number of injections and thereby to increase the compliance and vaccination coverage [17]. In Germany diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, *Haemophilius influenzae* type b (DTPa-IPV-HBV-Hib) vaccinations are recommended at the age of 2, 3 and 4 months and a booster at the age of 11–15 months [18]. Since October 2000, two hexavalent vaccines licensed by the European Commission, have been used in Germany and are subsequently denoted Vaccine A and Vaccine B.

Sudden unexpected death (SUD) following the administration of hexavalent vaccines in the 1st and 2nd years of life have recently been reported in Germany and Austria [11]. Most of these deaths occurred between 2–12 months, a period when SUDs are prevalent and accounted for 420 of a total of 1058 deaths in this age period in Germany in 2002. Some of the deaths following the administration of hexavalent vaccines, however, were observed in the 2nd year, when SUDs are less common. A total of 24 to 42 cases have been coded annually under the ICD 10 codes R96 (sudden death with unexplained cause), R98 (death in absence of other persons) and R99 (other unclear causes of death) in Germany in the 2nd year in 1998–2002. Does the number of SUDs after administration of hexavalent vaccines exceed the number expected?

Methods

Case ascertainment

Reporting of adverse events possibly linked to vaccination to the Paul Ehrlich Institute (PEI) is mandatory according to the German Infection Protection Act (Infektionsschutzgesetz). A post-mortem examination by a forensic pathologist is generally required for all unexpected or unclear deaths. Sudden unexpected deaths are called SUD in this paper, irrespective of whether they occurred in the 1st or the 2nd year of life. Cases occurring in the 1st year of life, conventionally called SID (Sudden Infant Death) are included in the SUD definition. All reported cases in temporal association with administration of hexavalent vaccines in the 2nd year of life and the majority of cases in the 1st year of life had a post-mortem examination. For each reported case, the vaccination history was documented with respect to the brand name of the vaccine and time of vaccination. Cases reported in Germany between November 1st 2000 and June 30th 2003 were used for analysis.

Background incidence

Mortality data were obtained from the Federal Bureau of Statistics in March 2004. Causes of death were classified according to ICD 10 as indicated on the death certificate. It should be noted that the death certificate is completed by physicians. They document the death, and the presumed cause of death does not need to correspond with the final diagnosis following autopsy. In the 1st year of life, Sudden Infant Death with the ICD 10 code R95 accounts for most sudden unexplained deaths below referenced as SUD. SUD also included deaths with the ICD 10 codes R96, 98 and 99. The latter (ICD10 codes R96, R98 and R99) constitute all SUD cases in the 2nd year of life. The estimated rate for SUD from October 2000 up to the end of 2002 in the 1st year of life was 0.663/1000 and in the 2nd year of life 0.040/1000 based on weighted averages of the respective annual data provided by the Federal Bureau of Statistics.

The age distribution of sudden unexpected death cases in the 1st and 2nd years of life

Unfortunately, age-specific numbers of SUD cases by month of age could not be obtained from the Federal Bureau of Statistics. We used the age distribution of SUD cases obtained in a case-control study (BMBF study) of SUD risk factors. This study recruited SUD cases in the 1st year of life from about 50% of the German population between November 1998 and October 2001 (unpublished data).

For the 2nd year of life, the age distribution was estimated from the analysis of the death certificates of 317 deaths within the 2nd year of life in Bavaria from 1996 to 2002 which revealed 27 SUD cases: eight cases in month 12, six in month 13, five in month 14, one in months15 and 16 each, zero in months 17, 18, and 19, 3 in month 20, and one in months 21, 22 and 23 each.

Vaccine coverage and age distribution

As no precise vaccine coverage data for the whole population of children are routinely available in Germany, we had to rely upon a vaccine survey for German children born between January 1997 and December 1998 [17]. The proportion of all children given any DTPa-Hib containing vaccine in the ith month ($i = 0–23$) was calculated as the number of children given a DTPa-Hib containing vaccine in month (i) divided by the number of children for whom information on vaccination up to the respective month (i) was available.

To extrapolate these estimates to coverage of hexavalent vaccines, we used sales data from the Institute of Medical Statistics. The total number of DTPa-Hib containing vaccines (in 1000 doses) sold in 1997 and 1998 ($1683 + 2181 = 3864$) was similar to the total number of both hexavalent vaccines (in 1,000 doses) sold in 2000, 2001 and 2002 ($212 + 1632 + 2112 = 3956$). The proportion of children vaccinated with DTPa-Hib containing vaccines each month in 1997/1998 was used to estimate the proportion of children vaccinated with hexavalent vaccine in 2000, 2001, 2002 to June 2003 divided by a correction factor of 0.9, to account for the lower birth rates in these compared to 1997/1998 but similar sales figures.

Calculation of standardised mortality ratios

SMRs were calculated by dividing the number of observed deaths by the respective number of expected deaths. The CI for the SMRs were determined based on exact Poisson CIs.

The monthly number of expected deaths in vaccinated children is based on the proportion of children given a hexavalent vaccine in the respective month and the age-specific death rate for SUD. Calculations were based on cohort sizes estimated from the official German vital statistics, populations eligible for vaccination with a hexavalent vaccine, data from a vaccination survey for the proportion of children receiving DTPa-Hib combination vaccines of interest by month, Institute of Medical Statistics sales figures to estimate the share between the two brands of hexavalent vaccines and, the SUD mortality by year and the monthly proportion of SUD deaths from two surveys (BMBF and Bavarian study) (see Appendix).

For SUD in the 1st year of life, we included the entire birth cohorts born between 1st October 2000 and 30th June 2002. Children of birth cohorts born before October 2000 or born after June 2002 were included according to the proportion of time they contributed to the observation period as less than 1-year-old. Accordingly, for SUD in the 2nd year, the birth cohorts with birth dates 1 calendar year earlier were included.

The monthly SUD mortality was recursively estimated (see Appendix). To obtain the expected number of SUD deaths by day for the 1st and 2nd years, we divided the monthly number expected by 30.4.

All calculations were performed in SAS 8.2 (SAS Institute Inc., Cary, NC, USA) and R (http://www.r-project.org).

Results

Table 1 lists the SUD cases observed in Germany by hexavalent vaccine, age, date of vaccination and time since vaccination. Most cases after Vaccine A occurred within 24 h of vaccination (8/11) compared to 1/8 cases after Vaccine B (P =0.019, Fisher's exact test). Of the 11 SUD cases following vaccination with Vaccine A, 3 cases occurred in children in their 2nd year of life as compared to 1/8 cases after Vaccine B. In the 2nd year there were no cases of SUD within 48 h after Vaccine B vaccination compared to three after Vaccine A.

The SMRs and their respective 95% confidence intervals for deaths within 1–28 days after the administration of Vaccine A or Vaccine B in the 1st year of life are shown in Fig. 1 and Fig. 2 depicts the respective SMRs and their 95% confidence interval in the 2nd year of life. In the 1st year of life, the number of cases observed in children given Vaccine A did not exceed the numbers expected significantly for any day post vaccination. In the 2nd year of life, the numbers observed exceeded the numbers expected, with corresponding SMR estimates of 31.3 (95% CI 3.8–113.1) for within 1 day after vaccination (two cases observed; 0.06 cases expected) and 23.5 (95% CI 4.8–68.6) for within 2 days after vaccination (three cases observed; 0.13 cases expected). For Vaccine B, the numbers observed were consistently below the numbers expected, irrespective of the day since vaccination or age at death.

Table 1 Deaths in temporal association with administration of a hexavalent vaccine by type of vaccine (A = Vaccine A; B = Vaccine B), age at death and interval between vaccination. Observation period October 2000 to June 30th 2003 (as of September 11th 2003)

PEI ID-number	Vaccine	Age at death (months)	Date of vaccination	Time since vaccination (days)
5408–2000	A	23	16.11.2000	1
1120–2003	A	17	26.02.2003	1
2242–2001	A	12	26.04.2001	2
3088–2003	A	7	13.02.2002	1
3611–2003	A	7	30.052001	5
6310–2002	A	5	24.06.2002	1
2856–2002	A	4	22.04.2002	1
3089–2003	A	4	20.01.2001	2
5409–2000	A	4	17.11.2000	1
3463–2001	A	3	11.06.2001	1
2679–2002	A	3	23.04.2002	1
2050-2003	B	21	07.05.2003	13
3610–2003	B	6	19.07.2001	2
614–2003	B	4	27.01.2003	2
2680–2002	B	4	16.04.2002	1
3612	B	4	14.06.2001	7
2485–2001	B	3	17.05.2001	3
7967–2001	B	2	03.12.2001	4
2868–2003	B	2	21.12.2000	4

All cases arose from passive, spontaneous reporting. Therefore, it was not possible to have them all autopsied according to a common standardised protocol. The individual centres used their own ''standardised protocols'' which are more or less in line with the internationally agreed protocols. All cases in temporal association with the use of hexavalent vaccines had been classified as SUD by the local forensic pathologists. Details of forensic pathologists' report on the three cases accounting for the signal related to vaccine A are listed. Death scene investigations were performed by the police and details were available for the legal pathologist. Two (case PEI-ID 1120–2003 and case PEI-ID 5408–2000) of the three cases have also been discussed with an international panel of experts. The conclusions of these discussions are publicly availablehttp://www.emea.eu.int/pdfs/human/press/pus/851903en.pdf.

Case PEI-ID 2242–2001 Male, death at the age of 12 months (11.5 kg, 83 cm, brain weight 1260 g) within 48 h after administration of a hexavalent vaccine (vaccine A).

Vaccination history: three previous vaccinations with a tetravalent vaccine and *Haemophilus influenzae* type b vaccine plus hepatitis B vaccine were well tolerated. Booster-vaccination with vaccine A in the afternoon, 2

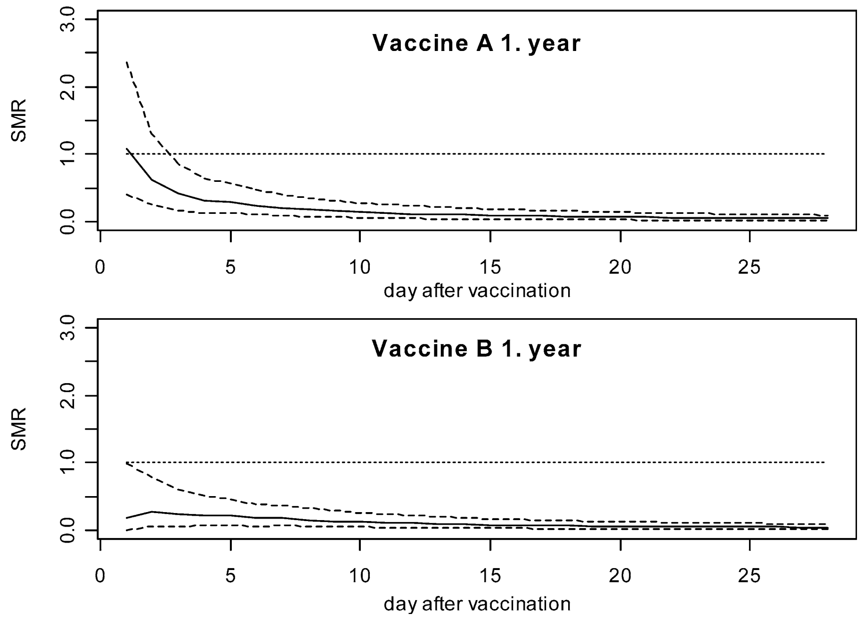

Fig. 1 Standardized Mortality Ratios (SMR *continuous line*) for sudden infant death in the first year of life by Vaccine A and Vaccine B (*dotted line* unity; *dashed lines* 95% confidence limits)

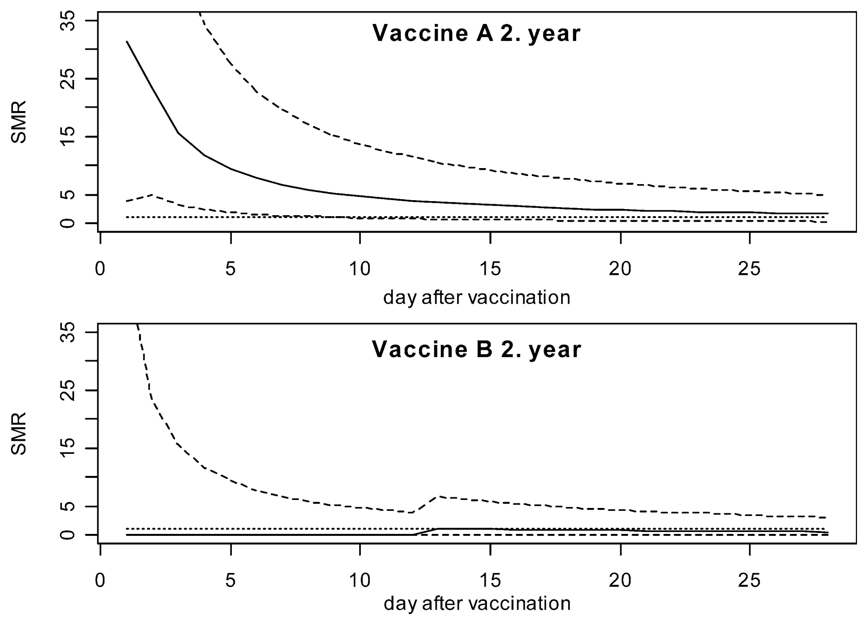

Fig. 2 Standardized Mortality Ratios (SMR *continuous line*) for sudden infant death in the second year of life by Vaccine A and Vaccine B (*dotted line* unity; *dashed lines* 95% confidence limits)

days later in the morning, at about 8 a.m., he was found dead in bed lying on his side. The head was covered with a blanket.

Patient history: according to the paediatrician, pregnancy was without complications with no history of previous diseases. Obstructive bronchitis at the end of December 2000. Pregnancy was normal.

Autopsy: toxicological investigations revealed no suspicious findings. Signs of acute circulatory failure; histology: brain: oedema, cytolytic neurons, heart: some myocardial cells with undulate structure, lung: sporadic inflammatory cells (granulocytes); no PCR testing performed; no tests for acylcarnitines and organic acidurias performed; final diagnosis: SUD

An independent forensic pathologist (Prof. Randolph Penning, Munich) assessed the autopsy report and confirmed the local pathologist's final diagnosis.

Case PEI-ID 1120–2003 Female, death at the age of 17 months (84 cm, 11.3 kg, brain weight 1195 g), found dead in bed in the morning after vaccination, "usual" position.

Vaccination history: within the 1st year, vaccinated three times with vaccine A, after each vaccination restlessness and unusual crying, treated with paracetamol. During the 3–4 weeks prior to the fourth vaccination with vaccine A, sometimes cough, no fever. At the time of clinical examination before vaccination in the morning no indication of an infection, body temperature measured by the vaccinating paediatrician was 36.8°C. Unusually tired after the vaccination in the morning (slept twice), in the evening temperature increase to 39.0°C, no antipyretic agent given. Brought to bed around at 19:00 h, restlessness around 21:00 h and 22:00 h, calmed down rapidly with a dummy. Found dead by the mother around 7 a.m.

Patient history: mother had been treated with valproate prior and during the pregnancy (plasma level below 70 µg/ml). Caesarean delivery without complications, newborn period was uneventful. Newborn metabolic screening included normal acylcarnitines, amino acids and organic acids.

Autopsy: markedly enlarged neck lymph nodes, slight pericardial effusion. Mucus in the mastoid cells (left side). Significant bleeding into the injection area in the thigh. Neurohistology: brain oedema, a few single inflammatory cellular infiltrations. Indication of disturbance in the blood-brain-barrier. No inclusion bodies found in the examined areas.

Laboratory findings: PCR negative for adeno-, entero-, influenza A and B, parainfluenza 1–4- and also respiratory syncytical viruses in the cerebrospinal fluid. PCR negative for adeno-, entero-, HHV6, influenza A and parainfluenza viruses in the pericardial fluid. PCR positive for enteroviruses in a lymph node. PCR positive for adenoviruses in the brain. Mast cell tryptase far above reference values. Total IgE was not increased. Final diagnosis: SUD.

Case PEI-ID 5408–2000 Male, death at the age of 23 months (91 cm, weight 14–15 kg) within 24 h after dose 4 of a hexavalent vaccine (vaccine A). Found dead by mother in the morning.

Vaccination history: three vaccinations with a pentavalent vaccine plus hepatitis B vaccine in his 1st year, well tolerated. Booster-vaccination with vaccine A; no fever. Death within 8–15 h after vaccination.

Patient history: pregnancy was normal. According to the paediatrician, no important preceding diseases. Physical and mental development according to age. Treated for obstructive bronchitis three times in 1999.

Autopsy: profound lobular structure of the liver, pronounced structure of the of the spleen with medium enlargement of the organs, classified as a sign of a slight chronic congestion. Aspiration of stomach contents. Heart macroscopically inconspicuous; microscopically, small spots of newly formed connective tissue in the heart muscle and few smaller round-shaped cellular accumulations. Brain oedema (brain weight ca. 1600 g).

Neurohistopathology: a few lymphocyte and macrophage infiltrations into the pia mater.

Laboratory findings: PCR in the lung tissue negative for adeno–, influenza A- and B- and respiratory syncytical viruses, positive for cytomegaloviruses. No disease-specific pattern in the organic/amino acid and acylcarnitine profile (blood on filter paper, detection by tandem-mass-spectroscopy) final diagnosis: SUD

Sensitivity analyses on the excess of deaths within 1 or 2 days following the administration of Vaccine A in the 2nd year of life were performed: (1) to take account of different distributions of SUD deaths over the 2nd year of life, (2) for an underestimation of the numbers vaccinated, (3) for over and underestimations of the SUD rate in Germany and (4) deleting the first SUD case in the 2nd year of life, which was observed within 2 months of the introduction of Vaccine A in Germany and generated the initial signal.

Since the age distribution of SUD in the 2nd year of life was estimated from only 27 cases, we assumed alternatively a uniform distribution of SUD deaths in the 2nd year of life or a pattern which followed exactly the distribution of vaccinations. The latter maximises the number expected and minimises the respective SMRs. For both, a uniform distribution and for a distribution of deaths following exactly the vaccination pattern the SMRs were lower; however, with lower limits of the 95% CIs of at least 2.4.

Under the assumption that all children eligible had been given hexavalent vaccines in the 2nd year of life. the SMRs for within 1 and 2 days of vaccination remained high with a lower limits of the 95% CI of 2.9 and 3.7 respectively.

While any overestimation of the cumulative incidence of SUD would inflate the SMRs, an underestimation of this cumulative incidence would reduce the respective SMRs. However, even an underestimation of by a factor of up to 3.78 for the 1st day and 4.83 for the 2nd after vaccination would still yield an SMR with a lower limit of the 95% CI above 1.

Excluding the index case, the lower limit of the 95% CI for within 1 day after vaccination was below 1 and 1.9 for within 2 days after vaccination.

Discussion

There are several publications addressing the issue of SUDs after vaccinations in the 1st year of life [1, 4, 7, 8, 10, 13, 15]. In all of these papers, the alleged causal association between the administration of any vaccine and SUD in the 1st year of life has been refuted. Most studies even indicated a ‘‘protective effect’’ of vaccination against SUD in the 1st year of life [4, 7, 8, 13, 15]. Several risk factors for SUD in the 1st year of life, such as a low maternal age, smoking in pregnancy, low birth weight, low parental education and a recent history of infections [5, 8, 14] are likely to be associated with a lower or delayed vaccine uptake [6, 9, 12, 16] and may account for an apparent protective effect of vaccinations against SUD due to confounding. Fewer SUD cases after vaccination might therefore reflect the lower prevalence of infections in vaccinated children and indicate a ‘‘healthy vaccinee effect’’ as described by Fine and Chen [3].

The unexpected finding in our data was the high SMRs for deaths in the 2nd year of life within days 1 and 2 after vaccination with Vaccine A with lower limits of the 95% CI's clearly above 1 suggesting a low probability that the observations are a chance coincidence. In accordance with the generally accepted definition of a signal in pharmacovigilance, these data constitute a signal for Vaccine A [2]. There are some limitations of the data set, however, which need consideration.

Estimation of the numbers exposed to the respective vaccines

To estimate the population eligible for vaccination with hexavalent vaccines in the 2nd year of life, we included children born from November 1st 1998 to June 30th 2002 and assumed that during this period a constant proportion had received hexavalent vaccines for booster vaccination in the 2nd year of life. Usually the same type of vaccine is used for booster immunisation against the six antigens contained in the hexavalent vaccines as for the primary vaccination course. Children born 2 months or more before the introduction of hexavalent vaccines in October 2000 are therefore less likely to have been given hexavalent vaccines for booster than those born thereafter. Assuming that coverage of hexavalent vaccines among these children is as high as among those born later therefore leads to a conservative estimate of the SMR.

The proportion of children given hexavalent vaccines in each month of the 2nd year of life was based on a survey of data for the use of any DTPa containing vaccines in the 1997/1998 birth cohorts, when 69.7% of all the cohorts had been given DTPa containing vaccines. In a sensitivity analysis, assuming that all children eligible for vaccination had been given hexavalent vaccines, the lower limits of the CIs were still 2.9 and 3.7 for within 1 or 2 days of vaccination with Vaccine A.

Estimation of the time of vaccination and SUD in the reference population in the 2nd year of life

The timing of vaccination and age distribution of SUD have both been estimated from surveys. Both can influence the numbers expected: the number expected would be highest when the distribution of deaths per month of life followed exactly the pattern of vaccinations given in the respective month, whereas a completely disjunctive distribution would result in zero cases expected. Even for an identical pattern of the distributions of vaccination and deaths in the sensitivity analyses, the lower level of the 95% CI of the SMRs for within 1 or 2 days of vaccination with Vaccine A remained far above 1.

Estimation of the sudden unexpected death rate in the 2nd year of life

The SUD rate in the second year of life is a key figure in the assessment of the numbers expected. There is no stringent case definition for SUD cases in the 2nd year of life. Some of the cases reported in this category might have a valid cause of death (thus not SUD). On the other hand, other deaths might have occurred suddenly and unexpectedly but not have been coded as SUD because the physician signing the death certificate was aware of an alternative cause of death. The unique feature of deaths labelled as SUD, however, is that the cause of death is not only unclear but also sudden and unexpected according to the judgment of the physician who signs the death certificate. The characteristics of deaths being sudden and unexpected make the cases observed after vaccination similar to the other sudden and unexpected deaths listed in the SUD category.

To check the plausibility of the rate of SUDs in the 2nd year of life in Germany, we compared the proportion of SUD cases among all deaths occurring in the 2nd year of life between two European countries, Germany and England and Wales. In 2001, the 33 SUD cases accounted for 8.7% of all 377 deaths in the 2nd year of life in Germany. In 2001 in England and Wales, 24 cases of SUD were reported under the ICD 10 codes R95, R96, R98, and R99 among 243 cases of death in children aged 12 to 24 months. The respective proportion of SUD and related terms was therefore 9.9%. This figure is very similar to that found in Germany (8.7% vs. 9.9%). The proportion of SUD cases in the 2nd year of life is therefore unlikely to be biased by erroneous national coding practices in Germany. Additionally, the sensitivity analyses showed that an inflation of the SUD rate in the general population by a factor of up to 3.78 for the 1st day and 4.83 for the 2nd day after vaccination would still yield a SMR with a 95% CI above 1.

Absence of an a priori hypothesis

There was no formal a priori null hypothesis—stating that there are no cases of death within a few days of vaccination with either vaccine in the 1st or 2nd year of life. The German authorities had already been alarmed by the first SUD case in a child aged 23 months occurring within 24 h of vaccination with Vaccine A in November 2000. When this first case was excluded form the calculations, the lower limit of the 95% CI of the SMR for SUD after within 48 h of administration of Vaccine A in the 2nd year of life was still above 1.

Although the limitations of the SMR approach in the available data set could not invalidate the findings as discussed above there are some more general concerns to be discussed.

Small numbers

There were only three SUD cases after the administration of Vaccine A in the 2nd year of life. The autopsy protocols of the cases included a number of investigations to exclude alternative causes of death. Copies of the death certificates for all three SUD cases in temporal association with Vaccine A were obtained by the PEI. In all three death certificates the tick box "unclear death" was marked. The codification of these cases in the vital statistics is not known due to data protection requirements in Germany, but it appears to be likely that these cases were indeed coded as SUD cases (R96, R98 and R99).

Although the autopsies of the three cases of SUD in temporal relation with the administration of vaccine A failed to give a conclusive alternative cause of death, it is difficult to rule this out definitely. This, however, also holds true for the SUD deaths for which the numbers expected have been calculated—possibly even more, since these may not all have been investigated with the same vigour at autopsy.

Nevertheless, there might be a problem, if one or two cases already make up for a significant association as in data reported here. The numbers expected for day 1 (0.06) and day 2 (0.13) are clearly below 1. A case, however, can only occur or not occur—and be 1 or zero. A number of 0.06 expected cases means that there can either be 1 or no case, the latter being more probable.

Absence of biological plausibility

All three cases after Vaccine A in the 2nd year of life were observed after the fourth dose and all had high brain weight, a possible but unspecific indicator for brain oedema reported. Additional neuropathological and immunological investigations of cases of SUD in the 2nd year of life are required to rule out that this is not a common finding for SUD cases in the 2nd year of life.

The pharmaceutical preparation of the two vaccines differ. One combines six vaccines in one syringe in a liquid ready-to-inject preparation, whereas the other one is not a fully liquid vaccine: the diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis component is a turbid white suspension. The lyophilised *Haemophilus influenzae* type b component is a white pellet powder. Prior to administration, the lyophilised Hib pellet powder has to be reconstituted with the liquid suspension for injection containing the diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis components. There is, however, no immunological or physiological explanation why this galenic difference might be relevant regarding the safety of the vaccines.

The specificity of the presumed effect is another issue: Although the unexpected association of vaccination and subsequent death within 2 days was found for Vaccine A alone, this does not rule out the possibility that there might be a SUD problem in the 2nd year of life with other hexavalent or any other vaccines, e.g. measles-mumps-rubella, as well, although no such cluster of cases has emerged from spontaneous reports. This possibility cannot be ruled out with case ascertainment from a spontaneous reporting system. A spontaneous reporting system can generate a valid signal, however, as reported for Vaccine A [19].

Artificial separation of sudden unexpected death cases in the 1st and 2nd years of life

Finally, it might be surprising that an adverse effect of a hexavalent vaccine—if the alleged association between the use of Vaccine A and SUD in the 2nd year of life were true—would be confined to the 2nd year of life. The separation of SUD deaths into the 1st and 2nd year was based on the clinical experience that SUDs within the 1st year constitute a common cause of death with a specific ICD code for SUD, whereas after the 1st year of life, SUD is definitely a less common cause of death.

For neither of the hexavalent vaccines marketed in Germany did the number of SUD cases in the 1st year of life observed up to 28 days after vaccination significantly exceed the number expected. The much lower numbers of SUD cases observed than expected after 3 or more days after vaccination probably reflects underreporting of later cases, for which a temporal relationship may remain unnoticed. This perception is supported by unpublished data from the BMBF study: Of six SUD cases in the 1st year of life occurring within 14 days after administration of a hexavalent vaccine (Vaccine B or Vaccine A), only one, occurring within 24 h of administration was reported to the PEI whereas the cases occurring on days 3, 4, 5, 6 and 8 had originally not been reported.

The lower numbers of SUD cases observed than expected within 2 days after vaccination with Vaccine B may be partially be explained by a "healthy vaccinee" effect, which was most pertinent within the first days after vaccination and faded thereafter in a study by Griffin et al. [7]. Chance might be an explanation for the absence of such a "healthy vaccinee effect" for Vaccine A. An alternative explanation might be an extension of the signal for Vaccine A in the 2nd year of life into the 1st year, which might remain unnoticed in the "noise" due to SUD from other causes. If this hypothesis holds and especially if the developing immune system might have in influence on the risk for SUD, cohorts with increasing age will show a signal already during the 1st year if life. Applying a sliding window of 12 months with cohorts of age 0 to 11 months, the of age 1 to 12 months, 2 to 13 months and so on, a signal can be detected already for the cohort 7 to 18 months of age (data not shown).

Conclusion

An unexpected occurrence of deaths in temporal association with booster vaccination in the 2nd year of life was found for one hexavalent vaccine. This signal related to vaccine A is unlikely to be explained by limitations of the available data sources. There is no indication for a similar signal in the 1st year of life, although it is possible that such a signal might remain unnoticed in the "noise" of SUD due to other causes in the 1st year of life.

Enhanced surveillance for unexpected deaths in temporal association with the administration of vaccines in the 1st and 2nd years of life is recommended.

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Appendix

Let T denote the time to death from SUD by months. To derive the expected deaths needed in calculating the denominator of SMRs, estimations of the following quantities are available:

$$c_1 = \text{cumulative incidence of SUDs in the } 1st \text{ year of life} = P(0 \leqslant T < 12)$$

$$c_2 = \text{cumulative incidence of SUDs in the } 2nd \text{ year of life} = P(12 \leqslant T < 24)$$

$$p_{1,i}^{(d)} = \text{proportion of the number of deaths from SUD occurring in the month } [i, i+1) \text{ of the } 1st \text{ year of life} = P(i \leqslant T < i+1 | 0 \leqslant T < 12) = \frac{1}{c_1} P(i \leqslant T < i+1),\ i = 0, 1, \ldots, 11$$

$$p_{2,i}^{(d)} = \text{proportion of the number of deaths from SUD occurring in the month } [i, i+1) \text{ of the } 2nd \text{ year of life} = P(i \leqslant T < i+1 | 12 \leqslant T < 24) = \frac{1}{c_2} P(i \leqslant T < i+1)\ \ i = 12, 13, \ldots, 23$$

$$p_i^{(v)} = \text{proportion of children receiving a DTPa - Hib containing vaccine in month } [i, i+1) \text{ to the number of children in this age class for whom information on vaccination is available, } i = 0, 1 \ldots$$

Let $\lambda_i = P(i \leqslant T < i+1 | T \geqslant i)$ denote the mortality from SUD for month $[i, i+1)$. From

$$\lambda_i \cdot P(T \geqslant i) = \begin{cases} p_{1,i}^{(d)} \cdot c_1 \ for\ i = 0, 1, \ldots, 11 \\ p_{2,i}^{(d)} \cdot c_2 \ for\ i = 12, 13, \ldots, 23 \end{cases} \ and\ P(T \geqslant i) = \exp\left(-\sum_{j=0}^{i-1} \lambda_j\right)$$

we obtain the following recursive formula for the λ_i's

$$\lambda_0 = p_{1,0}^{(d)} \cdot c_1 \text{ and } \lambda_i = p_{1,i}^{(d)} \cdot c_1 \cdot \exp\left(\sum_{j=0}^{i-1} \lambda_j\right), \quad i = 1, 2, \ldots, 11$$

and

$$\lambda_i = p_{2,i}^{(d)} \cdot c_2 \cdot \exp\left(\sum_{j=0}^{i-1} \lambda_j\right), i = 12, 14, \ldots, 23$$

Let S denote the set of all birth cohorts crossing the rectangle, and let N_k be the number of children from cohort $k \in S$ who contribute to the study period (being the rectangle in the Lexis diagram). Furthermore, let I_k denote the number of age classes of cohort $k \in S$ which fall into the study period. Because, children vaccinated in month $[i, i+1)$ of age are at risk of sudden death in the following month with incidence

$$\frac{(\lambda_i + \lambda_{i+1})}{2}$$

on average, concerning cohort $k \in S$, for the number of expected deaths among the vaccinated children in age class $i \in I_k$ contributing to the study period we obtain the expression $\frac{\lambda_i + \lambda_{i+1}}{2} p_i^{(v)} N_k$. Thus, the expected number from SUD cases in the 1st month after vaccination is

$$N_{Exp} = \sum_{k \in S} N_k \sum_{i \in I_k} \frac{\lambda_i + \lambda_{i+1}}{2} p_i^{(v)}$$

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