Robert Koch Institute

Study on deaths in young children (2^{nd} to 24^{th} month of life) (TOKEN Study)

STUDY REPORT

Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat (TOKEN-Studie)

Studienbericht

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1. Summary

1.1. Background and objectives

Since 2005, about 680,000 babies are born in Germany each year. Fortunately, cases of sudden unexplained death in the first two years of life are rare events and have been on the decline for 20 years. While there were more than 1000 such cases in Germany in 1991, the figure decreased to 248 cases in 2007. Reasons for this decline are the significantly improved medical care of preterm babies and the identification and increased avoidance of prone sleeping, the most important risk factor for Sudden Infant Death Syndrome (SIDS).

On 23 October 2000, two hexavalent vaccines, Infanrix Hexa® and Hexavac®, were authorised to be marketed in Europe. After authorisation, suspicion about a possible relationship between hexavalent vaccination and sudden unexpected deaths arose from several spontaneous notifications on children who had died suddenly and unexpectedly shortly after receiving a hexavalent vaccine during the first two years of life.

A first statistical analysis of these cases by VON KRIES [1] – in which observed deaths were compared with the number of expected cases – revealed no statistically significant increased standardised mortality ratio (SMR) for children below the age of one year. For children in their 2nd year of life, however, a statistically significantly increased SMR was calculated for within two days after vaccination with one (Hexavac®) of the two licensed hexavalent vaccines. This initial analysis, however, had several limitations.

The TOKEN study therefore aimed to comprehensively assess a possible causal relationship between vaccination and unexplained sudden unexpected death (uSUD) of children between their 2nd and 24th month of life. The study was supported and sponsored by the Paul-Ehrlich-Institute (PEI) and the Federal Ministry of Health (Bundesministerium für Gesundheit). In addition, study sponsoring was provided by the pharmaceutical companies, GlaxoSmithKline Biologicals and Sanofi-Pasteur MSD. The study was developed and conducted in close co-operation with an international Scientific Advisory Board. The contracts between the RKI and the pharmaceutical industry sponsors ascertained that the sponsors neither had influence on study design and analyses, nor had access to any data.

Specifically, it was the main objective of this study to answer the following study questions:

1. Is there a temporal association between vaccination and risk of sudden death in the first two years of life?
2. Is this potential association qualitatively and quantitatively the same at different ages?

The primary study analyses examined the following hypotheses:

- After vaccination with hexavalent vaccine, the number of deaths within 72 hours is higher than expected.
- After vaccination with hexavalent vaccine, the number of deaths within seven days is higher than expected.

Additionally exploratory study questions were:

3. Does this potential association have the same magnitude for hexavalent and non-hexavalent vaccines?

4. Is there a common pathological mechanism for cases of sudden death following vaccination?

The most important, known risk factors for sudden infant death are prone sleeping and maternal smoking. During the statistical analyses it became obvious that it made sense to differentiate between children who were exposed or not exposed to these risk factors. Questions and analyses generated only during the course of study analyses are considered 'post-hoc' or 'exploratory' analyses. According to the 'Good Epidemiological Practices (GEP)' such analyses should be regarded less meaningful than pre-planned analyses.

1.2. Methods

The TOKEN study had two complementary parts: an 'epidemiological study part' and a 'pathological study part'. For the 'epidemiological study part', reports of sudden death were collected through a nationwide active surveillance system implemented for the purpose of this study. On a monthly basis all death certificates of children who died within their 2nd to 24th month of life were requested from Local Health Authorities (LHAs, "Gesundheitsämter") between July 2005 and July 2008. In addition, case reports of sudden death were received from the forensic institutes participating in the 'pathological study part'.

The case reports that were received from an LHA, classified to an International Classification of Diseases (ICD-) 10 code 'R95-99' as the cause of death, and for whom parents agreed to study participation, were included as cases in the epidemiological analyses. The procedure for obtaining parental consent involved up to three contact attempts: two consecutive letters followed by a personal contact by telephone, or a 3rd letter if no telephone contact could be established. If the parents agreed to study participation, detailed information about these cases, including vaccination history, was obtained via parent and physician questionnaires. These data were statistically analysed by two methods. Temporal association of uSUD to vaccination was examined in a self-controlled case series (SCCS)[1] design. Relative risks associated with vaccination in comparison to prospectively recruited controls were estimated by multivariate models in a case-control design[2].

In addition, case reports gathered in the framework of the 'pathological study part' by 25 participating pathological institutes were included in the epidemiological study. The catchment area of the participating institutes covered about 60% of Germany. Due to resource limitations, this study part initially only enrolled cases of sudden unexpected death who died within the 10th to 24th month of life. Because of the very low number of cases in this age group, inclusion criteria were broadened to enrol also those infants who died within one week after vaccination during their 2nd to 9th month of life. The 'pathological study part' comprised standardised *post mortem* examinations including morphological, histological, micro-biological, virological and metabolic investigations as well as an investigation of the immune system and a descriptive summarisation of the findings.

[1] SCCS analyses investigate whether uSUD cases were more frequently vaccinated shortly before death. The estimate calculated using this method is called 'relative risk' (RR)

[2] Case-control analyses investigate whether uSUD cases were more frequently vaccinated shortly before death than living control children. The estimate calculated using this method is called Odds Ratio (OR).

1.3. Results

Within the framework of the study 676 uSUD cases were reported by LHAs. Of these, 37.6% (254 cases) could be included in the study, whereas parental consent could not be obtained for 62.4% of the reports. Eleven of the 254 cases enrolled in the TOKEN study had died within three days after hexavalent vaccination. Two cases had died between the 4th and 7th day and 142 cases more than six days after hexavalent vaccination (range 7-536 days). Ninety-nine cases were not hexavalently vaccinated.

Preferential self-selection of cases who had died in close temporal relationship to a vaccination was evident from the analysis of the response proportions per enrolment step. No method can correct for this selection bias, which can be assumed to have led to an overestimation of risks in this study. This severe limitation should be considered when interpreting the study results.

A second source of selection bias was introduced by preferential enrolment of recently vaccinated cases by the forensic and pathological institutes: among the children who had died within the 2nd to 9th month of life, parental participation was more than twice as high for children who had died within one week after vaccination (80.0%) as for children who had not been vaccinated within one week prior to their death. To account for this bias, inverse-probability weighted analyses were conducted in addition to the pre-planned, unweighted analyses. The results obtained from these weighted analyses are regarded as more valid and are therefore presented in this summary. For reasons of completeness, the unweighted analyses are reported in the full study report in addition to the weighted risks estimated. However, weighted analysis could only account for the selection bias among the exposed cases aged up to nine months and enrolled by the forensic institutes. Therefore, the results of the weighted analyses are likely to still overestimate the risk of uSUD. Thus, whereas selection bias further impedes interpretation of all study results, it can be assumed that the true risk most likely does not exceed the estimates calculated in the TOKEN study.

Primary analyses

The main study question asked for a temporal association between hexavalent vaccination[3] and uSUD. The main study analysis showed no increased risk of sudden death within one week after hexavalent vaccination (relative risk (RR) 0.59; 95% confidence interval (CI) 0.26-1.33). The multivariate case-control analysis (adjusted odds ratio (OR) 0.53; 95% CI 0.20-1.37) was in accordance with this finding and did not suggest a risk increase within one week after hexavalent vaccination.

In the SCCS analysis, the risk of uSUD was not statistically significantly elevated during the first three days after hexavalent vaccination (RR 1.54, 95% CI 0.67-3.54). Of note, after this initial phase (not statistically significant) risk reduction during the days 4-7 (RR 0.27; 95% CI 0.06-1.12) followed. The multivariate case-control analysis (adjusted OR 1.11; 95% CI 0.36-3.43) was in accordance with this finding and did not suggest a risk increase within the first three days after vaccination.

These results were obtained for children who died within their 2nd to 24th months of life. Results were virtually identical for infants aged up to one year. No reliable statistical analysis of the risk after hexavalent vaccination specifically during the second year of life was possible as, throughout the three-year period of the TOKEN study, consent for enrolment could only

[3] On 20 July 2005 the European Medicines Agency (EMEA) recommended the suspension of the marketing authorisation for Hexavac® due to concerns about the long-term protection against hepatitis B. Therefore, study results are mainly related the hexavalent vaccine Infanrix Hexa®.

be obtained for one child who had died in the second year of life and within three days after a hexavalent vaccination.

Explorative analyses

The a priori study question whether the absolute risk of vaccinated children may differ from unvaccinated children was approached by the case-control analysis. The multivariate odds ratio for uSUD during the first year of life was 1.20 (95% CI 0.60-2.40). Thus, there was no indication that the risk of uSUD during the first year of life is different between vaccinated and unvaccinated children. Because almost all children above the age of one year were vaccinated, no conclusive statistical analysis was possible for older children.

The a priori study question whether or not a potential association of hexavalent and other vaccines and uSUD may be of the same magnitude was also addressed. However, the low number of pentavalently vaccinated cases and controls impeded stratification by vaccine type. In the SCCS analysis, the risk estimate for uSUD after hexavalent vaccination was not higher than the combined estimate for vaccination with either a hexa- or a pentavalent vaccine. In fact, the combined estimate showed a slightly higher relative risk within three days after hexa- or pentavalent vaccination (RR 2.19; 95% CI 1.08-4.45) than the SCCS analysis of hexavalent vaccination alone. Although limited by this low case number, explorative SCCS analyses of the pentavalently vaccinated case group yielded an elevated relative risk of 8.11 (95% CI 1.81-36.24). However, only 14 pentavalently vaccinated cases (four of whom had died within three days after vaccination) contributed to these analyses. In addition, response rate was especially high for parents whose deceased child was recently vaccinated with a pentavalent vaccine. This self-selection and the very low number of cases substantially limits interpretation of these findings. While a potential association between pentavalent vaccination and uSUD was noted in an exploratory analysis based on small case numbers, no increased risk was observed in this study within one week of hexavalent vaccination, hexa- or pentavalent vaccination combined, or vaccination with any non-hexavalent vaccine, regardless of the type of statistical analysis.

The a priori study question whether there may be a common mechanism for cases of sudden death following vaccination was addressed in the pathological part of this study. Parental informed consent for participation was obtained in 43 of the 101 cases (42.6%). In 16 of the 43 enrolled cases (37%), the cause of death could be explained after autopsy. The brain weights of vaccinated cases were within the expected range and there was no indication towards brain oedema in these cases. Results of the morphological, histological, microbiological, virological and metabolic investigations as well as the investigations of the immune system did not indicate towards a common pattern among vaccinated cases and no differences between vaccinated and unvaccinated cases were found that were considered indicative of a causal role of vaccines in uSUD.

1.4. Conclusions and discussion

By implementing a nationwide active surveillance system in the context of a standardised epidemiological study over a period of three years, this study was expected to overcome the methodological and sample size limitations of a first evaluation of a potential risk between hexavalent vaccination and uSUD in the 2nd year of life. Unfortunately, the response proportion of parents was low despite careful planning and all attempts towards better study participation.

The greatest study limitation was however the self-selection of parents whose child had died shortly after a vaccination, whereas parents were less likely to participate if their child had died in more remote temporal relationship to a vaccination. Moreover, the number of parents

of recently vaccinated infants enrolled through the participating forensic institutes was disproportionately high as compared to the overall population of uSUD cases. Both of these effects introduced important selection bias into the TOKEN study. Whereas the latter source of bias could be at least partially accounted for in the analyses by inverse-probability weighting, the former source was uncontrollable and most probably led to an overestimation of the risk in the studied population. For this reason it can be assumed that the true risk most likely does not exceed the estimates obtained in this study.

Within these limitations, the risk of uSUD in the studied population within one week after hexavalent vaccination is concluded to be not different from the risk of uSUD more than one week after vaccination. This conclusion is supported by the case-control analyses which yielded similar results.

Only one of 13 analysed cases died within one week after vaccination and in their second year of life. Due to this low number of cases, no conclusions can be drawn with regard to the second year of life.

Additional exploratory analyses that were not pre-planned and for which no a priori study hypothesis had been formulated, indicated that the uSUD risk may differ depending on the presence of additional risk factors. Nine out of 10 cases who had died within the first 3 days after hexavalent vaccination and for whom information on additional risk factors were available had at least one of the generally accepted SIDS risk factors prone sleeping position or maternal smoking. Both are important and preventable risk factors that should be consequently avoided especially after vaccination.

The pathological study part focussed on the question whether a common pathological mechanism of sudden deaths after vaccination could be identified. Prior observations had led to the suspicion of an increased frequency of brain oedema in infants who died shortly after vaccination. However, the brain-body-ratios measured in this study do not support the view that vaccination may be associated with severe brain oedema. None of the extensive *post mortem* investigations revealed results indicating towards a common mechanism behind the deaths occurring after vaccination.

Given the significant limitations of this study, many of the study questions posed cannot be answered with certainty. Despite national and federal support as well as support by the local health offices in Germany the low proportion of parental participation precluded to establish a sufficient data base. Data protection concerns which mandated that the initial contact with parents was to be established indirectly by the LHAs proved to impede recruitment considerably. Resilient answers to the questions posed in this study can only be expected in Germany if both a vaccination and a mortality register are established that are linkable on a case-by-case basis.

The TOKEN study specifically examined only sudden *unexplained* deaths. Protective effects of vaccination on infant mortality from *explained* death such as lethal *Haemophilus influenzae*- or Pertussis infections were not investigated and are not reflected in the calculated risk estimates. Thus, the statistics produced in the TOKEN study do not provide an overall estimate of the effect of vaccination on infant mortality.

Despite all study limitations, it is concluded that the risk of sudden unexplained death within one week after hexavalent vaccination is not increased. The results of this study give no reason to deviate from the vaccination schedule currently recommended by the German Standing Vaccination Committee (STIKO).

As for any infant during its first year of life, the Recommendations for Prevention of Sudden Infant Deaths (SIDS) issued by the Deutsche Akademie für Kinderheilkunde should also be followed for recently vaccinated infants:

- Infants should sleep on their backs during their first year of life.
- Infants should be placed in a way that no bedding (covers or pillows) can cover the head.
- Infants should sleep in the parental bedroom, but in their own bed.
- Infants should not be exposed to tobacco smoke pre- nor postnatally.
- Room temperature and sleeping bag should ensure to keep the infant comfortable – neither too warm, nor too cold
- Infants should be breast-fed if possible.

2. Zusammenfassung

2.1. Hintergrund und Studienziele

Seit 2005 wurden jedes Jahr in Deutschland um die 680.000 Babys geboren. Plötzliche, ungeklärte Todesfälle in den ersten beiden Lebensjahren treten glücklicherweise nur sehr selten auf. In den letzten 20 Jahren hat sich ihre Zahl stetig verringert. Während im Jahr 1991 über 1.000 Fälle auftraten, waren es 2007 in Deutschland nur noch 248. Gründe für diesen Rückgang liegen in der deutlich verbesserten medizinischen Versorgung Frühgeborener und der Entdeckung und stärkeren Vermeidung des wichtigsten Risikofaktors für den plötzlichen Kindstod: das Schlafen von Säuglingen in Bauchlage.

Am 23. Oktober 2000 wurden in europäischen Zulassungsverfahren zwei Sechsfach-impfstoffe, Infanrix Hexa® and Hexavac®, zugelassen. Nach der Zulassung erweckten Spontanmeldungen über plötzliche und unerwartete Todesfälle von Kindern im Alter von bis zu 2 Jahren kurz nach einer Sechsfachimpfung den Verdacht, es könne ein Zusammenhang zwischen Sechsfachimpfungen und dem Risiko für einen plötzlichen, unerwarteten Tod bestehen.

In einer ersten statistischen Analyse dieser Fälle verglich VON KRIES [1] die Anzahl beobachteter mit der Anzahl erwarteter Fälle. Diese Auswertung zeigte kein statistisch signifikant erhöhtes Sterberisiko (‚standardised mortality ratio') für Säuglinge im ersten Lebensjahr. Jedoch war für Kinder im zweiten Lebensjahr das Sterberisiko innerhalb von 2 Tagen nach Impfung mit einem der beiden zugelassenen Impfstoffe (Hexavac®) signifikant erhöht. Die Aussagekraft dieser ersten statistischen Auswertung unterlag jedoch diversen methodisch bedingten Einschränkungen.

Das Ziel der TOKEN-Studie war deshalb die umfassende Untersuchung eines möglichen Zusammenhangs zwischen Impfungen und ungeklärten, plötzlichen und unerwarteten Todesfällen (‚unexplained sudden unexpected death'; uSUD) von Kindern im 2. bis 24. Lebensmonat. Die Studie wurde vom Bundesministerium für Gesundheit (BMG) und dem Paul-Ehrlich-Institut (PEI) inhaltlich und finanziell gefördert. An der Finanzierung waren zusätzlich die beiden pharmazeutischen Firmen Sanofi Pasteur MSD und GlaxoSmithKline Biologicals beteiligt. Es war vertraglich festgelegt, dass die Sponsoren der pharmazeutischen Industrie weder Einfluss auf das Design und die Durchführung der Studie noch Zugang zu den Daten hatten. Die Planung und Durchführung der Studie wurde von einem hierzu berufenen international besetzten, interdisziplinären Wissenschaftlichen Beirat begleitet.

Insbesondere sollte die Studie die nachfolgend aufgeführten Fragen beantworten:

1. Besteht in den ersten zwei Lebensjahren ein zeitlicher Zusammenhang zwischen Impfungen und dem Risiko, plötzlich zu versterben?
2. Sind Art und Ausmaß dieses möglicherweise bestehenden Zusammenhangs in verschiedenen Altersgruppen gleich?

Die Hypothesen für die Hauptstudienanalyse wurden wie folgt definiert:

- Die Anzahl von Todesfällen ist innerhalb von 72 Stunden nach Sechsfachimpfung höher als erwartet.
- Die Anzahl von Todesfällen ist innerhalb von 7 Tagen nach Sechsfachimpfung höher als erwartet.

Weitere exploratorische Studienfragen lauteten:

3. Besteht dabei ein Unterschied zwischen Sechsfachimpfstoffen und anderen Impfstoffen?

4. Zeigen Todesfälle, die sich kurz nach Impfungen ereignet haben, in pathologischen Untersuchungen Gemeinsamkeiten, die auf einen gemeinsamen Pathomechanismus hindeuten?

Die stärksten bekannten Risikofaktoren für den plötzlichen Kindstod sind das Schlafen in Bauchlage und das Rauchen der Eltern. Während der Datenauswertung erwies es sich als sinnvoll, zwischen Kindern mit und ohne diese Risikofaktoren zu unterscheiden. Fragestellungen, die erst im Laufe einer Studie hinzukommen, werden als ‚post-hoc-exploratorisch' bezeichnet und besitzen gemäß den Leitlinien „Gute Epidemiologische Praxis" gegenüber den vorab festgelegten Auswertungsschritten geringere Aussagekraft.

2.2. Methoden

Die TOKEN-Studie bestand aus einem epidemiologischen und einem rechtsmedizinischen Studienteil. Für den epidemiologischen Studienteil wurde ein deutschlandweit aktives Fallerfassungssystem eingerichtet, über das Berichte von plötzlichen Todesfällen abgefragt wurden. Zwischen Juli 2005 und Juli 2008 wurde monatlich bei den örtlichen Gesundheitsämtern um die Zusendung der pseudonymisierten Totenscheine aller im 2. bis 24. Lebensmonat verstorbenen Kinder gebeten. Die Todesursachen der von den Gesundheitsämtern gemeldeten Todesfälle wurden entsprechend dem internationalen Klassifikationssystem der WHO ‚ICD-10' kodiert. Fälle mit ungenau bezeichneter oder unbekannter Todesursache (Kodierungen R95-99), bei denen die Eltern der Studienteilnahme zustimmten, wurden in die epidemiologische Auswertung eingeschlossen. Um Eltern zur Teilnahme zu gewinnen erhielten sie eine erste und – bei Bedarf – eine zweite schriftliche Einladung zur Studienteilnahme. Im nächsten Schritt wurde telefonisch versucht, Kontakt zu den Eltern herzustellen. Gelang dies nicht, erfolgte die Versendung eines dritten Briefes. Wenn die Eltern der Studienteilnahme zustimmten, wurden detaillierte Informationen, auch zum Impfstatus, über je einen Fragebogen für die Eltern und den Kinderarzt erhoben. Die Untersuchung eines zeitlichen Zusammenhangs zwischen Impfungen und uSUD erfolgte mittels der Self-Controlled-Case-Series-Methode[4] (SCCS). Die Schätzung relativer Risiken erfolgte mittels einer prospektiven Kontrollgruppe im Fall-Kontroll-Design[5].

Zusätzliche wurden im Rahmen des rechtsmedizinischen Studienteils Fallberichte von 25 teilnehmenden rechtsmedizinischen Instituten einbezogen, die 60% der Bundesrepublik abdecken. In diesen Studienteil wurden aus Kapzitätsgründen anfänglich nur solche Kinder aufgenommen, die im 10. bis 24. Lebensmonat plötzlich und unerwartet verstorben waren. Wegen der sehr geringen Anzahl von Todesfällen in dieser Altersgruppe wurden die Einschlusskriterien erweitert und auch jüngere Säuglinge im zweiten bis neunten Lebensmonat) in diesen Studienteil aufgenommen, wenn sie innerhalb einer Woche vor dem Tod geimpft worden waren. Im Rahmen des rechtsmedizinischen Studienteils wurden standardisierte Autopsien einschließlich morphologischer, histologischer, mikrobiologischer, virologischer und metabolischer Untersuchungen sowie Untersuchungen des Immunsystems durchgeführt und die Ergebnisse ausgewertet.

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[4] Mit der SCCS-Methode wurde untersucht, ob bei den uSUD-Fällen überzufällig häufig kurz vor dem Tod eine Impfung stattgefunden hatte. Das errechnete statistische Maß heißt ‚relatives Risiko' (RR)

[5] Mit der Fall-Kontroll-Methode wurde untersucht, ob bei uSUD-Fällen häufiger als bei lebenden „Kontroll"-Kindern kurz zuvor eine Impfung stattgefunden hatte. Das errechnete statistische Maß heißt Odds Ratio (OR).

2.3. Ergebnisse

Im Rahmen der dreijährigen Studie wurden 676 uSUD-Fälle durch die Gesundheitsämter gemeldet. Von diesen 676 gemeldeten Fällen konnten 37,6% (254 Fälle) in die Studie aufgenommen werden, die Eltern der anderen 422 Fälle stimmten einer Studienteilnahme nicht zu. Von den 254 in die Studie aufgenommenen Todesfällen waren 11 Fälle innerhalb von 3 Tagen nach einer Sechsfachimpfung verstorben, weitere 2 Fälle zwischen dem 4. und 7. Tag nach einer Sechsfachimpfung. Bei 142 Fällen lag die Sechsfachimpfung länger als eine Woche zurück (8-536 Tage), und 99 Fälle hatten keine Sechsfachimpfung erhalten.

Eine Auswertung der Teilnahmequoten für den epidemiologischen Studienteil ergab, dass Eltern von Kindern, die kurz nach einer Impfung verstorben waren, sich eher bereiterklärten, an der Studie teilzunehmen. Diese Selbstselektion von Eltern exponierter Fälle (‚selection bias') kann in der Auswertung nicht korrigiert werden und führt zu einer verzerrten Risikoberechnung. Das in der TOKEN-Studie berechnete Risiko überschätzt deshalb das ‚wahre' Risiko. Dies muss bei der Interpretation der Ergebnisse berücksichtigt werden.

Eine zweite Quelle für ‚selection bias' zeigte sich bei der Teilnehmergewinnung über die rechtsmedizinischen Institute. Diese sollten Eltern von verstorbenen Säuglingen sowohl für eine Teilnahme am rechtmedizinischen als auch am epidemiologischen Studienteil gewinnen. Aus Kapazitätsgründen wurden allerdings (in der Altersgruppe 2 bis 9 Monate) nur diejenigen Eltern für eine Studienteilnahme angesprochen, deren Kinder innerhalb der letzten Woche vor ihrem Tod geimpft worden waren. Die von den rechtsmedizinischen Instituten erreichte Teilnahmequote war bei Eltern dieser Fälle mehr als doppelt so hoch wie bei allen anderen Eltern. Bei der Berechnung der Ergebnisse für den epidemiologischen Studienteil konnte dieser ‚selection bias' durch gewichtete Analysen (‚inverse-probability weighting') ausgeglichen werden. Die Ergebnisse der gewichteten Auswertungen werden als die aussagekräftigeren (‚valideren') Zahlen angesehen und in dieser Zusammenfassung berichtet. Im ausführlichen Fachbericht zur TOKEN-Studie sind der Vollständigkeit halber die Ergebnisse sowohl der gewichteten als auch der ungewichteten Analysen dargestellt.

Es muss jedoch berücksichtigt werden, dass das Gewichtungsverfahren nur für den ‚selection bias' korrigiert, der in der o.g. Gruppe von Säuglingen im Alter bis zu 9 Monaten aufgetreten ist, die über die rechtsmedizinischen Institute in die Studie aufgenommen wurden. Deshalb muss davon ausgegangen werden, dass die epidemiologischen Studienergebnisse trotz der Gewichtung das Risiko eines plötzlichen unerklärten Todes weiterhin überschätzen. Aus diesem Grund kann jedoch auch mit hoher Wahrscheinlichkeit davon ausgegangen werden, dass das ‚wahre' Risiko nicht über den hier berechneten Risiken liegt.

Hauptanalysen

Die Hauptstudienfrage betraf einen möglichen zeitlichen Zusammenhang zwischen Sechsfachimpfung[6] und uSUD. Die Hauptauswertung der Studie zeigt, dass das Risiko für einen plötzlichen Tod innerhalb einer Woche nach Sechsfachimpfung nicht erhöht ist (Relatives Risiko (RR) 0,59; 95%-Konfidenzintervall 0,26-1,33). Die Fall-Kontroll-Auswertung stützt dieses Ergebnis (adjustiertes Odds Ratio (OR) 0,53; 95%-KI 0,20-1,37) und gibt ebenfalls keinen Anhalt für ein erhöhtes Risiko innerhalb von einer Woche nach Sechsfachimpfung.

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[6] Da am 20.07.2005 die europäische Arzneimittelagentur EMEA in London aufgrund von Hinweisen auf eine herabgesetzte Immunogenität der Hepatitis-B-Komponente, die möglicherweise zu einem verminderten Langzeitschutz gegen Hepatitis B führen könnte, das Ruhen der Zulassung für den Sechsfachimpfstoff Hexavac® empfohlen hat, beziehen sich die folgenden Ergebnisse zu Sechsfachimpfstoffen nur auf das Präparat Infanrix Hexa®.

Nach der SCCS-Analyse ist das Risiko für uSUD innerhalb der ersten 3 Tage nach Sechsfachimpfung nicht statistisch signifikant erhöht (RR 1,54; 95%-KI 0,67-3,54). In den Tagen 4-7 zeigte sich ein ebenfalls nicht signifikantes geringeres Risiko (RR 0,11; 95%-KI 0,01-1,01). Auch die Fall-Kontroll-Auswertung stützt die Aussage, dass innerhalb von 3 Tagen nach Sechsfachimpfung kein erhöhtes Risiko besteht (adjustiertes OR 1,11; 95%-KI 0,36-3,43).

Diese Ergebnisse gelten für Kinder im zweiten bis 24. Lebensmonat und nahezu unverändert auch dann, wenn man das erste Lebensjahr allein betrachtet. Für das zweite Lebensjahr dagegen war keine aussagefähige statistische Auswertung möglich, weil während der dreijährigen Laufzeit der TOKEN-Studie nur für ein Kind die elterliche Zustimmung zur Studienteilnahme erhalten wurde, das im zweiten Lebensjahr innerhalb von 3 Tagen nach Sechsfachimpfung verstorben war.

Exploratorische Analysen

Die Untersuchungen zur Klärung der Studienfrage, ob sich das absolute Risiko von geimpften Kindern und ungeimpften Kindern unterscheidet, erfolgten mit der Fall-Kontroll-Methode. Das multivariate OR für uSUD im ersten Lebensjahr betrug 1,20 (95%-KI 0,60-2,40). Damit weisen die Auswertungen nicht auf ein unterschiedliches Risiko von geimpften und ungeimpften Säuglingen hin, plötzlich und unerklärt zu versterben. Eine aussagefähige statistische Auswertung dieser Studienfrage für Kinder im zweiten Lebensjahr war nicht möglich, da in dieser Altersgruppe fast alle Kinder bereits eine Impfung erhalten hatten.

Die Studienfrage, ob ein möglicher Zusammenhang zwischen uSUD und Impfungen sich danach unterscheidet, welches Impfpräparat verwendet wird, wurde ebenfalls untersucht. Die meisten Kinder werden mit Sechsfach- oder Fünffachimpfstoffen geimpft. Allerdings ist eine fundierte Beurteilung von möglichen Unterschieden zwischen Sechsfach- und Fünffachimpfstoffen wegen der geringen Anzahl fünffach geimpfter Fälle und Kontrollen nicht möglich. Die SCCS-Analyse ergab kein höheres Risiko von Sechsfachimpfungen im Vergleich zur gemeinsamen Auswertung von Sechsfach- und Fünffachimpfungen. In den ersten 3 Tagen nach Impfung liegt nach den Ergebnissen der gemeinsamen Auswertung von Sechsfach- und Fünffachimpfungen das berechnete relative Risiko etwas höher (RR 2,19; 95%-KI 1,08-4,45) als nach Sechsfachimpfung. Trotz der sehr geringen Fallzahlen für Fünffachimpfungen wurde für diese Untergruppe eine zusätzliche, ungeplante (‚exploratorische') SCCS-Analyse durchgeführt und ein relatives Risiko von 8,11 (95%-KI 1,81-36,24) berechnet. Allerdings trugen nur 14 fünffach geimpfte Fälle, von denen vier Fälle innerhalb von 3 Tagen nach Impfung verstorben waren, zu dieser Berechnung bei. Zusätzlich gibt es eine besonders hohe Teilnahmebereitschaft bei Eltern, deren Kinder kurz nach einer Fünffachimpfung gestorben sind. Diese Selbstselektion und die sehr geringe Fallzahl schränken die Möglichkeit einer Interpretation entscheidend ein. So bleibt festzuhalten, dass weder in den Auswertungen von Sechsfachimpfungen noch in den kombinierte Auswertung von Fünffach- und Sechsfachimpfungen noch von anderen Impfungen ein erhöhtes Risiko für uSUD festgestellt wurde.

Die Studienfrage, ob es gemeinsame pathologische Veränderungen bei kurz nach Impfungen verstorbenen uSUD-Fällen gibt, wurde im rechtsmedizinischen Studienteil untersucht. Für 43 der 101 Fälle, die den Einschlusskriterien des rechtmedizinischen Studienteils entsprachen, erteilten die Eltern ihr Informiertes Einverständnis zur Studienteilnahme (42,6%). Die standardisierten Autopsien deckten für 16 der 43 in die Studie eingeschlossenen Fälle eine erklärende Todesursache auf. Bei den geimpften Fällen lag das in der Studie berechnete Verhältnis von Körper- zu Hirngewicht im erwarteten Bereich, und es wurden keine Hinweise auf Hirnödeme festgestellt. Die Ergebnisse der morphologischen, histologischen, mikrobiologischen, virologischen und metabolischen Untersuchungen sowie der

Untersuchungen des Immunsystems ergaben keinen Hinweis auf einen gemeinsamen Pathomechanismus bei geimpften Fällen, und es wurden keine Unterschiede zwischen geimpften und ungeimpften Fällen festgestellt, die auf eine todesursächliche Wirkung von Impfstoffen hindeuten würden.

2.4. Diskussion und Schlussfolgerungen

Für die dreijährige, standardisierte, epidemiologische TOKEN-Studie wurde ein Deutschland-weites aktives Fallerfassungssystem aufgebaut. Mit diesem Vorgehen war die Erwartung verbunden, dass methodische Schwächen und Fallzahl-bedingte Einschränkungen, wie sie bei der ersten statistischen Auswertung eines möglichen Risikos von uSUD nach Sechsfach-impfungen durch VON KRIES [1] aufgetreten waren, überwunden werden. Allerdings blieb trotz sorgfältiger Studienplanung und intensiver Bemühungen um das elterliche Einverständnis die Teilnahmequote relativ gering.

Die Aussagekraft der Ergebnisse des epidemiologischen Studienteils wird jedoch am schwerwiegendsten dadurch eingeschränkt, dass Eltern von Kindern, die kurz nach einer Impfung verstorben waren, eher an der Studie teilnahmen als Eltern von ungeimpften Kindern oder Kindern, bei denen die Impfung schon länger zurücklag. Zudem wurden auch im rechtmedizinischen Studienteil kürzlich geimpfte Säuglinge durch die rechtsmedizinischen Institute mit einer höheren Teilnehmerquote in die Studie eingeschlossen, als das für die Gesamtgruppe der plötzlich und unerklärt verstorbenen Kinder der Fall war. Durch diese beiden Quellen der bevorzugten Teilnahme exponierter Fälle liegt in der Studie ein bedeutsamer ‚selection bias' vor. Während für die zweite beschriebene Quelle des ‚selection bias' durch das statistische Verfahren des ‚inverse probability weighting' korrigiert werden konnte, ist die Selbstselektion von Eltern kürzlich geimpfter Kinder nicht korrigierbar. Es muss daher davon ausgegangen werden, dass die in dieser Studie ermittelten Ergebnisse sehr wahrscheinlich das Risiko überschätzen. Es kann auf der anderen Seite davon ausgegangen werden, dass das ‚wahre' Risiko nicht über, sondern vielmehr deutlich unter den in der Studie berechneten Ergebnissen liegt.

Unter Beachtung dieser Einschränkungen kann festgestellt werden, dass sich das uSUD-Risiko innerhalb der ersten Woche nach Sechsfachimpfung nicht von dem uSUD-Risiko nach dieser Woche unterscheidet. Diese in der SCCS-Auswertung erhaltene Aussage wird durch vergleichbare Ergebnisse der Fall-Kontroll-Auswertung gestützt.

Nur 1 von 13 teilnehmenden Fällen, die innerhalb von einer Woche nach Sechsfachimpfung verstarben, war zum Zeitpunkt des Todes bereits im zweiten Lebensjahr. Die altersspezifische Unterauswertung erlaubt deshalb aufgrund der geringen Fallzahlen keine gesicherten Aussagen.

Zusätzliche, nicht ursprünglich geplante ('post-hoc-exploratorische') Auswertungen, für die nicht ‚a priori' eine Studienfrage formuliert war, deuten darauf hin, dass sich das Risiko von uSUD danach unterscheidet, ob zusätzliche Risikofaktoren vorliegen. 9 von 10 Kindern, die innerhalb von 3 Tagen nach Sechsfachimpfung verstarben und für die Informationen über zusätzliche Risikofaktoren vorlagen, hatten mindestens einen weiteren (anerkannten) Risikofaktor für SIDS: Schlafen in Bauchlage und/oder Rauchen der Mutter. Beide sind wichtige, vermeidbare Risikofaktoren, vor denen Kinder konsequent bewahrt werden sollten, auch und gerade nach Impfungen.

Mit dem rechtsmedizinischen Studienteil sollte die Frage geklärt werden, ob ein gemeinsamer Pathomechanismus für plötzliche Todesfälle nach Impfungen identifiziert werden kann. Aus früheren Beobachtungen war der Verdacht entstanden, dass bei Todesfällen kurz nach Impfungen gehäuft ein Hirnödem vorliegen könnte. Das in der Studie berechnete Verhältnis

von Körper- zu Hirngewicht stützt jedoch die Hirnödem-These nicht. Keine der umfassenden postmortalen Untersuchungen führte zu Ergebnissen, die auf einen gemeinsamen Pathomechanismus bei Todesfällen nach Impfungen hindeuten.

Angesichts der erheblich eingeschränkten Aussagekraft der Studie können viele Studienfragen nicht mit letzter Sicherheit beantwortet werden. Trotz der Unterstützung durch Bundes- wie Landesregierungen sowie der lokalen Gesundheitsämter war es mit der TOKEN-Studie aufgrund der geringen Beteiligungsquote nicht möglich, eine sichere Datenbasis zu schaffen. Die aus Datenschutzgründen notwendige Einschränkung, mit den Eltern verstorbener Kinder nur indirekt über Gesundheitsämter Kontakt aufnehmen zu dürfen, erwies sich als besondre Erschwernis bei der Gewinnung von Studienteilnehmern. Aussagekräftigere Antworten auf die Studienfragen sind deshalb in Deutschland nur bei Einführung eines Impf- und eines Mortalitätsregisters zu erwarten, sofern die Daten dieser Register valide und auf Fallebene verknüpfbar wären.

In der TOKEN-Studie wurden ausschließlich plötzliche, unerklärte Todesfälle untersucht. Vor kindlichen Todesfällen schützende, spezifische Impfwirkungen wie der Schutz vor tödlichen *Haemophilus influenzae*- oder Keuchhustenerkrankungen waren nicht Gegenstand der Untersuchung und gingen nicht mit in die Auswertungen ein. Die statistischen Berechnungen der TOKEN-Studie schätzen somit nicht den Gesamteffekt von Impfungen auf Kindersterblichkeit ab.

Trotz aller Einschränkungen kann festgehalten werden, dass das Risiko, innerhalb einer Woche nach Impfung plötzlich und unerklärt zu versterben, bei sechsfach geimpften Kindern nicht erhöht ist. Es besteht daher kein Grund, die von der Ständigen Impfkommission empfohlenen Impfungen nicht zu verabreichen.

Für kürzlich geimpfte Säuglinge gelten – wie insgesamt im ersten Lebensjahr – die von der Deutschen Akademie für Kinderheilkunde herausgegebenen Empfehlungen zur Verhinderung des plötzlichen Säuglingstods (SIDS):

- Säuglinge sollten im ersten Lebensjahr nur in Rückenlage schlafen.
- Säuglinge sollten so ins Bett gelegt werden, dass ihr Kopf nicht durch Bettzeug bedeckt werden kann.
- Säuglinge sollten im elterlichen Schlafzimmer, aber im eigenen Bett schlafen.
- Säuglinge sollten sowohl vor als auch nach der Geburt in einer rauchfreien Umgebung aufwachsen.
- Raumtemperatur und Schlafsack sollten so gewählt werden, dass es für das Kind angenehm, d. h. weder zu warm noch zu kalt ist.
- Säuglinge sollten – wenn möglich – gestillt werden.

3. Introduction

3.1. Background

Since 2005, about 680,000 babies are born in Germany each year. Fortunately, cases of sudden unexplained death in the first two years of life are rare events and have been on the decline for 20 years. While there were more than 1000 such cases in Germany in 1991, the figure decreased to 248 cases in 2007. Reasons for this decline are the significantly improved medical care of preterm babies and the identification and increased avoidance of prone sleeping, the most important risk factor for Sudden Infant Death Syndrome (SIDS).

On 23 October 2000, two hexavalent vaccines, Infanrix Hexa® and Hexavac®, were authorised in Europe via central authorisation procedures. Belgium and Germany were rapporteur and co-rapporteur for Infanrix Hexa® while, for Hexavac®, Germany and Italy took on these roles. After the first licensing of hexavalent vaccines in 2000, spontaneous notifications on children who had died suddenly and unexpectedly within 2 days of receiving a hexavalent vaccine were received by the German Paul-Ehrlich-Institute (PEI). These reports included 4 children in their second year of life. In April 2003 and again in November 2003, the scientific committee of European Medicines Agency (EMEA), the Committee for Medicinal Products for Human Use (CHMP), conducted a re-assessment of the benefit-risk profile of these hexavalent vaccines. These new evaluations were initiated by sudden cases of death that had occurred in close temporal association with the administration of hexavalent vaccines. The new evaluations of the EMEA led to an unchanged positive judgement on the benefit-risk profile of the hexavalent vaccines. The conclusions of these discussions are publicly available [2].

A statistical analysis of these cases by VON KRIES [1] – in which observed deaths were compared with the number of expected cases – revealed no statistically significant increased standardised mortality ratio (SMR) for children below the age of 1 year. For children between 1 and 2 years of age, however, a statistically significant increased SMR (SMR 23.5; 95% CI 4.8-68.6) was calculated for within 2 days after vaccination with one of the two licensed hexavalent vaccines. This result (that more cases were observed than expected) was taken as a signal for a potential association between hexavalent vaccines and an increased risk of sudden death in children between 1 and 2 years of age.

This initial analysis, however, had several limitations. The most relevant limitation was that data on observed and expected cases came from different data sources and different case definitions werde applied. The estimates given for expected cases in both the first and second years relied on justified, but naturally vague assumptions when extrapolating bridge information from different sources, thereby limiting the reliability of the SMR denominators. In relying on a very low number of cases, especially for the second year of life (n=4), the result would be substantially affected by a single misclassified case. Cause of death was determined in a non-standardised manner and interpretation of results from post-mortem examinations are likely to have differed between pathologists. In some cases, it is not known whether natural causes of death were excluded. Although brain oedema has been a feature repeatedly detected in cases of death associated with vaccination, it was not investigated in a standardised manner. Furthermore, reporting bias is a known risk of the spontaneous reporting system. Observed-versus-expected calculations performed for the first year of life indicated a considerable degree of underreporting.

Therefore, a prospective study was deemed necessary in order to systematically examine a potential association between unexplained sudden unexpected deaths (uSUD) in children who had died between the 2nd to 24th month of life and the administration of vaccines.

The study design was developed in close co-operation with an international Scientific Advisory Board (for members, see Section 11). Members of the Scientific Advisory Board were appointed by the Robert Koch Institute (RKI) with prior agreement by the Federal Ministry of Health (Bundesministerium für Gesundheit). Prior agreement for protocol amendments was obtained from the Scientific Advisory Board. Regular status reports and interim analyses were presented to the Board. The contracts between the RKI and the pharmaceutical industry sponsors ascertained that the sponsors neither had influence on study design and analyses, nor had access to any data.

The initial study protocol which mainly focussed on a comparison between both hexavalent vaccines was changed after the CHMP recommended the suspension of the marketing authorisation for Hexavac® due to concerns about the long-term protection against hepatitis B [3] in September 2005.

3.2. Objectives

This study aimed to comprehensively assess a possible causal relationship between vaccination and sudden death of children between 2 and 24 months of age.

Specifically, it was the objective of this study to answer the following study questions:

Primary study questions

1. Is there a temporal association between vaccination and risk of sudden death in the first 2 years of life?
2. Is this potential association qualitatively and quantitatively the same at different stages of life?

Specifically, the primary study analyses examined the following hypotheses:

- After vaccination with hexavalent vaccine, the number of deaths in the first interval of 72 hours is higher than expected.
- After vaccination with hexavalent vaccine, the number of deaths in the first 7 days is higher than expected.
- This is only true in the second year of life (booster vaccination).

Exploratory study questions

3. For what length of time after vaccination is the risk of death potentially increased?
4. Does this potential association have the same magnitude for hexavalent and non-hexavalent vaccines?
5. Is there a common pathological mechanism for cases of sudden death following vaccination?
6. Is the risk of sudden death in vaccinated children different from unvaccinated children?

4. Methods

4.1. Ethical and data protection aspects

4.1.1. Governmental authorisation

The Ministries of Health of 15 of the 16 German federal states granted permission for a direct interaction of the approximately 400 Local Health Authorities (LHAs, "Gesundheitsämter") with the study team at the RKI for the purpose of this study. In the 16th state (Baden-Württemberg), permission for such direct cooperation was rejected and case reporting by the LHAs to the study team was therefore mediated via the respective State's Health Authority (Landesgesundheitsamt). Each LHA was asked to take part in the study. In Germany, LHAs are sovereign with regard to their decision to participate.

4.1.2. Ethical approval

The study protocol and both protocol amendments (10 March 2006 and 15 February 2007) were approved by the ethics committee of the Hannover Medical School (see Annex 19).

4.1.3. Data protection assessment

The study protocol and related documents such as informed consent forms and questionnaires were approved by the Federal Data Protection Officer (Bundesbeauftragter für den Datenschutz; Annex 18). Advice of considerable variability was received from the Data Protection Officers of the 16 federal states (Landesbeauftragte für den Datenschutz) and required modifications of the initially planned study procedures, including pseudonymisation of death certificates resulting in a need to involve LHAs in obtaining parental informed consent, and modification of the informed consent form to specify that a possible association between vaccination and uSUD was the aim of the study. These recommendations and additional remarks of the data protection officers were taken into account.

Personal data were only used for the scientific purposes of the study, and were not passed on to other parties. Organisational measures – e.g. the design of the RKI's internal data access system – ensured that only staff involved in the study had access to the data. All participating staff members were bound to strict rules on confidentiality.

After linking all data to a certain case (death certificate, physician and parent questionnaires and the *post mortem* examination results, if any), data on individual name and address were separated from the epidemiological and medical data, and replaced by a case number. A list holding case numbers and names/addresses was stored in a secure place in case any implausibilities, questions or checks required later reference. This list will be destroyed no later than 2 years after finalisation of the study. All data were stored and evaluated in a pseudonymised form.

The German Federal Data Protection Officer performed an inspection of the study on 06 December 2007. No objections were made to the data management of the study.

4.2. External quality controls

Independent quality controls were performed by external organisations (see Section 12). These quality controls included checks of data quality as well as re-analyses of the weighted and unweighted SCCS and case control analyses presented in this report.

4.3. Study design – epidemiological study part

The study had 2 complementary parts: an 'epidemiological study part' and a 'pathological study part'.

For the 'epidemiological study part', reports of sudden death were collected through a nationwide active surveillance system implemented for the purpose of this study by requesting on a monthly basis from LHAs all death certificates of children deceased within the 2nd to 24th month of life. In addition, case reports of sudden death were received from the forensic institutes participating in the 'pathological study part'. Detailed information including vaccination history was then obtained via parent and physician questionnaires. These data were statistically analysed by 2 methods. Analyses of a possible temporal association were performed by a self-controlled case series (SCCS) design (see Section 4.3.6.1). Relative risks of uSUD associated with vaccination were estimated by a case-control design, using participants of a German Child and Youth Health Survey (KiGGS) and prospectively recruited subjects as controls (see Section 4.3.4).

A flow chart depicting the overall study concept and the interaction between the 2 study parts is given in Figure 2.

4.3.1. Study duration

The duration of the field phase was scheduled to last for 3 years. As one federal state started the death reporting only with 1 month delay, it was decided to extend the field phase to a total period of 3 years and 1 month. Therefore, for the whole study region a period of at least 3 years was covered: the case reports comprise any deaths occurring from July 2005 (Baden-Württemberg: August 2005) up to July 2008.

4.3.2. Study region

The TOKEN study was conducted throughout the Federal Republic of Germany. Participating LHAs covered 97% of live births in Germany (see 4.3.3.1).

4.3.3. Study population – cases

4.3.3.1. Reporting of children's deaths from LHAs and forensic institutes

On a monthly basis, the RKI queried all collaborating LHAs whether any deaths had occurred in children within their 2nd to 24th month of life. The LHAs responded by sending either a negative reply or pseudonymised copies of the eligible death certificates.

The total number of LHAs in Germany in charge of collating death certificates decreased during the study period from 408 to 402, due to several local government reforms. Six LHAs did not participate in the study. Another 3 LHAs did not participate for the full study duration. The LHAs that did not participate at all, or not for the full study duration – mainly due to reasons of high workload – were: Rendsburg-Eckernförde and Hansestadt Lübeck (Schleswig-Holstein), Bezirksamt Reinickendorf von Berlin and Bezirksamt Mitte von Berlin (Berlin), Odenwaldkreis (Hesse), Stadt Oberhausen and Kreis Mettmann (North Rhine-Westphalia), Alb-Donaukreis (Baden-Württemberg), Kreis Merzig-Wadern (Saarland). Their location and geographical dimension can be seen in Figure 1.

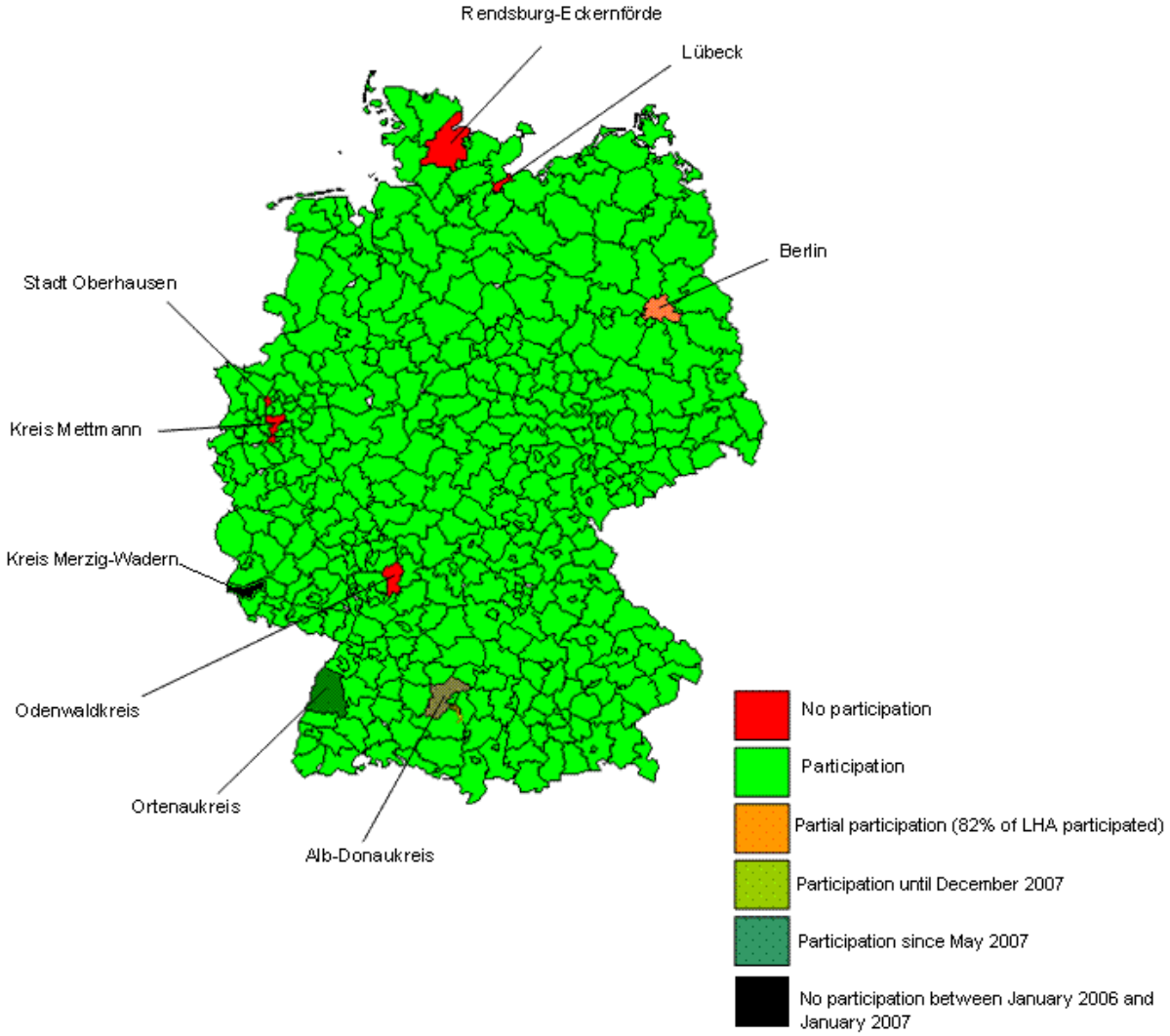

Figure 1: Map of administrative districts in Germany, colours indicating participation of local health authorities in the TOKEN study.

On the basis of the number of live births in 2006, it is estimated that the participating LHAs covered 97% of live births in Germany. However, in Schleswig-Holstein and in Berlin, the proportion of live births for whom no death reports could be collected within the study was higher (17.4% and 17.9%, respectively).

In addition, cases of sudden unexpected death (SUD) were recruited via the forensic institutes participating in the pathological study part. Of importance, a first protocol amendment in March 2006 required enrolment via participating forensic institutes of infants who had died between the ages of 2 and 9 months if had came to the attention of the pathologist that the child had been immunised within 7 days prior to its death.

The death certificates received from LHAs were checked at the RKI for meeting the study criteria (i.e., age at death between the 2nd and 24th month of life and ICD-10 classification of cause of death R95-99;[7] see Section 4.3.3.2) and to ensure that the report was not a duplicate of a report already enrolled in the pathological study part or received by another LHA. The path of the data flow is illustrated in Figure 2.

[7]The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) is a coding system of diseases and signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or diseases, as classified by the World Health Organization (WHO). ICD-10 is used to classify the underlying cause of death. The categories R95-99 code ill-defined and unknown causes of mortality:

R95 Sudden infant death syndrome

R96 Other sudden death, cause unknown

R96.0 Instantaneous death

R96.1 Death occurring less than 24 hours from onset of symptoms, not otherwise explained

R98 Unattended death

R99 Other ill-defined and unspecified causes of mortality

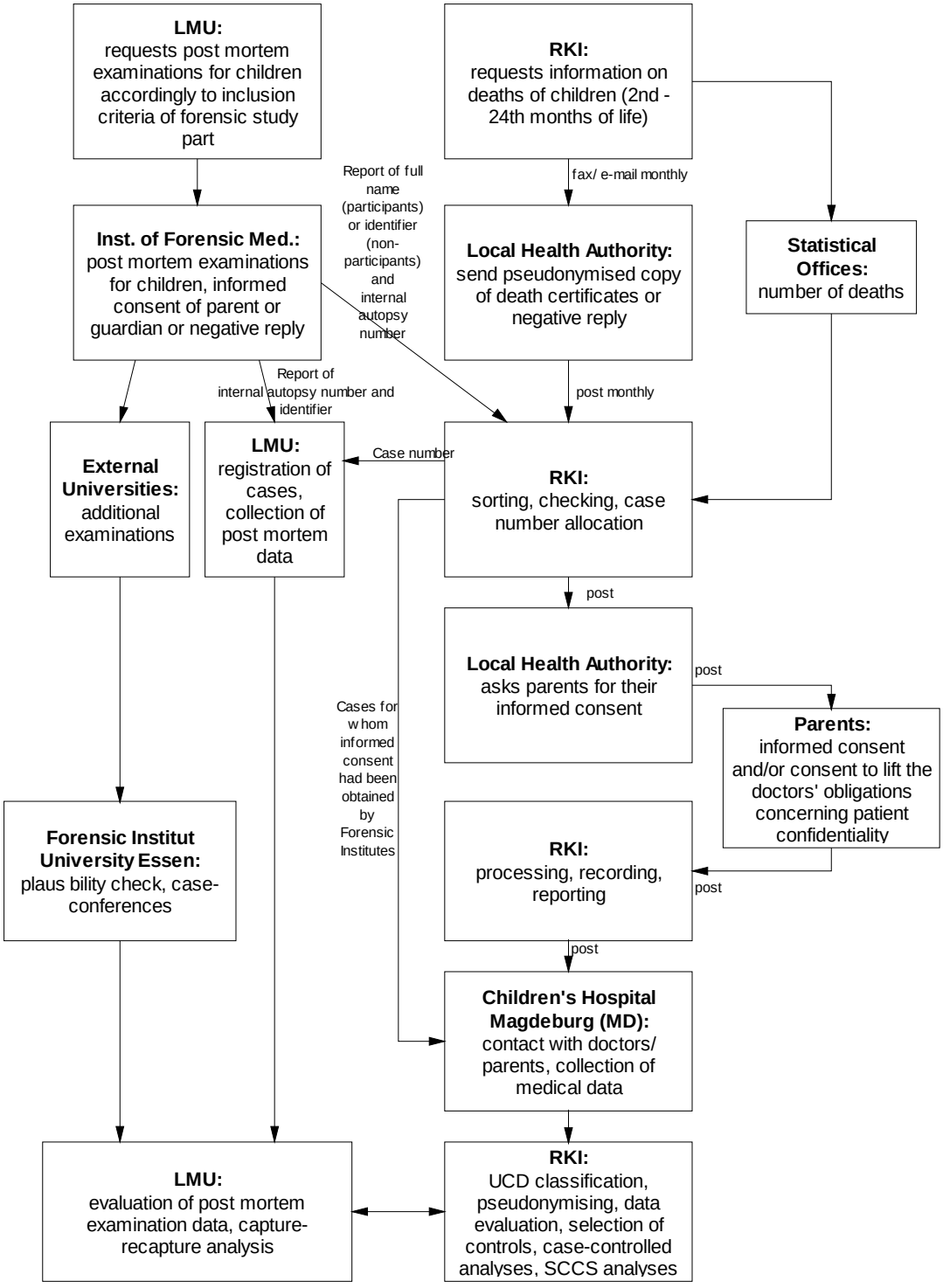

Figure 2: Chart of activities and data flow

(For abbreviations used in this figure see Section 9)

4.3.3.2. Case definition

Cases for the SCCS and the case-control analysis were defined as follows:

1. Age at death between the 2nd and 24th month of life (i.e., after the first month of life has been completed and before the 24th month of life has been completed)
2. Case report received from an LHA
3. ICD-10 classification of cause of death is R95-99 (classification based on information from death certificates and parent and physician questionnaires, from potential clinical reports and any available autopsy reports; see Section 4.3.3.3)
4. Permanent residency in Germany
5. Informed consent of parent or guardian

In addition, for the SCCS analyses the following criterion had to be met (for methodological details, see Section 4.3.6.1):

6. At least one hexavalent or pentavalent vaccination within the last 183 days (28 days for the first and second dose) prior to death

Throughout this report, the term unexplained sudden unexpected death (uSUD) describes deaths classified to ICD-10 codes R95-99.

4.3.3.3. Classification procedure of the underlying cause of death

Two paediatrician experts at the RKI, who had been specially trained in ICD-10 classification by the Deutsches Institut für Medizinische Dokumentation und Information (DIMDI), independently classified the cause of death based upon the information available from the death certificate, parent and physician questionnaires, potential clinical reports, and any available autopsy report. If one or both of these experts classified the cause of death as ICD-10 category R95-99, the death certificate was sent to the DIMDI for additional classification by the National Expert for ICD-10 Classification. Additionally, a random 10% sample of all death certificates was also re-assessed by the DIMDI National Expert. Complete data of children classified to a R95-99 category by at least one expert at the RKI or the DIMDI was provided to a multi-disciplinary case conference together with the assessments of the 3 coding experts. At this case conference, each case was adjudicated as

- R95
- R98-99 (reported as R95, but age >1 year)
- R98-99 (with autopsy)
- R98-99 (without autopsy), or
- Explained cause of death

The adjudication procedure was developed taking into account the recommendations of the Working Group on Sudden Infant Death Syndrome (SIDS) of the Brighton Collaboration [4]. Classification to R95-R99 was necessary for a death to qualify as a case as defined above (see Section 4.3.3.2).

Cases for whom the results of the additional post-mortem investigations as described in the pathological study part (see Section 4.4.3.1) were available, were classified according to the ‘San-Diego‘ case definition of SIDS [5] and thus at a higher level of diagnostic certainty [4].

To ensure maximum consistency, a final review and (re-)assessment of all cases who had been previously classified as R95-99 at any time, as well as of all cases of myocarditis, pneumonia, aspiration, and suffocation, was done and, at the end of the study, a final case conference re-assessed cases for whom interpretation of clinical symptoms or autopsy findings could have lead to disparate results concerning the classification of the underlying cause of death.

All persons involved in coding of diagnoses of causes of death were blinded to the exposure history obtained in the epidemiological part of the study at all times of the case classification process, except for those cases where vaccination shortly before the death had been recorded on the death certificates or in the autopsy reports. In such cases it was not possible to perform the ICD-10 classification in a blinded fashion.

4.3.3.4. Enrolment of cases

For all unique death reports, the RKI asked the LHA involved to identify the parents or guardians, to inform them about the study, and to obtain their consent for study participation. Before the LHA case enrolment procedure was started, it was ensured that the case had not been already enrolled in the pathological study part. Case enrolment via LHAs was done by a standardised letter of the RKI to the parents that contained information about the study and a consent form and alternatively a form for declaration of withholding consent (see Annexes 10-12). If there was no response after 14 days, a second letter was sent by the LHA. If there was still no response after another 14 days had passed, the LHA was asked by the RKI to make additional attempts to contact the parents by telephone or personally. A third letter was sent to the parents if no phone number could be obtained, no contact could be established, or if the LHA did not agree to perform the phone call. Within this third letter, the parents were asked whether they were willing to release the child's doctor from the obligation concerning confidentiality. The third letter also included a short questionnaire (non-responder questionnaire, NRQ, see Annex 6).

All attempts to contact parents and to obtain informed consent were recorded for evaluation. The enrolment process is illustrated in Figure 3.

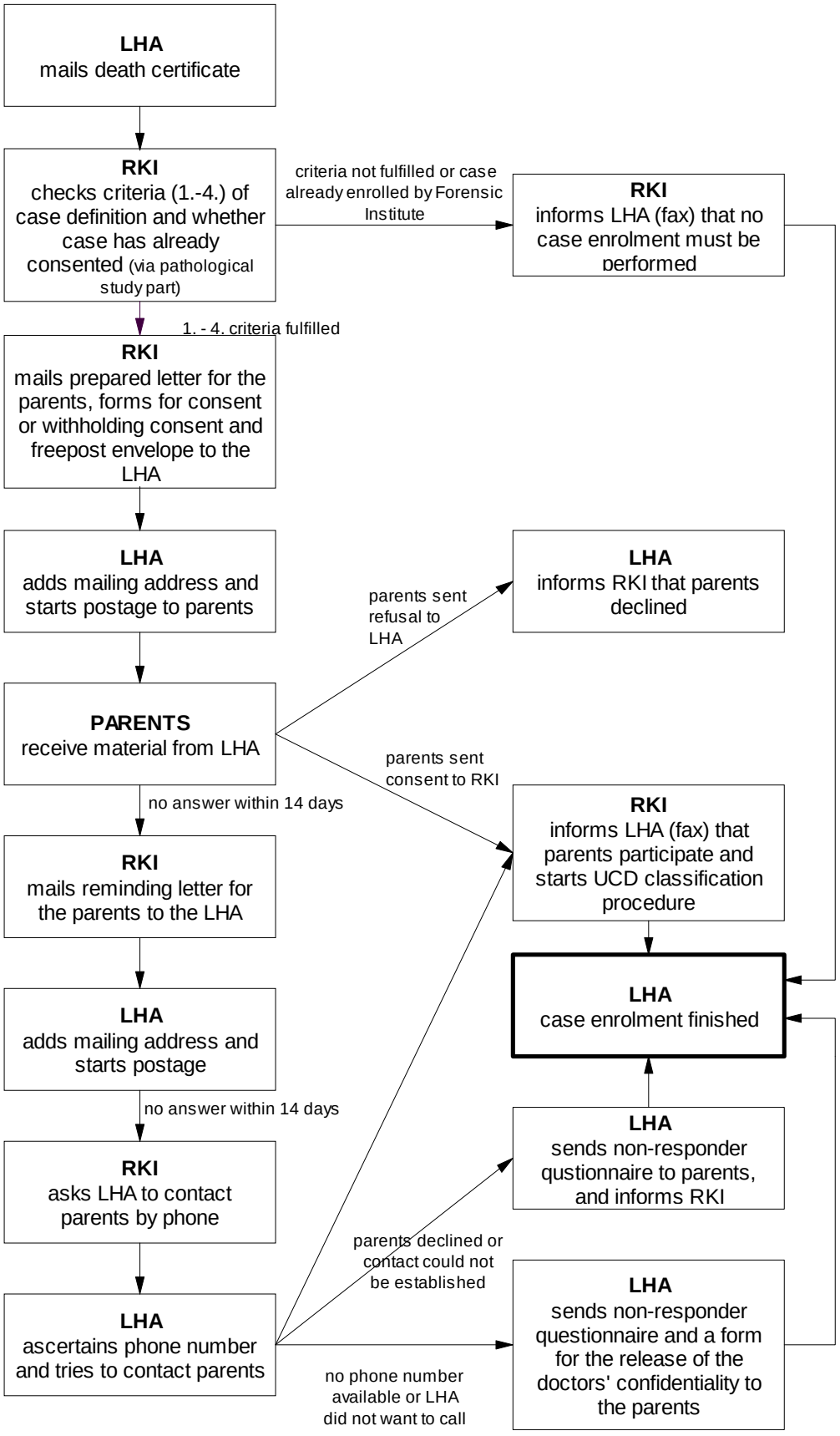

Figure 3: Case enrolment process

(For abbreviations used in this figure see Section 9)

4.3.3.4.1. Efforts to increase response proportion

In addition to the enrolment procedure with repeat letters and, if needed, additional contact by telephone or in person, several measures were undertaken to maximise response proportion. In February 2006, bereaved parents who had participated in the TOKEN study were contacted and asked to report on their experiences and feelings with the study and comment on feasibility. On the basis of this answers, a compilation of parental experiences was produced and added to the letters (see Annex 13).

To better reach the country's Turkish minority, the informed consent form, the letter to the parents, the information leaflets (see below) and the compilations of participating parents' experiences as well as the NRQ were translated into Turkish.

Public awareness of the study in the general public and in relevant professional groups (paediatricians, emergency doctors, criminal investigation departments) was sought by articles in several journals such as 'Baby und Familie' 6/2006, 'Monatszeitschrift Kinderheilkunde' 6/2006 , 'Der Notarzt' 4/2006, 'Deutsches Ärzteblatt' 2/2006, and 'Epidemiologisches Bulletin' 1/2006. Information leaflets and a letter asking for cooperation were distributed to all paediatric hospitals and to the police units in charge of SIDS/SUDI cases. Collaboration of the German SIDS Parents Organisation (GEPS) was established to ensure that bereaved parents were informed about the TOKEN study and encouraged to take part. GEPS was informed about the study progress on a regular basis to ensure motivation and further increase their commitment to encourage parents to participate.

In order to motivate the LHAs to follow the recruitment procedure, study presentations at congresses and meetings of LHAs were held repeatedly. LHAs were kept informed about the study progress and the performance of their case reporting by study progress reports 4 times a year. In collaboration with the 'Bundesverband Ärzte im öffentlichen Gesundheitsdienst', LHAs were encouraged to transfer the task of contacting parents to the 'Kinder- und Jugendgesundheitsdienst' (mainly paediatricians). Members of the 'Kinder- und Jugendgesundheitsdienst' were asked by a circular letter to support the TOKEN study by performing the telephone calls to parents inviting them to take part in the study.

An additional step focussed on parents who were not *per se* unwilling to participate, but who were not able to handle the emotional stress and flashback of memories in connection with a questionnaire. It was hypothesised that these parents could be willing to allow their child's doctor to answer a questionnaire. Therefore, parents who declared during the phone call that they did not want to take part were asked to consent that the child's paediatrician answered a physician questionnaire. Also parents who could not be contacted by phone were asked to give 'partial consent' by releasing their child's doctor from the obligations concerning patient confidentiality.

Transitionally the parent questionnaire was already enclosed with the first letter of invitation to parents of cases. Rationale for this experimental modification was that a review of case enrolment results in June 2007 had revealed that 12% of SUD parents agreed to take part in the study after they had received the third letter with the NRQ enclosed. Moreover, telephone contact to control parents revealed that some parents found it needlessly time-consuming to send back their consent first before being provided with the questionnaire itself. After clarification of data protection issues of this new procedure, the case enrolment was changed accordingly. The changed procedure started in August 2007 but was terminated on 06 November 2007 as the response proportion was observed to be lower than during the initial case enrolment procedure.

4.3.4. Study population – controls

Until April 2006, anonymous data of participants of the German Child and Youth Health Examination Survey (KiGGS) were selected as controls for the TOKEN study. As a result of the suspension of the marketing authorisation of Hexavac®, which was decided by the CHMP in September 2005, the exposure to hexavalent vaccines in the study population changed substantially and historic controls would have introduced serious bias. In order to avoid introducing such bias, the recruitment procedure for controls was changed during the study period. A second amendment of the study protocol was made in response to the CHMP decision, and as of May 2006, controls were prospectively enrolled.

4.3.4.1. Selection of controls from KiGGS data

The KiGGS methodology has been described elsewhere [6]. In brief, the KiGGS survey is based on a nationally representative sample of children and adolescents 0-17 years of age with main residence in Germany. A total of 17,641 children and adolescents were surveyed – 8985 boys and 8656 girls. Of these, 935 were investigated during the first year of life (480 boys and 455 girls) and 925 during their second year of life (457 boys and 468 girls). Study participants were enrolled from May 2003 to May 2006. A systematic sample of 167 primary sample units was drawn from an inventory of German communities stratified according to the BIK[8] classification system, which measures the grade of urbanisation, and the geographic distribution [7]. In order to ensure sufficient sample size for analyses stratifying according to residence in former East or West Germany, oversampling of children living in the eastern part of Germany was performed and a disproportionate number of sample units was included to represent former West (n=112) and East (n=50) Germany, and the city of Berlin (n=5). The overall response for eligible children and adolescents was 66.6% and showed little variation between age groups and sexes, but marked variation between resident aliens and Germans, between inhabitants of cities with a population of 100,000 or more and sample points with fewer inhabitants, as well as between the old West German states and the former East German states. An analysis of the short non-responder questionnaires gave evidence that the collected data give comprehensive and nationally representative evidence on the health status of children and adolescents aged 0 to 17 years.

The KiGGS survey and the TOKEN study ran simultaneously until May 2006, i.e., for about one third of the study period. Until 30 April 2006 a sufficient number of children aged up to the second year of life were surveyed to allow for selection of controls for the TOKEN study. During this period, controls were selected from the anonymous data of participants of the KiGGS survey. KiGGS controls were individually matched to TOKEN cases on age and date of examination. Matching was performed following these rules:

- The date of survey examination of a control is no more than 1 month earlier, and no more than 1 month later, than the date of death of the case

and

- The control is no less than 5 weeks older, and no more than (5 weeks + 2 months =) 13 weeks older, at survey examination than the case at the time of death

The reason for these rules is the mode of invitation and examination established in the KiGGS survey. Participants were invited 2 to 5 weeks prior to their scheduled date of examination. An effect on vaccination and doctors' appointments in this period is to be expected, not only

[8] BIK classes indicate size (population) and structure (urban – rural) of communities in Germany.

by participants avoiding additional appointments, but also possibly in their catching up on missed vaccinations.

The reference point to assess any exposure in controls was therefore defined as follows:

- The reference point is the date when the control was as old as the case on its day of death. Given the matching criteria (as described above), this reference point lies safely before the invitation to the KiGGS examination.

Exposure assessment in controls did not take vaccinations after the reference day into account. For each case, all KiGGS study subjects who fulfilled the above criteria were selected as controls. KiGGS study subjects suitable as a control for more than one case were selected only once. Even if the allocation of controls to a single case was primarily performed by chance, priority was given to cases who had no or a smaller number of controls.

4.3.4.2. Prospective recruitment of controls

In order to avoid introducing bias by recruiting historic controls from the KiGGS study, selection of suitable controls for cases who had died after 01 May 2006 was prospectively continued after the end of the KiGGS survey. Potential controls were randomly sampled from the same 167 communities that had already been selected for the KiGGS survey.

In order to achieve the best possible accordance to the sampling frame of KiGGS controls, the procedure of enrolling prospective controls was this:

1. After the photocopies of the death certificates had been received from the LHAs, the date of birth of each reported case was ascertained.
2. The acceptable birth date range for controls was calculated. To be eligible, controls had to be born on the same day as the case, plus/minus 1 month.
3. Two communities were randomly selected from the 167 KiGGS sample points.
4. A letter was sent to the registration offices in both selected communities asking to identify at random 5 children who were born in the specified time period and to send their names, dates of birth, gender and addresses (and the names of their parents) to the RKI.
5. From the RKI, a letter was sent to the parents with information about the study, asking them for consent to participate.
6. If parents did not respond within 14 days, a second letter was sent out as a reminder.
7. If parents still did not respond after another 14 days, attempts were made to contact them by phone at different times of day.
8. If parents declined participation, they were asked to complete the non-responder questionnaire.
9. If parents consented, they were sent a questionnaire similar to the questionnaire for cases. For obvious reasons, however,, questions about the circumstances of death were not asked. The reference date for answers was the age at death of the corresponding case.

The strategy for matching these controls to TOKEN cases was the same as for KiGGS participants.

4.3.5. Data collection

4.3.5.1. Parent and physician questionnaires

Upon receipt of parental informed consent, a team of specialist paediatricians and a psychologist who all have a strong background in SIDS and experienced in consultation of bereaved parents, was provided by RKI with all necessary information to contact the child's parents and paediatrician in order to obtain comprehensive data. This team, located at the Magdeburg university hospital, managed all contacts with parents and physicians. They requested all necessary data by postal standardised questionnaires (see parent and physician questionnaires, Annexes 4 and 5). The questionnaires gathered information and data on immunisation (date of immunisation, information on the vaccine product), on the child and mother and the event itself. Medical and epidemiological factors, known or suspected risk factors for SIDS and SUD as well as health-related behaviour with regard to vaccination were made available.

If the questionnaires were not returned after 4 weeks, the parents got a written reminder and if this did not prompt an answer, parents were contacted by phone 2 weeks later.

This specialist team was also available for medical and psychological consultation of bereaved parents if required.

4.3.5.2. Autopsy protocols

Autopsy protocols were requested from hospitals, forensic institutes or from the LHAs.

4.3.5.3. Non-responder questionnaires

Parents declining study participation by means of the non-participation form which was enclosed within both letters of invitation, were mailed a short non-responder questionnaire (NRQ) by the LHA. This NRQ queried reasons of non-participation, socio-economic status, the age of the mother, single parent status, parental smoking status and the vaccination status of the deceased child. Parents who declined participation during a phone contact with the LHA were asked to respond to the NRQ by phone.

In case no contact to parents could be established at all, a third letter was sent to the parents providing them with the form for the release of the doctor's obligation for confidentiality, and the NRQ (see Section 4.3.3.4). In such cases, parents were asked to send the NRQ back to the RKI. A freepost envelope was enclosed.

In order to preserve confidentiality, the LHAs withheld the names and addresses of all parents declining study participation from the RKI study team.

4.3.6. Data analysis and statistical methods

Analysis of the study data was planned by 2 methods: the self-controlled case series (SCCS) method and the case-control method. The SCCS method provides an alternative to traditional cohort or case-control methods for investigating the association between a time-varying exposure and an outcome event. It was developed in 1994 to investigate associations between vaccination and acute potential adverse events [8-10]. The special situation that the study investigated multiple exposures (single doses of vaccination) and a non-recurrent event (death) necessitated adaptations of the initially published method (see Section 4.3.6.1). The SCCS method does not produce estimates of absolute incidence in case of non-recurrent events such as death. Therefore, in the TOKEN study, the relative risks yielded by the case

series method do not estimate the magnitude of any potential effect of vaccination on risk of death, but rather describe the risk within a specified risk period in comparison to a control period and indicates whether there is an accumulation of deaths after vaccination. To overcome this limitation, the SCCS analysis was complemented by a simultaneously performed case-control study. A second reason for the case-control study was the high public health relevance of the study question, which mandated to have the study results of the SCCS analyses confirmed or not confirmed by analyses based on cases and controls.

Several subanalyses were not pre-defined in the study protocol but were considered relevant based on the results of the primary analyses. These exploratory subanalyses are thus considered hypothesis-generating but would need confirmation in separate studies. As these additional analyses also lead to an underestimation of the alpha error, the term "statistical significance" is not used when presenting the results of these subanalyses. The presented 95% confidence intervals are rather considered as a measure for the relative stability of the results.

4.3.6.1. Self-controlled case series analysis

In order to answer the first 4 study questions (see Section 3.2), deaths subsequent to vaccinations were analysed using the self-controlled case series method examining whether the time of death in these cases is in conspicuous proximity to the time of vaccination.

According to official German recommendations issued by the German Standing Vaccination Committee (STIKO), 4 doses of hexavalent vaccines should be administrated during the first 2 years of life [11-14]. These first 2 years of life are the observation time of this study. So far, no applicable model has been published to estimate the strength of any association between multiple vaccinations and the risk of death in terms of relative incidence.

Initially, it was planned to carry out the analyses according to the method published by Farrington in 1995 [8] for very rare, non-recurring events, and a model was considered predefining the observation period to start at the time of the last vaccination stretching up to 183 days. This model cannot distinguish between different doses, but does provide an estimation of the common estimate (relative incidence). However, a major limitation of this model was discovered: observation periods after the first, second, and third vaccination dose overlap each other. By simulation studies it was shown that this results in artificially truncated control periods and an underestimation of the vaccination effect.

One approach considered to avoid this problem was to extend the observation time up to the full relevant age period, i.e. up to 730 days of life. This approach would have allowed considering each dose separately and including each observed vaccination into the model. However, this model is only applicable for recurrent events and not for studies examining censoring events. The reason for the limited applicability is that the exposure history throughout the observation period must be known in the case series method. Clearly, it is not possible to know when a child might have been vaccinated had the child not died. These data on potential future exposure periods are therefore missing. For example, if the last dose before the death is dose 2, there is no way of knowing whether the child would have received doses 3 and 4 if the child had not died. Yet this information is required in the case series design.

As a consequence of this information gap, potential but unknown future risk periods count as control periods. This leads to an extension of the control period and a marked overestimation of the relative incidence which was clearly shown by simulation studies [15].

Therefore, the original SCCS approach was adapted to the special conditions of the TOKEN study. Adaptations were discussed with and assessed by the developer of the SCCS method, Paddy Farrington. In March 2007 agreement had been reached in that the adaptations result in valid estimates and are in line with the basic SCCS method. In this approach each dose is

considered separately. However, a prerequisite for this approach is that no vaccination occurs in the observation time of the preceding vaccination. According to the official immunisation schedule issued by the STIKO and according to the respective Summaries of Product Characteristics (Fachinformationen) of the authorised hexavalent vaccines, the time interval between two subsequent vaccinations has to be at least 28 days. The interval between the third and fourth dose has to be at least 6 months. Therefore, the duration of the observation periods was defined as follows: 28 days observation time for the first and second vaccination and 183 days for the third and fourth dose. Accordingly, separate estimates for each dose are obtained. Furthermore, this enables to combine the separate estimates and estimate a common effect at all doses.

Simulation studies showed that the new TOKEN adapted method estimates the effect for (censored) TOKEN events as reliable as the SCCS method estimates the effect for recurrent events [16]. This model is also applicable for the estimation of a common effect at all doses for the sequential analyses: the null hypothesis will be tested for each study period and in each analysis a p-value will be calculated. P-values of the predefined number of intervals (for sequential analyses) can be combined by means of an adaptive method.

The advantage of this method is that valid and independent estimates are obtained for each of the 4 doses. The disadvantage of the method is that it does not allow for the use of all data in one analysis, but only those events that occur in the relatively short observation periods. This inevitably results in some loss of power.

4.3.6.1.1. Sample size

In 2002, when the study size was planned, the necessary number of cases for the SCCS analysis was estimated according to FARRINGTON et al. [8, 10]. For the power analysis, it was assumed that the null hypothesis would be tested with an exact binomial test. The number of cases necessary to reach a power of 80%, in a one-sided test at the level $\alpha = 0.05$, was calculated as 561, 126, 35 and 29 for $\rho = e^{\beta} = 2$, 4, 8, and 10, respectively (StatXact version 6.0) using the parameter mentioned above. The formula quoted from Farrington gives the results 506, 81, 24 and 17.

In 2002, the total number of deaths in children aged 28 days to one year in Germany was 1058. Of these cases, 420 were attributed to ICD-10 categories R95-99. Assuming a response proportion of 50% for this younger age group, a sufficient number of cases were to be expected.

In 2001, the number of deaths in the second year of life was 377. Of these, 33 were attributed to ICD-10 categories R96 and R99. In 2002, the number of deaths described as SUD fell to 24. The number of deaths from 1999 to 2002 ranged from 24 to 42 per year in the second year of life. The number of cases necessary for the study, 29 (or 17) ($\rho = 10$) children vaccinated within 6 months of death, was considered realistic under the assumption of a 50% response proportion and a 3-year study duration.

Some degree of uncertainty existed because it was difficult to estimate the proportion of children who were immunised within the respective observation periods as data on vaccination status and especially on the timing of vaccinations were limited. Therefore, assumptions on vaccination coverage at different ages were mainly based on the recommended vaccination schedule by the official German recommendations issued by the STIKO at that time.

After having adapted the SCCS method to the special requirements (multiple exposures and a non-recurrent event), sample size calculations were updated. By means of a simulation study, the number of cases required in order to detect a relative incidence of 2, 4 or 8 with a study

power of 80% at the level alpha=0.05 was estimated. This calculation showed that 150 to 160 cases were necessary to detect a relative risk of 2 (30-35 cases to detect a relative risk of 4). However, detecting a relative risk of 2 (or 4) separately for each dose would require considerably more cases especially for doses 3 and 4 (see Table 1).

4.3.6.1.2. Definitions for implementing the SCCS method

Age was controlled for by using the following age categories [days]: >30.0 to 60.0; >60.0 to 91.0; >91.0 to 152.0; >152.0 to 183.0; >183.0 to 274.0; >274.0 to 365.0; >365.0 to 456.0; >456.0 to 730.0. Age was calculated taking into account the exact time of death, leading to an age stating days, hours and, if available, minutes. Time of birth was set at 00:00 h for all cases. These categories discriminate age groups of high, medium or low risk of SUD, derived from the age distribution of SUD deaths in Germany in 2001.

Three models were established in order to allow for the analyses of all 3 risk periods. Date of vaccination was calculated regarding the time of day which was obtained by the parent questionnaire. If no time of day was available for the respective vaccination, the vaccination time was set to 12:00 h noon.

The following definitions with regard to the risk periods and the respective control periods were made:

Model I:

- Risk period I: 1^{st}-3^{rd} day
- Control period: 4^{th}-28^{th} day (first and second dose) or 183^{rd} day (third and fourth dose)

Model II:

- Risk period I: 1^{st}-3^{rd} day
- Risk period II: 4^{th}-7^{th} day
- Control period: 8^{th}-28^{th} day (first and second dose) or 183^{rd} day (third and fourth dose)

Model III (exploratory analysis):

- Risk period I: 1^{st}-3^{rd} day
- Risk period II: 4^{th}-7^{th} day
- Risk period III: 8^{th}-14^{th} day
- Control period: 15^{th}-28^{th} day (first and second dose) or 183^{rd} day (third and fourth dose)

The hazard ratio in the risk period was estimated in relation to the control period with a 2-sided test of significance at the level α=0.05. Analogously, a 2-sided 95% confidence interval was calculated.

The risk periods represented categories with markedly different levels of incidence, according to cases of death after hexavalent vaccination observed so far. The 'high risk' interval of 1^{st}-3^{rd} day was defined according to the recommendations of the Brighton Collaboration Working Group on SIDS [4] The additional 'high risk' interval of 4^{th}-7^{th} day was defined in the light of the results of the Italian Hera Study [17]. This study suggested that the risk period

of a potential temporal association between vaccination and sudden death may extend up to 7 days, specifically from the 4th to 7th day after vaccination.

A cut-off of 14 days was set as a plausible, but arbitrary boundary for a possibly causal association. Due to the methodological requirements of the SCCS analyses for studies investigating multiple exposures and non-recurrent events, a risk period up to 28 days cannot be investigated as the observation periods after dose 1 and 2 of hexavalent vaccination end at day 28 (see Section 4.3.6.1).

Six seasonal classes *k* were defined (January/February; March/April; May/June; July/August; September/October; November/December) in order to adjust for any seasonal differences in the risk of sudden death.

Every case has a particular constant 'hazard', derived from the combination of age category, seasonal category and risk period. The hazard $h(t)$ for the time t is therefore a function of the age category at time t, of the seasonal class k, the risk period at time t and an individual set of time independent co-variables.

4.3.6.1.3. Null hypotheses formulated for the pr imary study question in the SCCS approach

Model I:

After adjusting for age and season, the hazard after vaccination with hexavalent vaccine in the first risk period of 72 hours is the same as in the control period (4th-28th day (first and second dose) or 4th-183rd day (third and fourth dose)).

Model II:

After adjusting for age and season, the hazard after vaccination with hexavalent vaccine in the first risk period of 72 hours, in the second risk period (4th-7th day) and in the combined risk period I + II (1st-7th day) is the same as in the control period (8th-28th day (first and second dose) or 8th -183rd day (third and fourth dose)).

The above null hypotheses were tested separately

a) for cases deceased in their 2nd to 24th month of life following any hexavalent vaccination during the respective observation period,
b) for cases deceased in their 2nd to 12th month of life following any hexavalent vaccination during the respective observation period,
c) for cases deceased in their 13th to 24th month of life following any hexavalent vaccination during the respective observation period.

Any effect estimate with a 95% confidence interval that did not include the 1 was considered statistically significant. This corresponds to a 2-sided P-value of 0.05.

4.3.6.1.4. Exploratory analyses

In addition to the primary analyses described above, exploratory analyses with an additional risk period (Model III) were performed for comparison to the risk periods set out *a priori* under the primary hypotheses.

In addition to these specific hypotheses, potential temporal associations of hexavalent or pentavalent vaccination – not only hexavalent products – and uSUD were investigated by exploratory analyses.

4.3.6.1.5. Interim analyses

As the results from this study were of particular importance to public health, sequential data analyses of the SCCS data were undertaken as a monitoring instrument while the study was running. The goal of the sequential analyses was to stop the study early if an unacceptable risk were apparent. It was focussed on the early detection of a potentially increased risk within the first risk period (Model I); thus the sequential test was performed one-sided. To adjust for multiple testing, an adaptive design was applied using the software ADDPLAN, Release 3, 2005 (Adaptive Designs – Plans and Analysis©; ADDPLAN GmbH). It was specified for 4 stages and used the inverse normal method for combining the separate p-values of each stage. The warning limit was calculated according to the method of WANG and TSIATIS [18] with a delta value of 0.25. Different lengths of interim intervals were accounted for by modifying the information rates.

As the application of the adaptive design was based on the p-values of the SCCS analysis, the results were adjusted for age and season. This adjustment turned out to be essential soon after the beginning of the study and gave reason to use the adaptive design instead of the initially intended sequential probability ratio test of Wald, for which the incorporation of covariates into the analysis is not possible.

Based on the observed association, the null hypothesis (H_0) could not be rejected since the observed inverse normal test statistic did not exceed the critical level. The ”stage specific overall p-value“ of the sequential analyses is the lowest significance level at which the limit had been crossed at the given stage. It controls a study throughout the sequential analysis: as long as it remains above the defined limit of 0.05, the null hypothesis (‘the risk 3 days after hexavalent vaccination is the same as in the control period’) cannot be rejected. The adjusted final analysis yielded a one-sided p-value of 0.151 [19].

The overall analysis of the adaptive design was performed in November 2008. Thereafter, additional information on vaccination status and/or cause of death was received for some cases, leading to slightly different case numbers in the final study analyses presented in this report.

4.3.6.2. Case-control analysis

In the case-control study, vaccination histories of cases (deceased children) and controls (living children) were compared in order to study the potential effect of vaccination on the risk of sudden death (study question 6). This method allowed for detection and assessment of risk factors and identification of vulnerable subgroups. Using the case-control approach in rare events, relative risks can be reliably estimated by odds ratios. Odds ratios can be adjusted for potential confounders by multivariate logistic regression.

Utilisation of data from the KiGGS study (see Section 4.3.4) led to oversampling of controls from the eastern part of Germany. This oversampling was corrected by adjusting all uni- and multivariate case-control analyses for ‘region of residence’.

The following parameters are factors known to be associated with sudden unexpected death (SUD; see Section 6.1.7) and were therefore explored in logistic regression models: sex, level of maternal education, maternal age, smoking during pregnancy, prematurity, neonatal

complications, multiple pregnancy, number of siblings, breast feeding, family status (both parents, single mother, or mother with a new partner), and maternal smoking. Some of these variables are also known to be associated with vaccination coverage.

Maternal smoking and smoking during pregnancy as well as prematurity and neonatal complication were highly correlated. Therefore, the variables with less missing values (i.e., maternal smoking and premature birth, respectively) were selected for modelling.

Variables were tested for inclusion in the final model, one at a time; and any variables that improved the maximum likelihood estimation of that model were added. Decisions were made on the basis of the Bayesian Information Criterion. Variables that did not add to the model were not retained. According to these criteria, the final model included the following variables: sex, maternal education level, maternal age, prematurity, number of siblings, breast feeding and maternal smoking. Additionally, family status was included as this variable increased the explained variance of the model further.

4.3.6.2.1. Sample size

The sample size calculation prior to the start of the study was performed under following assumptions:

The null hypothesis would be tested with a 2-sided chi-square test at level $\alpha = 0.05$ with a power of 80%. The average number of controls per case is 4.3. The number of cases necessary to detect an odds ratio of 20 for the risk of uSUD within 72 hours after hexavalent vaccination in comparison to no hexavalent vaccination within this period was calculated with $n_1 = 32$ cases and $n_2 = 4.3 * 30 \rightarrow 138$ controls. The numbers of cases necessary to detect an odds ratio of 5, 10 and 15 respective sample sizes of $n_1 = 190$, 70 and 43 cases were calculated.

4.3.6.2.2. Study hypotheses

During this secondary study analysis, the following hypotheses were tested:

1. The odds of being vaccinated (within the interval of 72 hours) are higher in cases than in controls.
2. This is only true in the second year of life (booster vaccination).
3. This is only true for a hexavalent vaccination.
4. The odds of being vaccinated at any time are higher in cases than in controls.

4.3.6.2.3. Null hypotheses formulated for the case-control approach

For hypotheses 1 and 2, the vaccination history was coded as

'0' = not vaccinated within 72 hours (reference category)

'1' = vaccinated within 72 hours

With multivariate conditional logistic regression, including the covariates sex, maternal education level, maternal age, premature birth, number of siblings, breast feeding, maternal smoking and family status, the following null hypotheses were tested:

Null hypothesis for hypotheses 1 and 2:

- The risk of uSUD is not increased within 72 hours after any vaccination (odds ratio = 1).

This null hypothesis was tested separately

a) for all cases (date of death between the 2nd and 24th month of life) and their controls,
b) for cases (date of death between the 2nd and 12th month of life) and their controls,
c) for cases (date of death between the 13th and 24th month of life) and their controls.

For hypothesis 3, the vaccination history was coded as

'0' = not vaccinated within 72 hours (reference category)

'1' = vaccinated within 72 hours with a hexavalent vaccine

'2' = vaccinated within 72 hours with a non-hexavalent vaccine

Within the multivariate conditional logistic regression model, including the covariates sex, maternal education level, maternal age, premature birth, number of siblings, breast feeding, maternal smoking and family status, the following null hypotheses were tested:

Null hypotheses for hypothesis 3:

- The risk of uSUD is not increased within 72 hours after a hexavalent vaccination (odds ratio = 1).
- The risk of uSUD is not increased within 72 hours after any non-hexavalent vaccination (odds ratio = 1).

These null hypotheses was tested separately

a) for all cases (date of death between the 2nd and 24th month of life) and their controls,
b) for cases (date of death between the 2nd and 12th month of life) and their controls,
c) for cases (date of death between the 13th and 24th month of life) and their controls.

For hypothesis 4, the vaccination history was coded as

'0' = no vaccination before death (cases) or reference date (controls), respectively (reference category)

'1' = any vaccination before death or reference date, respectively

Within the conditional logistic model, including the covariates sex, maternal education level, maternal age, premature birth, number of siblings, breast feeding, maternal smoking and family status, the following null hypothesis were tested:

Null hypothesis for hypothesis 4:

- The risk of uSUD is not increased after any vaccination (odds ratio = 1).

4.3.6.3. Completeness of case reporting

Completeness of case reporting in the framework of the active surveillance system established for this study in cooperation with the LHAs in Germany was assessed by two methods: comparison of reports with the data of the official German mortality register and by a capture-recapture analysis.

The number of reports in the German mortality register of children who had died in their 2nd to 24th month of life was compared to the number of case reports received by LHAs. This comparison excluded data from 2008 because national mortality data were not available for 2008 when the report was drawn. Data from July 2005 were also not compared because the state of Baden-Württemberg did not participate in the study during this month, thus impeding comparison of study data to nationwide mortality statistics.

Capture-recapture analyses (CRC) were conducted to estimate the completeness of the reporting of SIDS/SUD cases among children aged 9-23 months [20-23]. The aim was to estimate the completeness of case ascertainment in the TOKEN study and to analyse the completeness of the case reporting by institutes of forensic medicine for the study period.

Two reporting data sources, the local health authorities (LHA) and the forensic institutes were available. Analysis was restricted to children aged 9-23 months who were autopsied in a public or university forensic institute between 01 January 2006 and 31 December 2006 with the diagnosis (before autopsy) "suspected SIDS/SUD" on the death certificate or children who had died suddenly and unexpectedly.

4.3.6.4. Estimation of response

Response proportions were calculated according to the methods of SLATTERY [24] and STANG [25]. Assuming that non-participation of parents who moved home after the death of their child does not introduce any selection bias, the 'recruitment efficacy proportion' according to STANG [25] was also calculated.

4.3.6.5. Missing data

In cases for whom parents only permitted 'partial-consent' (see Section 4.3.3.4.1), no parent questionnaires were received. Each of these cases's vaccination status was therefore obtained from the physician questionnaire.

As the SCCS method has the advantage of an implicit control of all potential confounders that are stable over time, cases without parent questionnaires could be included in the SCCS analyses without any problem. The multivariate analyses of the cases-control study, however, required information on covariables. Data that could not be obtained from the child's doctor or from the autopsy protocol remained therefore missing. No substitution or imputation of missing data was performed. In the logistic models, separate categories for missing data were defined, allowing for all cases to be included.

4.3.6.6. Assessment of selection bias

Selection bias implies that the association between exposure (in this study vaccination within the last 3 or 7 days) and outcome (uSUD) within the study population is different from the overall population [26]. Selection bias occurs when exposed subjects are more or less likely to be enrolled in a case-control study than unexposed. Prerequisite for an unbiased SCCS or case-control analysis is that enrolment of cases (and controls for the case-control analysis) is performed irrespective of the exposure of interest. In this study therefore, it was to be proven that recently vaccinated or unvaccinated cases were not preferentially enrolled.

The study design, which required all LHAs in Germany to report and enrol all cases of death up to 2 years of age regardless of their vaccination status, would have sufficiently guaranteed for a non-preferential enrolment. Furthermore, LHA staff could not be aware of the vaccination status of a dead child unless this was stated on the death certificate or came to their attention by any other means. Cases enrolled by the pathological study part were a subset

of the cases reported by LHAs. That means cases were only included in the analyses, if they had been reported also by a LHA.

Following the first study protocol amendment, children who had died within the second to ninth month of life were also to be enrolled via the pathological study part. However, according to this protocol amendment, the forensic institutes enrolled these cases only if they were known to have been vaccinated within 7 days prior to death.

In order to investigate whether this change had led to a preferential case enrolment and, thus, potentially biased the study results, response proportions were calculated stratified by the initiator of case enrolment (forensic institute or LHA) as well as by age groups (2^{nd} to 9^{th} month or 10^{th} to 24^{th} month). Furthermore, separate response proportions were calculated for the recruitment of younger children by forensic institutes and by LHAs, as well as for the study periods before and after study protocol amendment (see Table 7 and Table 8).

The response proportions were found to differ between these strata (see Section 5.1.1.3). As the proportion of exposed cases could be assumed to be higher among the younger cases enrolled by forensic institutes after the first protocol amendment, this may have introduced some degree of selection bias. A weighting procedure was employed to adjust for this potential bias (see Section 4.3.6.6.1).

4.3.6.6.1. Weighting procedure

Statistical adjustment is increasingly described as an option to correct for selection bias [26, 27]. When information is available on factors that govern selection, inverse-probability weighting provides an analytical approach for selection bias. According to HERNAN [27] the use of inverse-probability weighting provides unbiased estimates of causal effects even in the presence of selection bias, because the method works by creating a pseudo-population in which censoring (or missing data) has been abolished and in which the effect of the exposure is the same as in the original population. The principle of inverse-probability weighting was used for correction of selection bias in a number of studies [28-30]. Inverse-probability weighting is based on assigning a weight to each included case so that the case accounts in the analysis not only for itself, but also for those with similar characteristics that were not selected. The weight is the inverse of the probability of the case's enrolment to the study.

As the forensic institutes had a higher probability of enrolling exposed cases of a certain age (see Section 5.1.1.3), weights were calculated on the basis of the different response proportions of cases primarily approached by forensic institutes or LHAs, respectively, and applied to all SCCS and case-control analyses. Given a number of 12 out of 15 cases who were successfully enrolled by forensic institutes and 138 out of 421 similar cases who were successfully enrolled by LHAs, the weight to be applied to cases enrolled by forensic institutes was calculated to be 0.41 (95% CI 0.31-0.55). In order to further assess the impact of the weighting procedure on the results, weighting of the primary analysis was also performed with weights that respresented the upper and lower limits of the 95% confidence interval of the weight's point estimate. As a differential response proportion was seen only in cases up to the age of 9 months, no weighting was performed for cases who had died in the age above the ninth month.

4.4. Study design – pathological study part

The pathological study part had 2 purposes. First, it intended to maximise the diagnostic validity of cases recruited into the epidemiological study part by identifying deaths sufficiently explained by any natural cause. Second, it aimed to answer study question 5 ("Is there a common pathological mechanism for cases of sudden death following vaccination?").

The 'pathological study part' included cases of sudden death for whom standardised *post mortem* examinations were undertaken. An active surveillance system was instituted by querying on a monthly basis all collaborating forensic and pathological institutes in Germany for any *post mortem* examinations that had been carried out in children who had died within the 2nd to 24th month of life. Initially, the pathological study part included only children who had died within the 10th to 24th month of life. Because only a very low number of cases of this age could be included, the case definition was broadened by protocol amendment for increased efficiency of this study part. After the protocol amendment, also younger cases were included, provided that they had been vaccinated within 7 days prior to death.

In this study report, the methodology and results of the pathological study part are only summarised. The full study report is provided in Annex 22.

4.4.1. Study duration

The pathological study part started 1 month after the epidemiological study part on 01 August 2005 and lasted until 31 August 2008.

4.4.2. Study region

The pathological study part was planned to be conducted throughout Germany. However, although all forensic and pathological institutes in Germany were informed about the TOKEN study and agreement for collaboration was sought, only 27 out of 33 institutes participated. Their locations and of catchment areas can be seen in Figure 4.

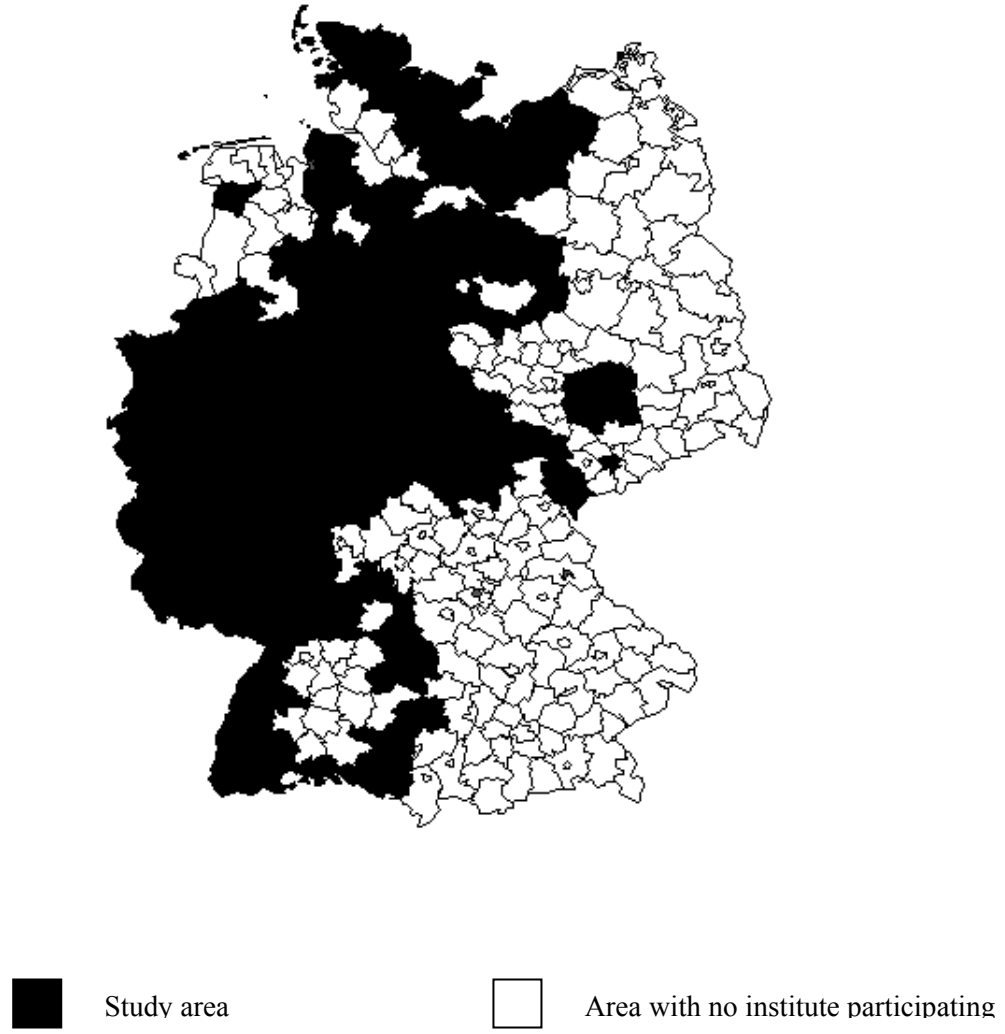

Figure 4: Map of area covered by forensic institutes that participated in the TOKEN study

4.4.2.1. Reporting of children's deaths by the forensic institutes

On a monthly basis, all forensic institutes were queried whether any *post mortem* examination had been carried out in children who had died between the 2nd (initially 10th) and 24th month of life during the past month. The queries were performed by the project partner at the Institute of Social Paediatrics of the Ludwig Maximilians University (LMU) in Munich. The institutes responded by sending either a negative reply or a brief report form, on which initials, dates of birth and death were stated. In addition, it was stated whether the *post mortem* examination had been performed according to the standardised autopsy protocol described in Section 4.4.3.1.

LMU matched these short reports with the case reports received spontaneously from collaborating institutes. If a case reported on request had not already been included in the study, the forensic institute or pathology was asked to contact the child's parents or legal guardians for their informed consent for study participation.

4.4.2.2. Case definition

Cases were defined as follows:

Every child who had died within the 10th to 24th months of life and for whom a standardised *post mortem* examination had been performed and informed consent of a parent or guardian had been obtained.

As of 2006, the inclusion criteria for the pathological study part were expanded by the first study protocol amendment, as follows: if post-mortems were performed in a child who had died in its 2nd to 9th month of life and it came to the attention of the pathologist that this child had been immunised within 7 days prior to death, the case was also to be included in this study.

4.4.2.3. Enrolment of cases

The study protocol, informed consent forms and case report forms were provided to all collaborating forensic and pathological institutes. The institutes identified eligible cases, asked parents for informed consent and passed on the case report forms and the informed consent forms to the RKI. In addition, this consent was extended to the release of the children's doctors from their obligations concerning patient confidentiality and to the questionnaires sent by the project team in Magdeburg.

4.4.3. Data collection

Data derived from the autopsies were collected and processed at the Institute of Forensic Medicine of the University of Essen. A plausibility check was performed and data completeness was verified. The RKI verified all case reports from the pathological and the epidemiological study part in order to avoid duplicates or repeated contacts of parents. The RKI transmitted personal data and case numbers to the project team in Magdeburg from where questionnaires were sent to parents and physicians. Completed questionnaires were returned to Magdeburg.

4.4.3.1. Standard autopsy protocol and questionnaires

Post mortem examinations were performed according to the standardised autopsy protocol (Annex 7) and the 'additional autopsy investigations' (Annex 8) as specified in the 'standardised autopsy manual' (Annex 9). This standardised autopsy protocol is in accordance with the European guidelines for medico-legal autopsies [31] and international recommendations [32], and closely reflects the international standardised autopsy protocol [33] as well as protocols used in other studies on SIDS including the GeSID study [34-36].

The autopsies included a thorough external examination, a complete internal examination, extensive histology, immunohistochemistry of the lungs and the myocardium, a full analytical toxicology screening, a metabolic screening, microbiological, virological, and immunological investigations as well as investigations for predisposing genetic factors.

Most neuropathological investigations were done at the Institute of Neuropathology of the Aachen University Hospital. The metabolic screening was performed by the Laboratory Olgemöller & Becker in Munich using tandem-MS spectrometry. For details please see the above mentioned Annexes.

4.4.3.2. Classification procedure of the underlying cause of death

The multidisciplinary case conference described in Section 4.3.3.3 adjudicated the underlying cause of death for all cases from the pathological study part. In the majority of cases, data from the standardised autopsy protocol and the additional autopsy investigations were available to the conference.

4.4.4. Evaluation strategy

4.4.4.1. Descriptive analyses

In the pathological part of the study, the following study question was investigated:

- Is there a common pathological mechanism for cases of sudden death following vaccination?

The data obtained from the standardised autopsies and the additional autopsy investigations were summarised in a descriptive manner. No analytical statistics were applied.

5. Results

5.1. Epidemiological study part

5.1.1. Cases

5.1.1.1. Number of case reports and completeness of case reporting

Figure 5 gives an overview of the number of cases reported to the RKI. A total of 2466 case reports were received from LHAs and 117 case reports from the forensic institutes. These figures include 38 duplicate reports, 129 unique reports that did not meet the study criteria, mainly due to ineligible age at death, and 1623 reports with explained causes of death. Thus, a total of 676 SUD reports were received during the total study period, 56 of which were first reported from the forensic institutes.

Consent for study participation was obtained for 258 of the 676 SUD reports (see Section 5.1.1.3). As no information on vaccination status could be obtained in 4 enrolled cases, the final number of cases with exposure information was 254. These cases were available for the SCCS and case-control analyses.

Assessment of completeness of reported cases occurring in the 2nd to 24th months of life in comparison to the total number of deaths in the official German mortality register published by the Federal Office of Statistics revealed that 72.2% of all deaths were reported by the LHAs within the framework of the study. In the group of cases classified to the ICD-10 codes R95-99, the proportion of reported cases was close to 90%. The proportion of missing R95-99 reports was highest in the federal states Berlin and Schleswig-Holstein. The absolute number of unreported cases was also high in North-Rhine Westphalia. However, as this was also the state with the highest absolute number of cases, the proportion of cases reported by the LHAs was still 85%.

The results of the capture-recapture (CRC) analysis are shown in Table 3. Within the age range and time period for which the CRC was performed, the analysis yielded an estimate of 116.9 cases and an overall completeness of 75.3% for the LHAs and of 72.7% for the forensic institutes. The age-specific CRC analyses showed that in the age group 9-11 months the proportions of cases reported by LHAs and forensic institutes were lower than in the age group 12-23 months. The completeness of the forensic institutes was lower than of the LHAs in the first year of life.

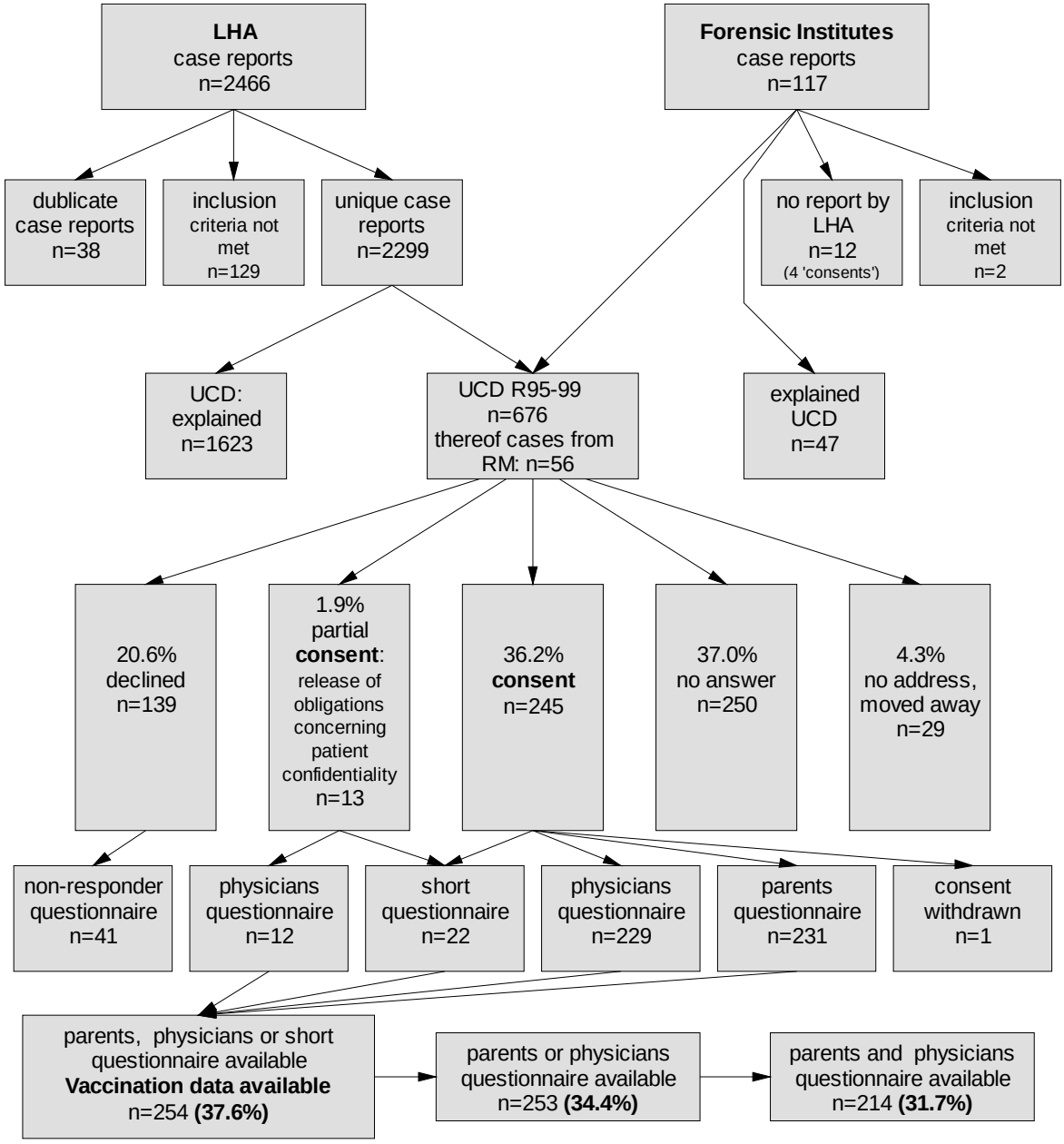

Figure 5: Overview of cases reported and enrolled in the TOKEN study

(For abbreviations used in this figure see Section 9)

5.1.1.2. Classification of the underlying cause of death

A total of 306 case reports were submitted to the case conference after one or both coding experts at the RKI had classified them into one of the ICD-10 categories R95-99. However, 48 cases who had died suddenly and unexpectedly turned out to have an explained cause of death, according either to the information on the death certificate or according to an available autopsy report. These cases had primarily died from pneumonia, myocarditis or sepsis and were ICD-classified accordingly. Two hundred and fifty-eight cases were classified to the ICD-10 categories R95-99. In one case, however, parents withdrew their consent later.

The data available for the final classification of the underlying cause of death by the case conference included the death certificate and the following (optional) documents: parent

questionnaire, physician questionnaire, hospital records and autopsy protocol. In 210 (81.7%) cases with an R95-99 code according to the death certificate, an internal *post mortem* examination had been performed somewhere. In 203 (97%) autopsied cases, an autopsy protocol (or at least a summary of the protocol) was available to the study group. The proportion of autopsied R95-99 cases differed considerably between the 16 federal states, with higher rates in the former East German states (range 83-100%) and lowest rates in Lower Saxony (56%) and Baden-Württemberg (54%).

However, in Germany no standardised data source is available indicating whether an autopsy was performed. Death certificates are not standardised and in most federal states the information had to be requested by the study team. In enrolled cases, this information was obtained from the parent questionnaires and from the LHAs. In cases without consent, the information was requested by the LHAs. Information could be obtained in all but one of the enrolled cases, but only 79.2% of the non-participants. Therefore, no conclusive statement can be made whether the proportion of autopsies performed was higher in participants than in non-participants.

A total number of 258 enrolled SUD cases were classified to the ICD-10 categories R95-99 (uSUD). For one case the initial consent was withdrawn, resulting in 257 final cases. For 3 of these cases no data could be obtained.

5.1.1.3. Response proportion

On the basis of the number of participants for whom at least one questionnaire was received (either parent, physician, or non-responder questionnaire), the overall response proportion was 37.6%. The proportion of parents who initially consented was 38.0%. For 3 enrolled cases no questionnaire was received (see also Table 5).

In addition to the overall response proportion, the response at each step of enrolment was determined. The cumulative response proportions were (see also Figure 6):

- After the case recruitment by the forensic institutes: 2.8%
- After the first letter of invitation: 19.1%
- After the second letter of invitation: 28.1%
- After the phone contact: 32.7%
- After the third letter of invitation: 37.6%

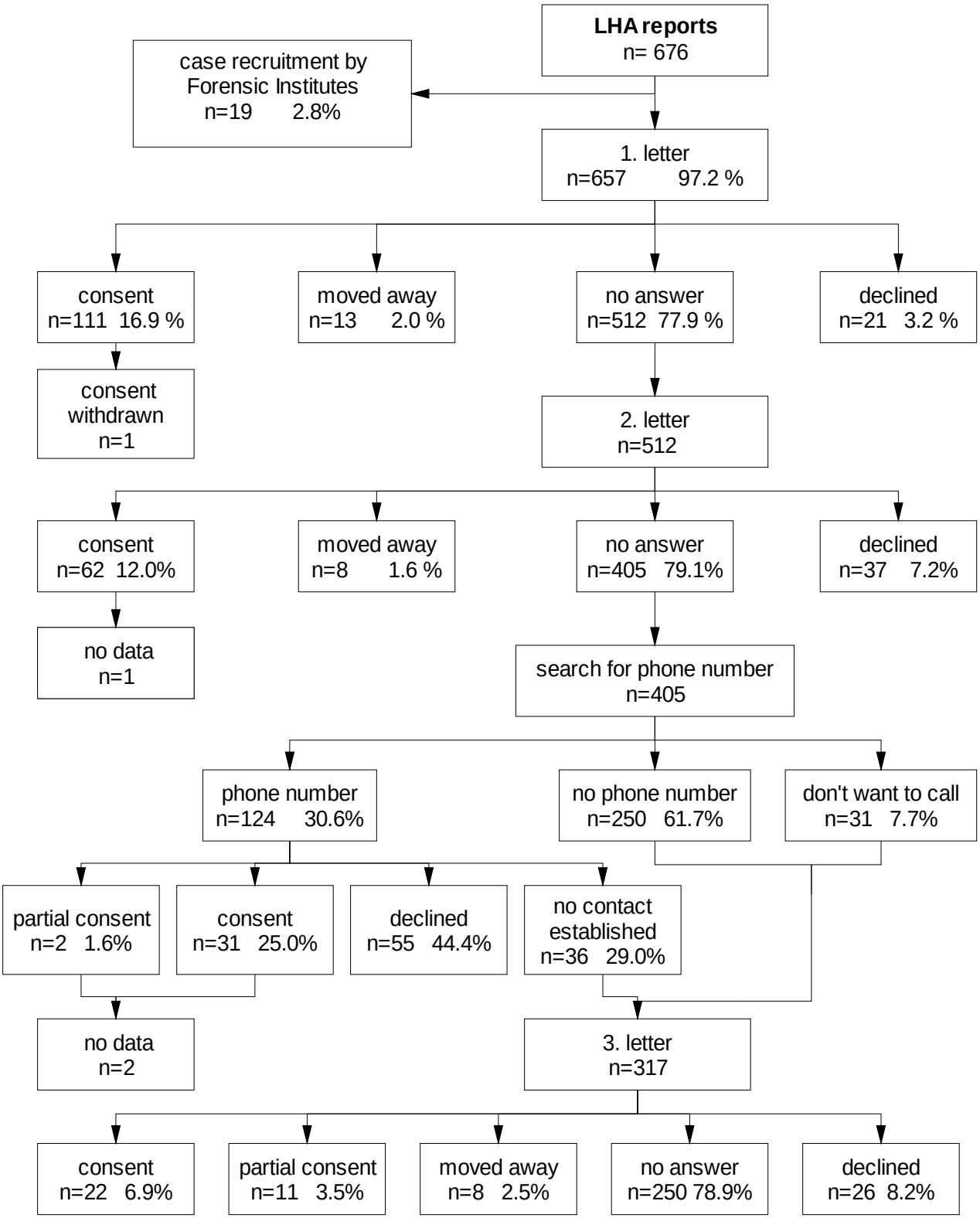

Figure 6: Participation of cases by step of study enrolment (all percentages are related to the absolute numbers in the next upper box)

(For abbreviations used in this figure see Section 9)

Stratified by age, the response was higher in cases who had died during the second year of life (47.6%) compared to the first year of life (36.2%; see Table 5).

Differences between the younger and older age group were even more pronounced when the cut-off was set to the age of 9 months. This cut-off is related to the preferential enrolment of recently vaccinated cases by the forensic institutes (see Section 4.3.6.6). The response proportion in cases who had died up to the age of 9 months was 35.0% in comparison to 48.1% in older cases (see Table 6).

Differences between response proportions of cases approached by LHAs or forensic institutes were marginal in cases older than 9 months (46.7% vs. 51.2%). However, in younger cases (2^{nd} to 9^{th} month of life) the response proportion was much higher in cases first contacted by forensic institutes (80.0%) than in cases approached by LHAs (33.7%; see Table 7).

Of importance, younger cases were only enrolled by the forensic institutes after the first study protocol amendment was made and only if the infant had been vaccinated within 7 days prior to death. Therefore, the response proportion in younger cases was broken down by initiator of case enrolment (forensic institute or LHA) and by study period (before and after the study protocol amendment). Of the 543 cases who had died up to the age of 9 months, 107 occurred before the study protocol amendment was made and 436 afterwards. Comparing the response proportion of young cases who had died after the study protocol amendment between the LHA (32.3%) and the forensic institutes (80.0%) reveals that response proportion was 2.5-fold in cases who had been vaccinated within 1 week prior to death in comparison to the response proportion in exposed or not exposed cases, for whom case enrolment was performed by the LHAs (see Table 8).

Table 9 shows the participation of cases by risk period in relation to hexavalent vaccination and the step of case enrolment in which parental consent was achieved. Overall, half of the consents (50.8%) were already obtained after the first contact of the forensic institutes or the LHAs with parents. When stratified by risk classes, however, differences became obvious: for 11 out of the 13 cases who had died within 7 days after vaccination, the consent was obtained after the very first step of case enrolment (85%). For cases who had died more than 13 days after a hexavalent vaccination or were not vaccinated at all, less than 50% of consents were obtained at this early stage of case enrolment. On the other side, in 20.4% of cases who had died after the first 3 hexavalent risk periods, parents consented only after having received 2 letters of invitation *and* having been contacted by phone or after an additional third letter (32.4% in unvaccinated cases).

Table 10 shows these data for the risk period in relation to pentavalent vaccination. It is noteworthy that all cases who had died within 3 days after pentavalent vaccination consented either by case enrolment of the forensic institute (n=1) or already after the *first* letter of invitation (n=3).

The number of parents with whom no contact could be established because they had moved home and their new address could not be determined was 30 of 676 (4.4%) in the TOKEN study. As some LHAs tried to update the current address by requests to the population registration office, this number is somehow mixed up with the intensity of recruitment efforts of the respective LHA.

Table 11 shows the recruitment efficacy proportion by age. Total recruitment efficacy was 39.3%. Recruitment efficacy was 37.9% in cases who had died within the first year of life and 49.4% in cases who had died within the second year of life, respectively.

5.1.1.4. Non-responder questionnaires

A total number of 41 non-responder questionnaires (NRQ) were obtained from the 136 parents who explicitly declined study participation. This corresponds to a proportion of 30.2%. However, related to the total number of eligibles who did not consent to participate, only 9.8% provided a NRQ.

5.1.1.5. Comparison of responders and non-responders

The information provided on the death certificates of reported cases could be used to compare responders and non-responders with regard to age, gender and place of residence. Data on nationality, maternal smoking, maternal education and maternal age as well as data on the vaccination status were only available from responders and non-responders who provided the respective questionnaires. Even if a questionnaire was provided, answers were sometimes missing for specific questions. The most frequently missing answers in the NRQ were those related to maternal education and vaccination status. A tabular comparison of the characteristics of responders and non-responders is given in Table 12. No differences were apparent with regard to age, gender and place of residence. Between responders and non-responders who completed the NRQ, no differences were seen with regard to maternal smoking and maternal age. The proportion of a high maternal education was considerably lower in the non-responder (7.3%) than in the responder group (21.4%).

5.1.2. Controls

5.1.2.1. Number of controls

A total of 1180 controls were enrolled to match the 254 cases. Three hundred and ninety-seven controls were selected from the KiGGS data for the 78 cases reported until April 2006, and 783 controls were prospectively recruited to match the 176 cases reported after April 2006.

5.1.2.2. Response proportion

On the basis of the number of participants who returned questionnaires, the overall response proportion was 48.3%. Initially 51.6% had consented, but 54 of those never returned the parent questionnaire.

The response proportion at each step of enrolment was also determined (see also Figure 7). The cumulative response proportion by step of enrolment was

- After the first letter of invitation: 27.4%
- After the second letter of invitation: 41.1%
- After the phone contact: 47.7%
- After the third letter of invitation: 48.3%

More than half of the consents (56.8%) were already obtained after the first letter to parents. After the second letter 222 consents (28.3%) were obtained and an additional 13.5% participated after a telephone contact was made by the RKI study centre. Only 1.4% of the consents were after the third letter. However, the proportion of NRQs received was highest after the third letter (n=70; 73.7% of parents to whom the third letter was sent).

The prevalence of eligibles who consented but did not return the questionnaire was lowest (2.6%) in participants who had consented after the first letter of invitation and was highest in participants who had agreed after the third letter of invitation (59.3%).

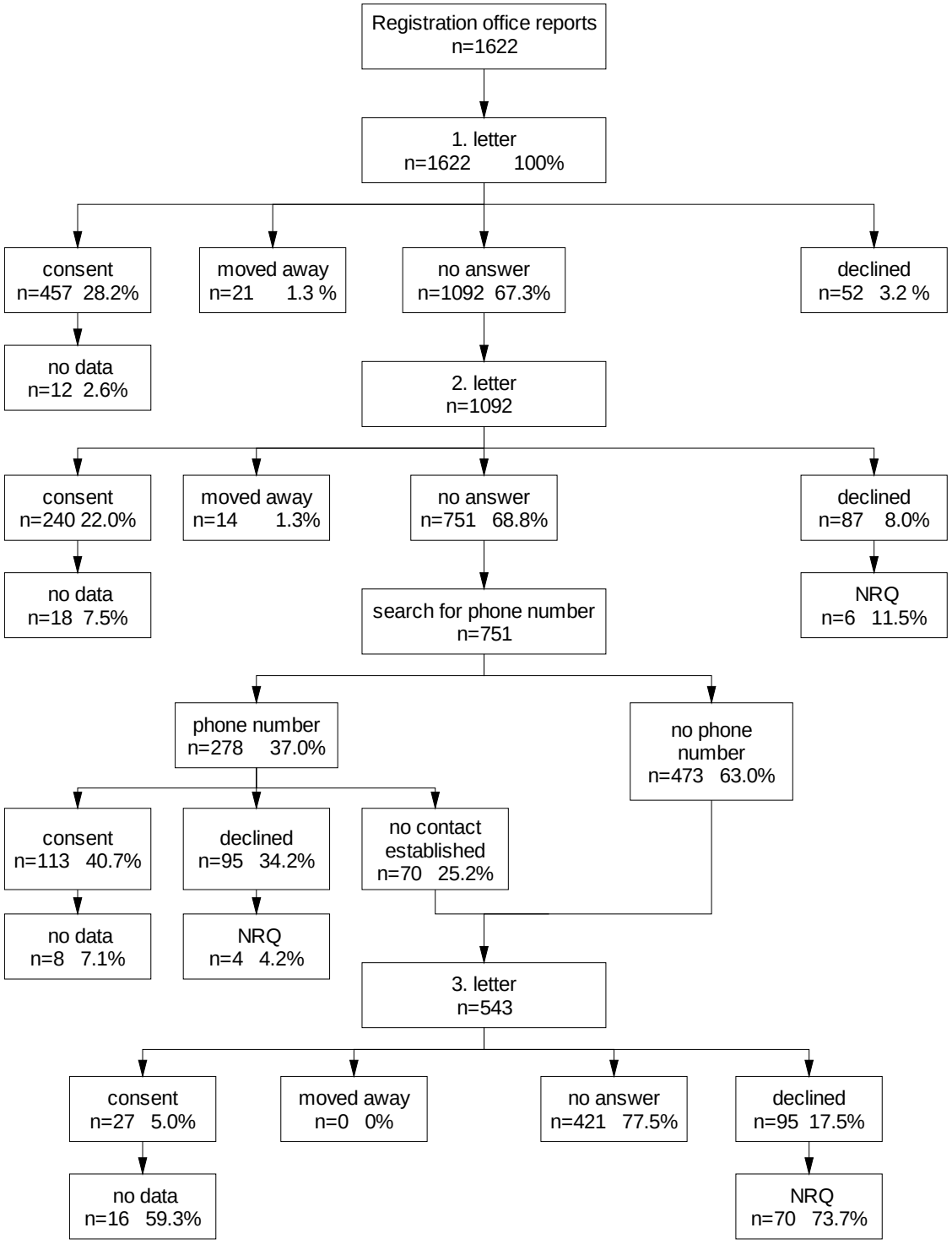

Figure 7: Participation of controls by step of enrolment (percentages are related to absolute numbers in the next upper box)

(For abbreviations used in this figure see Section 9)

Stratification of the response proportion by age revealed a slightly higher proportion of controls matched to cases who had died during their first year of life (49.0%) than during their second year of life (44.4%; see Table 13).

The relatively small differences between age groups are even less pronounced when the cut-off is set to the 9 months of age. The response proportion in controls of cases who had died up to the age of 9 month was 48.8% in comparison to 46.5% in older controls (see Table 14).

The number of control parents with whom no contact could be established because they had moved home was 35 (2.2%). The recruitment efficacy proportion of controls, stratified by age of the case, is given in Table15. The overall recruitment efficacy was 49.3%. The recruitment efficacy was 50.1% in controls of cases who had died in the first year of life and 45.2% in controls of cases who had died in the second year of life, respectively.

5.1.2.2.1. Number of controls per case

The number of controls per case is given in Table 16. The average number of controls per case was 4.7 (median 4). Eighty-five percent of cases had at least 3 matched controls (range 1-14).

The following tables summarise the numbers of controls per case for the study periods up to 31 April 2006 (date of death), and from 01 May 2006, respectively.

Up to the date of death of 31 April 2006, control children were retrospectively selected from the KiGGS data for the 78 cases recruited within this period. For this period, the average number of controls per case was 5.1 (median 5.5). Eighty-three percent of cases had at least 3 matching controls (range 1-14; Table 17). The average number of controls was lower for cases of up to 1 year of age (4.7, median 4.0); 75% of cases below the age of 1 year had at least 3 controls. Due to a lower KiGGS response in very young children, the number of suitable controls for 2- to 4-month-old cases was substantially lower than for older cases. For cases who had died in the second year of life, the average number of controls was 7.5 (median 7). All cases who had died in the second year of life had at least 4 controls.

After 01 May 2006, controls were prospectively enrolled. For 98% of the 176 cases recruited during this period, 5 or more controls were enrolled. One case had only 2 and another 4 controls, respectively (Table 18). In one case, no eligible control consented to study participation. In this case the control enrolment procedure was repeated and another 2 registration offices randomly selected.

The average number of *participating* controls per case was 4.5 (median 4). Eighty three percent of cases had at least 3 controls (range 1-9; see Table 19). No difference in control participation was observed between the first (4.5) and the second (4.0) year of life of the corresponding cases.

5.1.2.3. Non-responder questionnaires

In the control group, a total number of 80 non-responder questionnaires (NRQs) were obtained from 329 parents who declined study participation. This corresponds to a proportion of 25.3%. However, related to the whole number of non-responders (including those who did not answer or could not be contacted) this proportion was only 10.2%.

5.1.2.4. Comparison of responders and non-responders

Data from the registration offices included age, gender and place of residence of all eligible controls. Data on nationality, maternal smoking, maternal education and maternal age as well as data on the vaccination status were only available for responders and non-responders who provided the respective questionnaires. Even if a questionnaire was provided, answers were sometimes missing for specific questions. In the NRQs, the questions related to maternal education and vaccination status had the highest proportion of missing answers.

A tabular comparison of the characteristics of responders and non-responders is given in Table 20. No differences were apparent with regard to age, gender and place of residence. In parents who provided a NRQ, the proportion of children living in former East Germany and the proportion of female children was higher than in responders and non-responders without NRQ. Between responders and non-responders (with NRQ) no differences were seen in maternal smoking. The proportion of a high maternal education was lower in non-responders (18.8%) than in the responders (47.8%), whereas the proportion of responding and non-responding mothers with medium education level was similar. Maternal age below 25 years was more frequent in non-responders than in responders.

5.1.3. Self-controlled case series analysis

The self-controlled case series (SCCS) analysis aimed to investigate whether there was a temporal association between vaccination and risk of sudden death in the first 2 years of life among cases. Further objectives were to evaluate for what length of time after vaccination the risk of death was potentially increased, and whether the risk differed depending on the case's age or between hexavalent and non-hexavalent vaccines.

A description of the characteristics of cases included in the SCCS analysis is given in Section 5.1.3.1. Section 5.1.3.2 presents the results of the SCCS analyses for children vaccinated with hexavalent vaccines. The results of the SCCS analysis for children vaccinated with hexa- or pentavalent vaccines are shown in Section 5.1.3.3.

As described in Section 4.3.3.1, infants who had died between their 2nd and 9th month of life and who were known to have been recently vaccinated, were preferentially enrolled by the forensic institutes after March 2006. In an attempt to evaluate the potential impact of this preferential enrolment on risk estimates, weighted SCCS analyses were performed in addition to the initially planned ("unweighted") SCCS analyses (for methods, see Section 4.3.6.6.1). Results of the unweighted and the weighted analyses are presented separately in the following sections.

5.1.3.1. Characteristics of cases

An overview of the characteristics of cases included in the SCCS analyses is given in Table 21.

5.1.3.2. Hexavalent vaccination

5.1.3.2.1. Unweighted SCCS analysis

This primary analysis included 98 cases who had received a hexavalent vaccination within the observation period. The observation period lasted 28 days for the first and second hexavalent dose and continued up to 184 days for doses 3 and 4. The remaining 156 cases were either not hexavalently vaccinated, or were hexavalently vaccinated outside the observation period.

Table 22 summarises the relative risk of the various risk periods, estimated by the unweighted SCCS analysis. This approach yielded a statistically significant, increased risk of unexplained sudden death (uSUD) within the first 3 days after hexavalent vaccination as compared to the control period (Model I: RR 2.26; 95% CI 1.13-4.51).

In contrast, no indication towards an increased risk of uSUD was apparent when comparing the first 7 days after hexavalent vaccination to the control period (Model II: RR 0.96; 95% CI 0.49-1.86). The initially increased risk of uSUD within the first 3 days was followed by a (albeit statistically not significant) risk reduction between days 4–7 in this model (Model II: RR 0.27; 95% CI 0.06-1.12).

Similar results were obtained for the 0- to 3-day and 0- to 7-day risk periods in an exploratory analysis including days 8-14 as a third risk period with a slightly shifted control period (Model III). This model also did not show any increased risk of uSUD within the second week after a hexavalent vaccination (data not shown).

Stratification by age

Eighty-seven of the 98 cases who had received a hexavalent vaccine during the observation period had died within their first year of life, and 11 cases within their second year of life. The unweighted SCCS analyses of these subpopulations are shown in Table 23 and Table 24, respectively.

In these exploratory analyses, the relative risks for uSUD after hexavalent vaccination during the first year of life (see Table 23) were similar to the risk estimates for all cases as presented above.

Analyses for the second year of life are based on 11 cases, only one of whom had died in risk period 1. Therefore no meaningful conclusions can be drawn from these calculations. Table 24 is only shown for completeness.

Stratification by sleeping position

Information on the child's usual sleeping position during the last 4 weeks prior to death (prone vs. non-prone) was available from 84 cases. Of note, for a higher number of cases who had died in the control period (14 out of 88) in comparison to cases of the first risk period (1 out of 11) no parental questionnaire was obtained. The analysis therefore included only 84 of the 98 cases of the SCCS analysis (with a higher proportion of risk period cases) resulting in an overall estimate of 2.76 (95% CI 1.34-5.67).

Stratification of the SCCS analysis by sleeping position indicated towards interaction of this risk factor with the uSUD risk within the first 3 days after hexavalent vaccination: children who had usually slept in a prone position were found to have an increased risk of uSUD (RR 5.02; 95% CI 1.69-14.87) that was considerably higher than the risk in children who had not slept in a prone position (RR 1.92; 95% CI 0.73-5.05; Table 25, Model I). Although, it needs to be emphasized that the results are based on small numbers (n=5). A similar trend was seen also in the 0- to 7-day model (Table 25, Model II).

Stratification by other risk factors

All variables included in the multivariate model of the case-control analyses (see Section 4.2.6.3) were also tested in SCCS analyses with regard to interactions with the risk of uSUD within the first 3 days after hexavalent vaccination.

In addition to the interaction of sleeping position shown above, a notable difference in the relative uSUD risk of hexavalent vaccination (within the first 3 days) was apparent for prematurity (RR 4.02; 95% CI 1.08-15.01) as compared to maturely born children (RR 2.00; 95% CI 0.90-4.46).

Furthermore, stratification of the SCCS analyses indicated towards some interaction of low maternal education, younger maternal age at birth (<25 years), maternal smoking, not being breastfed and male gender with the uSUD risk of hexavalent vaccination within the first 3 days (data not shown). There was no indication, however, that having a high number of siblings, living with a single mother, or with a single mother who lived with a new partner modified any association of vaccination and risk of uSUD risk within 3 days.

In an analysis combining the modifiable SIDS risk factors 'prone sleeping position' and 'maternal smoking', the risk of uSUD within 3 days was higher in those children who either slept in the prone position or had a smoking mother (see Table 26). However, even in this group the point estimate and corresponding 95% confidence interval did not indicate towards a meaningful risk increase seen within 7 days after hexavalent vaccination. Cases who were not exposed to either modifiable risk factor had no increased risk of uSUD within any period after hexavalent vaccination.

5.1.3.2.2. Weighted SCCS analysis

The results of the weighted SCCS analysis of cases who had received a hexavalent vaccination within the observation period (n=98) are given in Table 27. In this analysis the preferential enrolment of young exposed cases was compensated by downweighting, as described in chapter 4.3.6.6.1. Whereas the trend towards an increased risk of uSUD during the first 3 days after vaccination persisted, the estimate was smaller than in the unweighted analysis presented in Section 5.1.3.2.1 and not statistically significant (RR 1.54; 95% CI 0.67-3.54). As was the case in the unweighted model, the trend towards an initially increased risk of uSUD within the first 3 days was followed by a considerable (albeit not statistically significant) risk reduction between days 4-7 (Model II: RR 0.11; 95% CI 0.01-1.01). There was no indication towards an increased risk of uSUD within the first 7 days after hexavalent vaccination (Model II: RR 0.59; 95% CI 0.26-1.33), or within the first 14 days in the exploratory analysis (Model III, data not shown). Weighting the data using the upper and the lower limits of the 95% confidence interval of the weight's point estimate led to similar results (RR 1.71; 95% CI 0.78-3.78, and RR 1.40; 95% CI 0.59-3.35, respectively).

Stratification by age

Table 28 summarises the results of the weighted SCCS analysis of cases who had received a hexavalent vaccine during the observation period and had died within their first year of life. In analogy to the unweighted analysis, the relative risks of uSUD after hexavalent vaccination during the first year of life were similar to the unstratified risk estimates.

As was the case in the unstratified models, the weighted analysis of cases who had died within their first year of life yielded consistently lower risk estimates than the unweighted analysis.

As the weighting procedure affected only infants who had died in the 2nd to 9th month, the results of the weighted analysis for cases who had died within their second year of life do not differ from the unweighted analysis presented above (see Table 24).

Stratification by sleeping position

The weighted analysis revealed less interaction of sleeping position with the vaccination effect than observed in the unweighted analysis. Whereas the trend towards a higher risk of uSUD in the first 3 days post-vaccination in children who had usually slept in a prone position was still apparent, the risk estimate was smaller than in the unweighted model (prone sleeping position: RR 2.78; 95% CI 0.70-10.98; non-prone sleeping position: RR 1.58; 95% CI 0.53-4.70; see Table 29).

Stratification by other risk factors

The weighted, exploratory analyses revealed less interaction between other risk factors and hexavalent vaccination than the unweighted analyses. Whereas the trend towards a higher risk of uSUD within the first 3 days after hexavalent vaccination of children who had an (additional) risk factor was still apparent, the risk estimates were smaller than in the unweighted model for the vaccinated cases exposed to additional SIDS risk factors as well as for the vaccinated cases without additional risks (data not shown).

Stratification between cases who were not exposed to either of the modifiable SIDS risk factors 'prone sleeping position' or 'maternal smoking' and cases with at least one of these risk factors still revealed a difference of the respective risk estimates (see Table 30).

5.1.3.3. Hexa- or pentavalent vaccination

5.1.3.3.1. Unweighted SCCS analysis

In addition to the 98 cases who had received a hexavalent vaccination, this exploratory analysis included 14 cases who had received a pentavalent vaccination within the observation period. The remaining 142 cases either did not receive a hexa- or pentavalent vaccination, or were vaccinated outside the observation period.

Table 31 summarises the relative risks of uSUD for the various risk periods, estimated by the unweighted SCCS analysis. This approach yielded an increased risk of uSUD within the first 3 days after hexa- or pentavalent vaccination (Model I: RR 2.98; 95% CI 1.61-5.52).

In contrast, no increased risk of uSUD was apparent when comparing the first 7 days after hexavalent vaccination to the control period (Model II: RR 1.33; 95% CI 0.74-2.39). As for the analysis of hexavalent vaccinations alone, the initially increased risk of uSUD within the first 3 days appeared to be followed by a considerable risk reduction between days 4-7.

Similar results were obtained for these risk periods in an exploratory analysis with a slightly later control period (Model III). This model also did not show an increased risk of uSUD in children within the second week after hexavalent vaccination (data not shown).

Stratification by age

Ninety-eight of the 112 cases who had received a hexa- or pentavalent vaccine during the observation period had died within their first year of life, whilst 14 cases had died within their second year of life. The unweighted, exploratory SCCS analyses of these subpopulations are shown in Table 32 and Table 33, respectively.

The relative risks of uSUD after hexa- or pentavalent vaccination during the first year of life (see Table 32) were similar to the risk estimates for all cases as presented above.

The analysis of cases in the second year of life and for the risk period 0-3 days revealed increased relative risks that were larger than the estimates for the overall population (Model I: RR 13.86; 95% CI 2.55-75.23). In contrast to the unstratified model, the risk of uSUD was also increased for the 0- to 7-day risk period (Model II: RR 5.27; 95% CI 0.99-28.17) and for the risk period 0-14 days (exploratory Model III, data not shown). Of note, all estimates for older cases were based on very small numbers of cases (2 exposed cases out of 14).

Stratification by sleeping position

The interactions between the exposures "usual sleeping position" and "vaccination" that were seen in the exploratory SCCS analyses of hexavalently vaccinated children were also present in hexa- or pentavalently vaccinated children, but somewhat lower (Table 34).

Stratification by other risk factors

All variables included in the multivariate model of the case-control analyses (see Section 4.2.6.3) were also explored in SCCS analyses with regard to interactions with the risk of uSUD within the first 3 days after hexa- or pentavalent vaccination.

In addition to the interaction of sleeping position shown above, a notable difference in the relative uSUD risk of hexa- or pentavalent vaccination (within the first 3 days) was apparent for prematurity (RR 6.03; 95% CI 2.08-17.82) as compared to maturely born children (RR 2.44; 95% CI 1.17-5.08). This interaction was even more pronounced than in the analysis only of the hexavalently vaccinated cases.

Furthermore, stratification of the SCCS analyses indicated towards some interaction of younger maternal age at birth (<25 years), maternal smoking and male gender with the uSUD risk of hexavalent vaccination within the first 3 days (data not shown). There was no indication, however, that having a high number of siblings, living with a single mother, or with a single mother who lived with a new partner modified any association of vaccination and risk of uSUD risk within 3 days.

In an analysis combining the modifiable SIDS risk factors 'prone sleeping position' and 'maternal smoking', the risk of uSUD was increased within 3 days in those children who either slept in the prone position or had a smoking mother (see Table 35). However, even in this group the point estimate and corresponding 95% confidence interval did not indicate towards a meaningful risk increase within 7 days after hexa- or pentavalent vaccination. Cases who were not exposed to either modifiable SIDS risk factor had no increased risk of uSUD within any period after hexa- or pentavalent vaccination.

5.1.3.3.2. Weighted SCCS analysis

Results of the weighted SCCS analysis of the 112 cases who received a hexa- or pentavalent vaccination within the observation period are given in Table 36. As was the case in the analysis of hexavalently vaccinated cases, risk estimates in all models and for all risk periods were smaller than in the unweighted analysis presented in Section 5.1.3.3.1. The risk estimate for uSUD for the 0- to 3-day risk period was 2.19 (95% CI 1.08-4.45). As in the unweighted model, risk estimates were not elevated within the first 7 days after hexavalent vaccination as compared to the control period (Model II: RR 0.92; 95% CI 0.47-1.81), or in the exploratory analysis of risk during days 0-14 (Model III, data not shown).

Stratification by age

Table 37 summarises the results of the weighted SCCS analysis of cases who had received a dose of hexa- or pentavalent vaccine during the observation period and had died within their

first year of life. The relative risks of uSUD after vaccination during the first year of life were similar to the unstratified risk estimates.

As was the case for the unstratified models, the weighted analysis of cases who had died within their first year of life yielded consistently lower risk estimates than the unweighted analysis presented above.

As the weighting procedure affected only infants who had died at the age of 2-9 months, results of the weighted analysis for cases who had died within their second year of life do not differ from the unweighted analysis presented above (see Section 5.1.3.3.1).

Stratification by sleeping position

The weighted analysis showed less interaction of the main effect with sleeping position compared to the unweighted analysis. Whereas the trend towards a higher risk of uSUD in vaccinated children who usually slept prone was still apparent, the estimate was smaller than in the unweighted model (prone sleeping position: RR 3.17; 95% CI 0.86-11.63; non-prone sleeping position: RR 2.34; 95% CI 0.93-5.85; see Table 38).

Stratification by other risk factors

The weighted analyses revealed less interaction between other risk factors and hexa- or pentavalent vaccination than the unweighted analyses. Whereas the trend towards a higher risk of uSUD within the first 3 days after vaccination of children who had an (additional) risk factor was still apparent, the risk estimates were smaller than in the unweighted model. However, even in the weighted analysis the risk of uSUD in prematurely born children (RR 3.90; 95% CI 1.09-13.90) was almost twice as high as in maturely born children (RR 1.90; 95% CI 0.82-4.38).

Stratification between cases who were not exposed to either of the modifiable SIDS risk factors ‘prone sleeping position’ or ‘maternal smoking’ and cases with at least one of these risk factors still revealed a difference of the respective risk estimates. In cases exposed to one or both of these additional risk factors, the risk estimate was increased 3-fold (see Table 39).

5.1.3.4. Pentavalent vaccination

Both the unweighted and weighted exploratory SCCS analyses for hexa- or pentavalent vaccination (see Section 5.1.3.3) yielded higher risk estimates than the SCCS analyses for hexavalent vaccination alone (see Section 5.1.3.2) for both risk periods. This difference prompted an exploratory analysis of the small group of pentavalently vaccinated cases.

5.1.3.4.1. Unweighted SCCS analysis

Fourteen pentavalently vaccinated cases contributed to this exploratory analysis. Table 40 summarises the relative risks of uSUD for the various risk periods as estimated by the unweighted SCCS analysis. Albeit based on a small number of cases, an increase in risk of uSUD that was considerably higher than the estimates calculated for hexavalent vaccination (see Section 5.1.3.2.1) was observed for both the 3-day and 7-day risk periods: compared to the respective control periods, a relative risk of 9.08 (95% CI 2.17-37.96) was estimated for the first 3 days after pentavalent vaccination, and of 5.75 (95% CI 1.38-23.97) for the first 7 days after pentavalent vaccination.

5.1.3.4.2. Weighted SCCS analysis

The risk estimates for uSUD after pentavalent vaccination were slightly attenuated by the weighted analysis, but remained considerably higher than the weighted estimates calculated

for hexavalant vaccination (see Section 5.1.3.2.2). A relative risk of 8.11 (95% CI 1.81-36.24) was calculated for the first 3 days after pentavalent vaccination, and of 5.40 (95% CI 1.25-23.33) for the first 7 days after pentavalent vaccination as compared to the respective control periods (Table 41).

5.1.4. Case-control analysis

The case-control analysis aimed to have the SCCS results confirmed or not confirmed by analyses based on cases and living controls, and to produce estimates taking into account the time period prior to vaccination, which the SCCS method is unable to deliver. An additional objective was to determine whether the risk of sudden death in vaccinated children differs from that of unvaccinated children.

A description of the characteristics of cases and controls included in the analysis is given in Section 5.1.4.1. Section 5.1.4.2 presents the risk estimates within 3- and 7-day time windows after vaccination with any (i.e., hexavalent or non-hexavalent) vaccine. Section 5.1.4.3 presents risk estimates for these time windows separately for hexa- and non-hexavalent vaccines. Finally, in Section 5.1.4.4, risk estimates are reported for exposure to any vaccine at any time within the first 2 years of life.

As in the SCCS analyses, the potential impact of the preferential enrolment of exposed cases aged between the 2nd and 9th month of life via the forensic institutes (see Section 4.3.3.1) on risk estimates produced by the case-control analysis was accounted for by inverse-probability weighting (see Section 4.3.6.6.1). The results of the unweighted and weighted case-control-analyses are presented separately within the following sections.

5.1.4.1. Characteristics of cases and controls

A total of 254 cases and 1180 matched controls were included in the case-control analysis. Table 42 to Table 45 summarise basic characteristics of cases and controls. Compared to their age-matched controls, cases tended to be more frequently male, have one or more siblings, resided more frequently in the western part of Germany, were more frequently born before the 38th gestational week, and had been less frequently breast fed. The cases' mothers tended to be younger, less educated, were more frequently single parents or had a new partner, and had smoked more frequently during pregnancy as well as at the time of data collection than the mothers of controls.

Information on the preferred position for putting the children to sleep was available only for the prospectively recruited controls but not from the controls recruited from the KiGGS data. In comparison to these prospectively recruited controls, cases had been more frequently put to sleep in a prone position (or in varying positions including prone).

Table 46 shows the characteristics of hexavalently and pentavalently vaccinated cases and controls. Mothers of pentavalently vaccinated children recruited as cases or controls tended to be older and better educated, and had smoked less frequently during pregnancy as well at the time of data collection than the mothers of hexavalently vaccinated children. Pentavalently vaccinated cases were more often male and breast fed than hexavalently vaccinated cases. The latter differences were less pronounced among controls.

5.1.4.2. Any vaccination

5.1.4.2.1. Unweighted case-control analysis

This unweighted analysis produced odds ratios (ORs) as risk estimates for uSUD in children who had received any (i.e., hexavalent or non-hexavalent) vaccination as compared to children who had not been vaccinated during the respective risk period. Table 47 presents uni- and multivariate odds ratios for a 3-day time window after vaccination and is based on 17 cases. For this 3-day period, the univariate odds ratio was 1.68 (95% CI 0.89-3.15) and the multivariate odds ratio was 1.67 (95% CI 0.71-3.91).

The odds ratios estimated for a 7-day time window after vaccination were based on 21 cases and are presented in Table 48. In this analysis, there was no indication towards an increased risk of uSUD (univariate OR 0.86; 95% CI 0.51-1.46; multivariate OR 0.95; 95% CI 0.48-1.88).

Stratification by age was impeded by the small number of cases who had died during the second year of life (2 and 3 cases within the 3-day and 7-day time windows, respectively). The uni- and multivariate risk estimates for the first year of life were thus similar to the unstratified estimates for both time windows. The risk estimates for the second year of life were somewhat higher and confidence intervals were wide (Table 47, Table 48).

The full results of these analyses, including the odds ratios for all covariables included in the respective multivariate models, are provided in Appendix Tables 1 to 6.

5.1.4.2.2. Weighted case-control analysis

Results of the weighted case-control analysis of cases who had received any (i.e., hexavalent or non-hexavalent) vaccination within the observation period are shown in Table 49. This analysis attempted to account for the effects of exposed young cases preferentially enrolled by the forensic institutes since 2006. The trend observed in the unweighted analysis (see Section 5.1.4.2.1) was even weaker in this weighted analysis: the univariate odds ratio for the 3-day period was 1.18 (95% CI 0.58-2.40) and the multivariate odds ratio was 1.28 (95% CI 0.50-3.28).

The weighted odds ratios estimated for a 7-day time window after vaccination are presented in Table 50. As in the unweighted analysis, there was no indication towards an increased risk of uSUD (univariate OR 0.60; 95% CI 0.33-1.10; multivariate OR 0.70; 95% CI 0.33-1.51).

As in the unweighted analysis, the age-stratified risk estimates for this age group were similar to the unstratified weighted estimates for both time windows (see Table 49; Table 50). By virtue of the weighting procedure, the weighted risk estimates were identical to the unweighted estimates for the small number of cases who had died in their second year of life.

The full results of these analyses, including the odds ratios for all covariables in the multivariate models, are provided in Appendix Tables 17 to 20.

5.1.4.3. Hexavalent and non-hexavalent vaccination

5.1.4.3.1. Unweighted case-control analysis

This analysis produced separate odds ratios for risk of uSUD during a 3- or 7-day risk period in children who had received a hexavalent or a non-hexavalent vaccination as compared to

children who had not received either vaccine during the respective risk period. Table 51 presents the uni- and multivariate odds ratios for a 3-day time window after vaccination and is based on 11 cases subsequent to a hexavalent vaccination and 6 cases subsequent to a non-hexavalent vaccination. For this 3-day period, the uni- and multivariate ORs were only moderately elevated and confidence intervals were wide for both, hexavalent and non-hexavalent vaccinations, although the ORs were slightly higher for the latter (hexavalent vaccination: univariate OR 1.54; 95% CI 0.73-3.23; multivariate OR 1.51; 95% CI 0.56-4.07; non-hexavalent vaccination: univariate OR 2.06; 95% CI 0.69-6.10; multivariate OR 2.12; 95% CI 0.51-8.79).

The odds ratios estimated for a 7-day time window after vaccination were based on 13 cases subsequent to a hexavalent vaccination and 8 cases subsequent to a non-hexavalent vaccination and are presented in Table 52. In this analysis, there was no indication towards an increased risk of uSUD within 7 days after hexavalent vaccination (univariate OR 0.74; 95% CI 0.39-1.39; multivariate OR 0.79; 95% CI 0.35-1.78). This analysis revealed a slightly increased risk within 3 days after non-hexavalent vaccination (univariate OR 1.21; 95% CI 0.52-2.84; multivariate OR 1.45; 95% CI 0.47-4.50).

Stratification by age was again impeded by the small number of cases who had died during the second year of life (1-2 cases within the 3-day and 7-day risk periods for either type of vaccine, respectively). The uni- and multivariate risk estimates for the first year of life were thus similar to the unstratified estimates for both time windows. Whereas the risk estimates for the second year of life were mostly higher for both vaccine types and time windows, confidence intervals were very wide (Table 51, Table 52).

The full results of these analyses, including the odds ratios for all covariables in the multivariate models, are provided in Appendix Tables 7 to 12.

5.1.4.3.2. Weighted case-control analysis

This analysis produced separate odds ratios for uSUD during a 3- or 7-day risk period in children who had received a hexavalent or a non-hexavalent vaccination as compared to children who had not received either vaccine during the respective risk period, weighted to account for the effects of young exposed cases preferentially enrolled by the forensic institutes since 2006.

The trends observed in the unweighted analysis (see Section 5.1.4.3.1) were even weaker in this weighted analysis (Table 53): for the 3-day time window after a hexavalent vaccination, the univariate OR was 0.97 (95% CI 0.40-2.35) and the multivariate OR was 1.11 (95% CI 0.36-3.43), and for the 3-day time window after a non-hexavalent vaccination, the univariate OR was 1.70 (95% CI 0.55-5.27) and the multivariate OR was 1.72 (95% CI 0.38-7.71).

The weighted odds ratios estimated for a 7-day time window after vaccination are presented in Table 54. There was no indication towards an increased risk of uSUD subsequent to vaccination with either vaccine type in this analysis (hexavalent vaccination: univariate OR 0.44; 95% CI 0.20-0.96; multivariate OR 0.53; 95% CI 0.20-1.37; non-hexavalent vaccination: univariate OR 1.06; 95% CI 0.44-2.57; multivariate OR 1.22; 95% CI 0.37-4.02).

As in the unweighted analysis, the age-stratified risk estimates for this age group were similar to the unstratified weighted estimates for both risk windows (Table 53, Table 54). By virtue of the weighting procedure, the weighted risk estimates were identical to the unweighted estimates for the small number of cases who had died in their second year of life.

The full results of these analyses, including the odds ratios for all covariables in the multivariate models, are provided in Appendix Tables 21 to 24.

5.1.4.4. Pentavalent vaccination

As an adjunct to the exploratory SCCS analysis estimating relative risks for pentavalent vaccination (see Section 5.1.3.4), corresponding odds ratios for pentavalent vaccination and risk of uSUD were calculated in an exploratory case-control analysis. Of note, this analysis was based on only 4 pentavalently vaccinated cases in the 72-hour time window, and 5 cases in the 7-day time window.

Table 55 summarises the results of this exploratory analysis. In the unweighted case-control analysis, an increased risk of uSUD was found within 72 hours of pentavalent vaccination (univariate OR 7.89; 95% CI 1.33-46.77), a value notably higher than the unweighted case-control estimate for hexavalent vaccination. For the 7-day risk period, the risk estimate was lower (univariate OR 3.24; 95% CI 0.93-11.22), but still considerably higher than the corresponding estimate for hexavalent vaccination (see Section 5.1.4.3.1).

The results of the corresponding weighted analyses are shown in Table 56. The risk estimates were similar to the unweighted ones and considerably higher than the corresponding weighted estimates for hexavalant vaccines.

Stratification by age group was not possible due to the small number of cases. The full results of these analyses are provided in Appendix Tables 13, 14, 25 and 26.

5.1.4.5. Ever vaccinated versus never vaccinated

5.1.4.5.1. Unweighted case-control analysis

This analysis aimed to determine whether the risk of uSUD in children vaccinated with any vaccine within their first 2 years of life differed from that of children who were unvaccinated. Results are presented in Table 57. Based on a total of 175 vaccinated and 79 unvaccinated cases, a slightly elevated univariate odds ratio was observed (univariate OR 1.37; 95% CI 0.84-2.23). The multivariate odds ratio was slightly higher (multivariate OR 1.78; 95% CI 0.93-3.41).

Stratification by age was limited to cases that had died during their first year of life, as all cases that had died during their second year of life had been vaccinated, as had been most controls. The odds ratios estimated for risk of uSUD during the first year of life were similar to the overall estimates.

The full results of these analyses, including the odds ratios for all covariables in the models, are provided in Appendix Tables 15 to 16.

5.1.4.5.2. Weighted case-control analysis

In this analysis, the risk estimates for uSUD in children vaccinated with any vaccine within their first 2 years of life differed from that of children who were unvaccinated, were weighted to account for the effects of young exposed cases preferentially enrolled by the forensic institutes since 2006.

The weighting procedure yielded lower risk estimate as compared to the unweighted analysis: the weighted, univariate OR was 1.20 (95% CI 0.73-1.97) and the weighted multivariate OR was 1.58 (95% CI 0.81-3.07) (Table 58).

Stratification by age was again limited to cases who had died during their first year of life, and the estimated odds ratios were similar to the overall estimates.

The full results of these analyses, including the odds ratios for all covariables in the models, are provided in Appendix Tables 27 to 28.

5.2. Pathological study part

The following section provides an overview on the results of the pathological study part. The full report is provided in Annex 22.

5.2.1. Case reports

The participating forensic institutes reported 365 cases of sudden death. One hundred and one cases met the inclusion criteria. Of these, 25 cases had died between the 2nd and 9th month of life and 76 cases were ≥9 months old.

5.2.1.1. Response proportion

Parental informed consent for participation in the pathological study part was obtained in 43 of the 101 (42.6%) cases who met the inclusion criteria. Of these, one case formally violated the inclusion criteria as the child had died more than 7 days after vaccination but was included as the initial onset of the subsequently fatal reaction was within the specified 7-day time period.

This response proportion differs from the figures reported for the epidemiological study part in Section 5.1.1.3 because of 3 reasons: the pathological study part included some cases that were not reported by LHAs and, thus, were not eligible for the SCCS and case-control analyses. On the other hand, some cases reported by the forensic institutes participated only in the epidemiological study part but refused their consent to the extended autopsy protocol. Moreover, the pathological study part started and ended 1 month later than the epidemiological study part.

5.2.1.2. Cause of death

In 16 of the 43 enrolled cases (37%), the cause of death could be explained after autopsy. The proportion of explained causes of death was higher in cases that had died in their 10th to 24th month of life (Table 59).

5.2.1.3. Possible pathomechanism for cases of sudden death following vaccination

The aim of the pathological study part was to seek for a common pathological mechanism in cases of sudden death following vaccination (study question 5). Only noteworthy results in this regard are presented in the following sections.

In the following, the term ‘vaccinated’ describes children immunised within 14 days prior to death while the term ‘unvaccinated’ describes children with longer periods between last vaccination and death.

5.2.1.3.1. Brain oedema

The brain/body-weight ratios of all vaccinated (N=14; Table 60) and unvaccinated cases (N=24; Table 61) with known brain weights were within the expected range with the exception of one outlier whose extreme brain weight was assumedly documented incorrectly. Thus, there was no indication towards brain oedema in these cases.

5.2.1.3.2. Immune system

In 13 vaccinated and 14 unvaccinated cases, concentrations of the immunoglobulins IgG, IgM, IgD, and IgA were quantitatively determined by radial immunodiffusion and (total) IgE concentrations by Enzyme Linked Immunosorbent Assay (ELISA) method. The concentrations of specific antibodies (IgE) against components of vaccines (streptomycin, neomycin, polymyxin B, and tromethanol) were determined using ImmunoCAP® technology. IgE concentration was slightly higher in the 'vaccinated' case group but no other differences were observed.

The following components of the complement system were measured in 13 vaccinated and 14 unvaccinated cases: C1 inactivator, glycoprotein C3 and the component C4. No meaningful differences between vaccinated and unvaccinated cases were observed.

Cytokine concentrations were also measured. While for TNF-α, IFN-γ, and IL-18 no obvious difference was observed between vaccinated and unvaccinated cases, IL-1β, IL-6, IL-10 values were higher in unvaccinated cases. However, the range was very high in both groups and values are considered to be most likely influenced by post-mortem changes.

Cytokine allele and genotype frequency were investigated in order to assess cytokine gene polymorphism. Although some differences in genotype frequencies were observed between vaccinated and unvaccinated cases, no meaningful differences were found.

5.2.1.3.3. Results of other investigations

Results of the morphological, histological, microbiological, virological and metabolical investigations as well as the toxicological screening were used to classify the underlying cause of death on a case-by-case basis. However, no common patterns among vaccinated cases or meaningful differences between vaccinated and unvaccinated cases were found.

6. Discussion

6.1. Methodological considerations and study limitations

According to the guidelines 'Good Epidemiological Practice' (GEP) [37], all primary and secondary analyses were defined in the study protocol before the study started. This is required by the GEP in order to minimise any chance that only selected results, which suit most to the authors' hypotheses, may be published later. In accordance to these requirements of transparency, all results of the pre-defined statistical analyses are presented in this report. However, in order to avoid underestimation of the alpha error due to multiple testing, the term "statistical significance" is not used when presenting any results of the pre-planned secondary analyses and these results should be interpreted with caution.

According to the STROBE recommendations [38], any analyses performed in addition to the study protocol should also be reported. Findings from these post-hoc exploratory analyses (e.g., subgroups or interaction analyses which deemed necessary during data analysis in the light of some results) are particularly prone to over-interpretation. Therefore, any post-hoc exploratory subanalyses are merely considered as hypothesis-generating and the term "statistical significance" is intentionally not used in conjuction with their results.

Any deviations from the original study protocol are explicitly mentioned in this report. There were some methodological adaptations of the SCCS method which were necessary due to multiple exposures and non-recurrent events being investigated in this study (see Section 4.3.6.1). The weighting procedure became necessary to control for the selection bias of exposed cases, introduced by the case enrolment in the forensic part of this study (see Section 4.3.6.6.1).

6.1.1. Completeness of case reporting

The active surveillance system employed for the TOKEN study was successful in terms that the vast majority (98.5%) of the more than 400 LHAs participated in this (voluntary) activity, thus covering approximately 97% of live births in Germany.

The number of cases reported by the LHAs within the framework of the TOKEN study was only 72.2% of the number of eligible cases captured in the German mortality register (see 5.1.1.1). According to these data, the number of reported deaths that were classified to the ICD-10 codes R95-99 was close to 90% of the number of cases captured under these ICD codes in the German mortality register. Of note, this figure may be imprecise because of the different coding procedures in place in the TOKEN study and the German mortality register. Specifically, coding for the German mortality register is usually performed in absence of any autopsy results, which may cause R95-99 codes to be assigned to deaths that were adjudicated as explained in the TOKEN study after review of the autopsy report. On the other hand, the coding procedures of the German mortality register mandate coding "suspicion of" diagnoses on death certificates to the "suspected" cause of death, whereas the adjudication procedure in the TOKEN study may have led to a R95-99 code after case review.

As a second method to estimate the completeness of case reporting within the TOKEN study, a capture-recapture analysis was performed in the subgroup of cases who should have been reported independently by both, forensic institutes and LHAs (see Section 5.1.1.1). Although this analysis was restricted with regard to age and geographical region, the result (75.3% completeness of case reporting by the LHAs) indicates a lower completeness of case reporting

than the comparison with the data of the German mortality register, and may indicate that the proportion of R95-99 cases reported within the study was in fact lower than 90%.

In addition to the 11 deaths included in the TOKEN study that occurred within 72 hours after hexavalent vaccination, a further 6 cases vaccinated within this risk period came to the attention of the study team from different sources but were not reported into the study: the comparison with the case reports by means of the Act on the Prevention and Control of Infectious Diseases in Man (Infektionsschutzgesetz, IFSG) which were performed in cooperation with the PEI revealed 5 spontaneous reports on hexavalently vaccinated cases for whom no death reports were obtained from the respective LHAs either because of non-participation or because of incomplete reporting. The 6th death was reported from the pathological study part but not from the concerned LHA. This number has to be seen in relation to a number of at least 750 sudden unexplained cases of death occurring within the study period in Germany (676 sudden unexplained cases of death were reported by LHAs. This number of cases is estimated to constitute less than 90% of all cases of unexplained sudden death).

It cannot be ruled out that the observed underreporting from the LHAs into the TOKEN study may have been selective, since completeness of reporting appears to have been lower for reports with an unexplained underlying cause of death than for reports for which the cause of death was considered to be explained. However, as all LHA staff was blinded against the vaccination status of most children, underreporting of cases from the LHAs into the TOKEN study is not expected to have introduced any substantial selection bias. Thus, whereas underreporting from the LHAs may have reduced the precision of the risk estimates presented in this study, it unlikely led to an over- or underestimation of risk.

6.1.2. Response proportion

The overall response proportion of parents of children who had died from an unexplained underlying cause of death was below 40% despite all attempts as outlined in Section 4.3.3.4.1. Although participation in epidemiological studies has generally declined over the past decades [39], this must be considered an unsatisfactory result.

In particular, in addition to the 11 deaths that were included in the study and occurred within 72 hours after hexavalent vaccination (and to the 6 cases who were not at all reported, see Section 6.1.1), further 6 cases of death within 72 hours after hexavalent vaccination came to the attention of the study team that were reported but did not participate: two cases were notified by means of the non-responder questionnaire. For 3 non-participants, hexavalent vaccination was either mentioned on the death certificate or reported by the LHA, which became aware of the vaccination by communication with the child's paediatrician. For one additional non-participant, the hexavalent vaccination became obvious by comparison with the case reports by means of the IFSG.

Study enrolment of bereaved parents is a delicate issue and was particularly complicated by of the strict data protection regulations in most federal states. The initial plan to contact parents and enrol cases directly by specially trained RKI staff needed to be abandoned because the LHAs were not permitted to forward the case's name and address to the RKI. Data protection officers allowed only death certificates with blackened names and addresses to be sent to the RKI. Therefore, the initial contact asking for parental consent was to be performed by the LHAs on behalf of the RKI. During the study it became apparent that LHAs were rather reluctant to perform the phone calls that were required if no response was obtained to the initial written invitation. Some LHAs outright refused to call parents, whereas others claimed not to be able to perform phone calls due to shortage of staff and high workload. The impact

of this requirement on case enrolment becomes apparent from a comparison of the success of case enrolment (by the LHAs) and enrolment of controls (by the RKI): in 37.3% of cases, but only in 26.0% of controls, the enrolment procedure was terminated without getting any response. In a nation-wide case-control study on SIDS conducted 1998-2001, when the study centre could approach bereaved parents directly for study participation, the response proportion in cases was 82.4% [40]. Direct case enrolment efforts in the TOKEN study, which could have been afforded by trained staff at a study centre, may have resulted in more favourable results. A more favourable response proportion was also achieved in the pathological study part where parents were contacted personally by the forensic institute staff. This supports the view that improvement of the response proportion can only be achieved by personal contact to bereaved parents, which is currently not allowed due to data protection regulations.

Among other efforts made to increase the low response proportion (see 4.3.3.4.1), the parent questionnaire was temporarily enclosed already with the first letter of invitation to parents of cases as of August 2007. This changed procedure was terminated in November 2007 after noting that the response proportion was even lower than during the initial procedure. This negative experience corresponds with a subsequently published experience of BYRNE et al. [41] who also found that sending a copy of the questionnaire in advance did not improve the response proportion of a telephone survey.

Another significant obstacle of case enrolment was the inability to obtain the parents' phone number. In 67% of the eligible cases, the concerned LHA was not able to obtain the phone number from any printed or on-line directories. The growing proportion of phone numbers that are off directory has been identified as an increasing and significant problem for the response proportion in epidemiological studies [42]. A *post hoc* telephone number search for both, parents of TOKEN cases enrolled already after written invitation and parents of enrolled controls, revealed similar proportions of phone numbers that were off directory (69% and 63%, respectively. Therefore the non-availability of phone numbers *per se* can be assumed to have been similarly distributed between these populations and is thus unlikely to have introduced any substantial selection bias.

6.1.3. Preferential enrolment of more recently vaccinated children

Two sources of important selection bias were identified in the TOKEN study. Both related to the preferential enrolment of more recently vaccinated children. Firstly, preferential self-selection of cases who had died in close temporal relationship to a vaccination was evident from the analysis of the response proportions achieved in each step of enrolment. Secondly, selection bias was introduced by preferential and highly successful enrolment of recently vaccinated cases by the forensic and pathological institutes. These two sources of bias and their implications for the interpretation of the results of the TOKEN study are discussed in the following Sections 6.1.3.1 and 6.1.3.2.

6.1.3.1. Self-selection

The analysis of the response proportion achieved in each step of enrolment (Table 9) suggests that case enrolment was indeed subject to an important selection bias: parents of children who had died in close temporal relationship to a vaccination were more likely to consent already after the initial written invitation than were parents of cases where the temporal relationship was more distant. Therefore, whereas recruitment of cases with a close temporal relationship to vaccination was less dependent on the ability to establish a phone contact, this personal contact by phone was important for enrolling parents of cases with a more distant temporal relationship. As only 21.7% of parents who did not consent after the two letters of invitation

could be reached by phone, the proportion of non-participating cases with a remote temporal association to a vaccination may in fact be much higher in non-participants than in participants.

An additional indicator for this bias is the fact that a higher proportion of parents whose children died in more distant temporal relationship to vaccination failed to return the parental questionnaire, whereas only for one case in risk period I the parental questionnaire could not be obtained.

A possible causative or at least aggravating factor for this preferential enrolment of recently exposed cases is the requirement mandated by the data protection officers of the Laender, to inform parents prior to consent of the study aim to investigate the potential association between vaccination and sudden death. By being aware of the primary study hypothesis, the parental decision to participate or not was apparently not – as intended by the TOKEN study – independent from the vaccination status of their child (see informed consent form Annex 11).

6.1.3.2. Preferential enrolment in the pathological study part

The TOKEN study was designed to include (a) epidemiological methods aiming to estimate the strength of a potential association between vaccine exposure and uSUD, and (b) pathological methods to investigate possible common patterns in the underlying patho-mechanisms. These two study parts, the 'epidemiological study part' and the 'pathological study part', were intended to complement each other. The design of the epidemiological study part aimed for a complete, non-preferential case enrolment, regardless of any vaccine exposure, by means of an active surveillance procedure and also kept LHA staff blinded to exposure in most cases, thus precluding any risk of selection bias.

Cases enrolled by the pathological study part were a subset of the epidemiological study: prerequisite for inclusion of a case, initially enrolled in the pathological study part by a forensic institute, in the epidemiological analyses was that the case was also reported by a LHA. However, the methodology of the pathological study part turned out to interfere significantly with the epidemiological study part. Specifically, the enrolment procedure of the pathological study part after the first protocol amendment led to preferential enrolment of recently vaccinated cases into the epidemiological study. Initially, only autopsied children aged 9 months or older were included in the pathological study part. Because this allowed only very few cases to be enrolled, the first protocol amendment extended the inclusion criteria for the pathological study part to children who had died between their 2nd and 9th month of life under the precondition that they were known to have been vaccinated within 7 days prior to death.

Stratification of the response proportions by the initiator of case enrolment showed that, among children who had died between their 2nd and 9th month of life, the response proportion was 80.0% for the forensic institutes and 33.7% for the LHAs (see Table 7). Given that the response proportion of cases that were older than 9 months was similar for the forensic institutes (51.2%) and the LHAs (46.7%), the different response proportions in the younger age group provide evidence for preferential participation of parents whose children had died in close temporal relationship to vaccination. Therefore, it has to be concluded that the TOKEN study results are biased and the calculated risk estimates most likely overestimate the association between uSUD and (hexavalent) vaccination.

As the subpopulation of cases that were subject to this bias was clearly defined (i.e., aged up to 9 months and enrolled by the forensic institutes) and a quantitative assessment of response in exposed and non-exposed cases was available, inverse-probability weighting could be employed as an analytical approach to correct for this selection bias (see Section 4.3.6.6.1).

The resultant weighted risk estimates were systematically smaller than the unweighted estimates, indicating the presence of some anti-conservative bias.

Additional analyses were performed in order to assess the appropriateness of the weighting procedure. The subgroup analysis of cases aged up to 9 month who were enrolled prior to the first study protocol amendment resulted in a relative uSUD risk of 1.52 (95% CI 0.33-6.94). The unweighted analysis of cases who were enrolled after the study protocol amendment yielded a relative uSUD risk of 2.92 (95% CI 1.23-6.92) whereas, the weighted analysis resulted in an estimate of 1.59 (95% CI 0.51-4.94), which is almost identical to the relative uSUD risk which was obtained for the study period prior to the study protocol amendment. Therefore we conclude that the selection bias introduced by the recruitment procedure in the pathological study part could be compensated by weighted analyses.

Although unweighted risk estimates are reported throughout the final report for reasons of transparency, the weighted analyses are regarded as the more valid risk estimates. As the magnitude of selection bias could be assessed only in those exposed cases aged up to 9 months and enrolled by the forensic institutes, results of the weighted analyses may still overestimate the risk of uSUD and the true association is likely to be even smaller in magnitude than the weighted risk estimates.

6.1.4. Possible misclassification - validity of ICD-10 classifications

Estimates of the proportion of explained deaths among all sudden unexpected deaths in children up to the age of 24 month vary considerably from less than 10% to 70% [43-45], raising the possibility of variability in the correctness of case classification.

In the TOKEN study, substantial misclassification of the initially reported underlying cause of death as reported on the death certificate was noted in comparison to the respective autopsy result (see 5.1.1.2). For example, in a subset of autopsied cases enrolled in the TOKEN study, death was concluded to be explained in 25% of cases initially coded as R95 in light of the results of the post-mortem examination, and 33% of autopsied cases who were initially coded with R98/R99 were concluded to have died of an explained cause of death.

As 81.7% of TOKEN cases were autopsied and the autopsy reports (or at least its summaries) were available to the study group in 97% of autopsied cases, classification of the underlying cause of death in the study is judged as sufficient. However, as the quality and thoroughness of post-mortem investigations differed considerably and causes of death were determined in a non-standardised manner, it cannot be ruled out that in some cases a more thorough post-mortem investigation may have been able to explain the cause of death, and misclassification to some extent is therefore likely. Also, a certain degree of differential misclassification cannot be ruled out, as cases hexavalently vaccinated within the last 3 days were more likely (>90%) to have been autopsied than cases with no hexavalent vaccination within the last 3 days (79%).

Validity of ICD-10 classification of the underlying cause of death in this study is thus concluded to be inferior to studies in which all cases underwent a standardised autopsy, but higher than in studies based solely on the German mortality register.

Misclassification of cases with regard to the exposure of interest can be ruled out: vaccination status was obtained on the basis of the vaccination card in 70.3% and on the basis of medical records provided by the children's physician in another 29.1% all cases. Only in a single case, the vaccination status was provided by the parents.

6.1.5. SCCS method

The self-controlled case series (SCCS) analysis examines shifts of the event under study in pre-specified time periods and only requires information on cases [8-10, 46]. It has the advantage of an implicit control of all potential confounders that are stable over time and can also control for age effects. Ascertainment of cases must be independent of exposure status [8]. For unique (non-recurrent) events, the method requires the additional assumption that the cumulative incidence of events in the population over the observed period is low.

As described in Section 4.2.6.2, the TOKEN study used an adaptation of the original SCCS method to allow its use for non-recurrent events such as death. The advantage of the modified method was that valid and independent estimates for each of the up to four vaccine doses were obtained. The disadvantage of the modified method was that it did not allow for the use of all data, but only those events that occur in the relatively short observation periods, thus resulting in some loss of power.

Farrington recently published an alternative modification of the SCCS method that can be used in situations where occurrence of the event censors post-event exposures [47]. This approach has the advantage that each case, even if unvaccinated, is included in the analysis and thereby contributes to the information on association of age and outcome. Explorative re-analyses of the TOKEN study by means of this method resulted in a relative uSUDrisk of 2.01 (95% CI 1.08-3.74) within 3 days of hexavalent vaccination as compared to the risk estimate in this study of 2.26 (95% CI 1.13-4.51). It thus appears that including more comprehensive data on age distribution of cases by using the alternative approach may lead to a slightly lower risk estimate without changing the overall magnitude.

Although inherently controlling for potential confounders that are stable over time, as well as including age and season as confounders in the analyses, the SCCS method, like cohort and case-control studies, remains susceptible to some bias if vaccination is timed to minimize the risk of an adverse event.

The SCCS method is not able to estimate relative risks of non-recurrent events such as death. Therefore, in the TOKEN study, the relative risks yielded by the case series method do not estimate the magnitude of any potential effect of vaccination on risk of uSUD, but rather describe the risk within a specified risk period in comparison to a control period and indicates whether there may be an accumulation of deaths after vaccination. Even if there was a general, but delayed protective effect of a vaccination or if the exposure was not associated at all with risk of uSUD, this may result in an accumulation of events shortly after vaccination. This limitation was overcome by complementing the SCCS method by a case-control analysis. Odds ratios obtained by the case-control analyses differ from the estimates derived from the SCCS method. The reason is that a case-control analysis also includes unvaccinated cases and controls and therefore is able to estimate whether the risk of uSUD may be different between recently vaccinated and not recently or unvaccinated cases.

6.1.6. Selection of controls

During the first 10 months of the TOKEN study, anonymised data from the German Child and Youth Health Examination Survey (KiGGS) were used as controls. This data source was chosen because it yielded data from a nationally representative sample of children with main residence in Germany, i.e., the same population from which cases were planned to drawn (see Section 4.3.4) and, when the study started, was therefore seen as a cost-efficient approach to concomitantly realize a case-control study. Approximately one third of the controls originated from the KiGGS survey. The matching criteria and the definition of the reference date were chosen to prevent introduction of bias due to a potential effect of KiGGS participation on

vaccination status (see Section 4.3.4.1). However, information on several established SIDS risk factors such as sleeping position, sleeping environment, or recent illnesses and medical treatment was not collected in the KiGGS survey. Consequently, interaction of vaccination with these established risk factors could not be investigated in the case-control analyses.

As of May 2006, controls were prospectively enrolled for the specific purpose of the TOKEN study to avoid introducing bias subsequent to the suspension of the marketing authorisation of Hexavac®. Two thirds of the controls were enrolled by this procedure. The sampling procedure and matching criteria of the prospective control group closely followed the KiGGS procedures. Prospective enrolment allowed collecting information about the favourite sleeping position and symptoms of illness and medical treatment. To avoid recall bias, information about the control's sleeping position on the reference date was not queried as the median time period between the reference date and the date when parents answered the questionnaire was considered to be too long (median, 204 days; range 62-837 days).

Exposure misclassification of controls can be almost completely ruled out for both, the controls recruited from the KiGGS survey as well as the prospectively recruited controls, since vaccination status was determined from the presented vaccination documents in all of the KiGGS controls and in 94.1% of the prospectively enrolled controls.

6.1.7. Adjustment for possible confounders

As outlined in Section 4.3.6.2, the following variables were included in the multivariable case-control analyses: sex, level of maternal education, maternal age, premature birth, number of siblings, breast feeding, family status (both parents, single mother or new partner), and maternal smoking.

This strategy was based on largely consistent reporting of these variables as risk factors for SIDS in previous studies [40, 48, 49] and/or for other explained and unexplained sudden unexpected deaths [49-51], and was considered appropriate based on the *a priori* assumption that some of these risk factors may be associated with the vaccination status of a child. Relevance of these covariables was supported by analyses on the basis of the Bayesian Information Criterion.

Former studies on the association of vaccination and SIDS have been frequently criticised because risk factors for SIDS were reported to be also associated with low vaccination coverage [52]. However, the direction in which parameters may confound results may vary by time and by country and also depend on the chosen endpoint (complete vaccination/no vaccination). For example, data from the United States mainly from the 1990s showed that black, young, unmarried mothers with a low level of education who lived close to the poverty line were less likely to have their children completely vaccinated [53], whereas in a more recent study, SMITH et al., from 2004 showed that white, married, well-educated mothers with a high household income and who described themselves as critical of vaccination were more likely to have their children not immunised [54].

In Germany, the situation is characterised by improving vaccination coverage and a rather low association between (low) socio-economic status (SES) and vaccination [55, 56]. On the other hand, however, a high SES is known to be associated with a critical approach towards vaccination in Germany [57].

The results of a recent analysis of the (as yet unpublished) KiGGS survey data on tetanus vaccination that gave current information on factors associated with the vaccination status of German children were therefore taken into consideration when analysing the TOKEN study. In this analysis which was restricted to children who were born between 2002 and 2006, maternal age and region of residence were found to be associated with timeliness and

completeness of the tetanus vaccination status. In the KiGGS survey data, timeliness of vaccination was less favourable in children of older mothers (maternal age at birth >30 years), whereas the completeness of vaccination at the end of the first year of life was less favourable in children of young mothers (maternal age at birth <20 years). Especially the timeliness of the first vaccination was less favourable in the western part of Germany than in the eastern part. Furthermore, timeliness and completeness of the vaccination within the first year of life was less favourable in children with 3 or more older siblings. The multivariate analyses of the KiGGS survey data indicated that the timeliness of vaccination was more favourable in children born preterm (not significant). This analysis of the KiGGS survey data confirmed the need to include these factors in the statistical analyses of the case-control study as covariables.

In the TOKEN study, maternal age at birth was ≥ 30 years in 54.2% of controls, and older mothers were more likely to participate than younger mothers (see 5.1.2.4). In contrast, maternal age at birth was ≥ 30 years in only 34.6% of cases, and no differences in the response proportions between older and younger mothers were apparent (see 5.1.1.5). As a result of these differences and in light of data suggesting that older maternal age may be associated with a lower level of timeliness of vaccination and hence a higher proportion of unvaccinated controls at the peak age of SIDS, the case-control analyses may be subject to residual confounding and hence may have overestimated of risk of death after vaccination.

As none of the variables included in the multivariable model can be assumed to be on the "causal pathway" between the exposure and outcome of interest in this study, their inclusion is unlikely to have led to overadjustment. This assumption is further supported by the fact that the univariate and multivariate risk estimates produced in the case-control analyses were mostly very similar if they were based on reasonably large numbers of cases and controls.

6.2. Interpretation in the context of other studies

6.2.1. Vaccination and risk of SIDS, regardless of any temporal association

At least 6 studies investigating a potential association between immunisation and SIDS noted a decreased risk of SIDS in vaccinated children [58-63]. In 3 of these studies the risk reduction was statistically significant [59-61]. Only one study did not indicate towards any risk reduction in vaccinated children (OR 1.08; 95% CI 0.49-2.36) [64]. Possible causal explanations for the risk reduction suggested in most studies that have been put forward considered possible associations of unrecognised infection with *Haemophilus influenzae* [65, 66] or *Bordetalla pertussis* infections [67] with SIDS and beneficial effects of vaccination due to induction of antibodies cross-reactive with pyrogenic *Staphylococcus* toxins induced by vaccination against Tetanus, Diphtheria and Pertussis [68]. Some of the above mentioned studies have however been repeatedly criticised as insufficiently controlled for confounding [69, 70]. Of the 4 studies that attempted to better control for confounding through multivariate analysis [60, 62-64], 3 also indicated a protective effect of vaccination [60, 62, 63], one of which reported a statistically significant risk reduction [60]. A meta-analysis of these four studies estimated a combined odds ratio of 0.54 (95% CI 0.39-0.76) [71].

The results from these studies are best compared to the case-control data of the TOKEN study obtained for children below the age of 1 year. In the weighted case-control analysis, the multivariate odds ratio for uSUD was 1.20 (95% CI 0.60-2.40). Given the wide confidence interval, this result is consistent with above mentioned studies.

Possibly, the slightly higher risk estimate observed in the TOKEN study as compared to earlier studies may be fully explained by inter-study variability or the methodological

limitations of the TOKEN study, such as residual confounding or the selection bias introduced by preferential enrolment of exposed cases. An alternative hypothesis that may explain this finding is a real secular trend in the associations between recognised and unrecognised SIDS risk factors and vaccination in Germany in recent years.

Indeed, overall improvements in vaccination timeliness and coverage have been observed in Germany, where recent data have shown a low relevance of SES, whereas very low as well as higher maternal age remain important risk factors for poor vaccination timeliness and coverage (Poethko-Müller, unpublished results from KiGGS data).

6.2.2. Case-control studies investigating temporal associations between vaccination and SIDS

Several studies investigated the risk of sudden infant death within a defined time period after vaccination. MITCHELL et al. found that in the New Zealand Cot Death Study in 1987-1990 the risk of SIDS within 4 days immediately after vaccination was reduced (OR 0.5; 95% CI 0.2-0.9) [60].

VENNEMANN reported that in the German GeSID study, SIDS cases were less often immunised within 14 days before death than were controls in the same time period before interview [63]. 307 SIDS cases were included, of them, of them 22 were hexavalently and 107 cases were non-hexavalently (mostly pentavalently) immunised. Even within the first days after vaccination, the univariate odds ratios indicated that the risk of death was rather decreased than increased, albeit not statistically significant.

FLEMING observed that in the CESDI study performed in the United Kingdom, the proportion of cases and controls who had been vaccinated within 48 hours was similar (5%) [62].

HOFFMAN analysed data from the National Institute of Child Health and Human Development (NICHD) SIDS Cooperative Epidemiogical Study carried out 1978/1979 at three sites in the United States. The proportion of cases (1.8%) and matched controls (2.2%) was almost identical in the first 24 hours after vaccination and was slightly higher in cases (32.6%) than in controls (25.3%) in the time interval from >24 hours to 2 weeks [59].

The European Concerted Action on SIDS (ECAS) examined risk factors in 17 European states between 1992 and 1996. The univariate odds ratio for being vaccinated within the last 7 days was 1.27 (95% CI 0.89-1.81) [72].

In comparison, in the TOKEN study, the weighted case-control analysis in infants up 1 year of age and receiving any vaccination within the last 3 days resulted in an odds ratio of 1.06 (95% CI 0.36-3.16) with no difference between the uni- and multivariate analysis. The unweighted analysis yielded an odds ratio of 1.49 (95% CI 0.57-3.90) with a slightly higher univariate estimate of 1.58. Even if not indicating a protective effect shortly after vaccination, these results provide supporting evidence for the statement there is not increased risk of uSUD within 3 days after vaccination during the first year of life.

Considering the first 7 days as risk period after vaccination, an odds ratio of 0.46 (95% CI 0.18-1.16) was estimated in the weighted case-control analysis and of 0.83 (95% CI 0.47-4.67) in the unweighted analysis, with no difference between the uni- and multivariate analyses. Thus, also within this time frame, this study is consistent with previous research in which no increased risk after vaccination was seen.

6.2.3. Studies in vaccinated infants that only investigated temporal relationship

Because the differences between vaccinated and unvaccinated children are believed to be important, several investigators studied only vaccinated children and examined timing of SIDS in relation to diphtheria-tetanus-pertussis (DTP) vaccine [59, 61, 73, 74].

In an ecological study from SOLBERG et al. [73] summarised in HOWSON [70], no increased risk of SIDS within 7 days after vaccination was reported.

GRIFFIN et al. reported a relative risk of SIDS within 0 to 3 days after DTP immunisation of 0.18 (95% CI 0.04-0.8); between 4 and 7 days of 0.17 (95% CI 0.04-0.7); between 8 and 14 days of 0.75 (95% CI 0.4-1.5); and between 15 and 30 days of 1.0 (95% CI 0.6-1.6) from a cohort of approximately 130,000 children who received at least one DTP immunisation during their first year of life.

WALKER et al. performed a case-control study in a US-American infant population and reported a 7.3-fold mortality rate (95% CI 1.7-31) within 3 days after DTP vaccination as compared to the period beginning 30 days after vaccination [61]. Mortality declined gradually over the 4 weeks after vaccination and confidence intervals for the relative mortality during the 4^{th} to 29^{th} day post vaccination extended well below 1. The authors therefore concluded that there was the possibility of a compensatory decline in SIDS mortality after a brief post-immunization rise.

Although the analyses was performed in a non-representative population with a very low SIDS incidence and included only 23 cases (only 4 of whom had died within 3 days after vaccination), similarities in patterns of temporal association of SIDS and vaccination between the WALKER study and the TOKEN study are noteworty: in the SCCS analysis, a relative risk was observed that was higher in the first 3 days after hexavalent vaccination (weighted analysis: RR 1.54; 95% CI 0.67-3.54; unweighted analysis: RR 2.26; 95% CI 1.13-4.51) and that was followed by a decreased risk resulting in an weighted estimate of 0.59 (unweighted analysis: RR 0.96; 95% CI 0.49-1.86) for the time period of 7 days after hexavalent vaccination. Combined estimates of hexavalent or pentavalent vaccination were somewhat higher but similar in terms of an elevated risk within the first 3 days after vaccination but no risk increase within 7 days after vaccination.

According to the "triple risk hypothesis", SIDS only happens if 3 conditions occur simultaneously: (1) a vulnerable developmental stage; (2) predisposing factors, including a certain genetic pattern; and (3) a triggering event [75]. In this model, an immunological stressor such as a mild infection has been hypothesised to be able to act as the triggering event in a "fatal triangle". The TOKEN study result of an increased risk of death within the first days after vaccination, followed by a decreased risk in the second half of the week after vaccination, is in line with this current concept of SIDS. The vaccination may lead to increased body temperature, comparable to the increase of body temperature during a common cold, which may trigger sudden infant death. However, increased body temperature after vaccination has not been described as a risk factor for SIDS in the literature and the immunological processes after vaccination are different from those after a viral infection. The TOKEN study results indicate that the higher incidence of uSUD shortly after vaccination may be followed by a period of decreased uSUD incidence.

However, considering the fact that the risk estimates of both studies are based on very small numbers of cases especially for the first risk period, and potentially affected by relevant methodological limitations, as well as the perspective of other studies consistently reporting a decreased risk even in the first post-immunisation period, this pattern may well be coincidental and should be interpreted with caution.

6.2.4. Sudden unexplained death and hexavalent vaccination

Hexavalent vaccines are only licensed since October 2000 and research on the temporal relationship of hexavalent vaccination and sudden death are limited. Several reports of deaths in close temporal relationship with hexavalent vaccination were received by the PEI as spontaneous reports. These reports prompted an evaluation by VON KRIES who analysed sudden unexpected deaths in temporal relationship with hexavalent vaccination by estimating standardised mortality ratios (SMR) [1]. Cases reported in Germany between November 2000 and June 2003 were included in this analysis. No significant exceed of SMRs were detected in the first year of life. However, in the second year of life, for one of the two hexavalent vaccines the SMR within 2 days of vaccination was 23.5 (95% CI 4.8-68.6).

In the report, the authors pointed out that there is no biological plausibility regarding an age specific effect and there is no immunological or physiological explanation why galenic differences between the two hexavalent vaccines might be relevant regarding the safety of the vaccines. However, as it could not be ruled out that there might be an association of sudden unexpected death in the second year of life with hexavalent vaccines in general or even any other vaccines, the findings were seen as a signal and intensified surveillance for unexpected deaths after vaccination was deemed necessary.

The SMR analysis by VON KRIES was limited due to several characteristics of the data used. Case ascertainment was based on a spontaneous notification system; age distribution of the background incidence and the vaccination coverage was neither representative for Germany nor simultaneously established for the study period. A major drawback was the small number of cases included in the analyses. The analysis was based on only 4 cases during the second year of life, 3 of whom had died within two days after vaccination.

Due to the nationwide, standardised case enrolment procedure which intended to include all cases within the 3-year study period, the TOKEN study was expected to provide a more comprehensive data base for the evaluation of any association between uSUD and (hexavalent) vaccination in the second year of life. However, of the 79 uSUD cases in the second year of life that had been reported in the framework of the study, only 39 could be enrolled. Of these, only one case from this age group had died within 7 days after hexavalent vaccination. Although inreased relative risks were estimated in the SCCS and the case-control analyses, the estimates had excessively wide 95% confidence intervals that clearly indicate that the results are not suitable to assess a possible risk of uSUD after hexavalent vaccination.

VENNEMANN et al. also analysed the GeSID data stratified by the type of vaccine and tried to focus on possible differences between hexavalent and non-hexavalent vaccines [63]. GeSID data are restricted to the first year of life. As hexavalent vaccines were licences in October 2000, they were only available for 1 year of the GeSID study period. During the first year after licensing, hexavalent vaccines had only been used in a minor proportion of infants. In the relevant time period, only 17.1% of cases and 26.5% of controls participating in the GESID study were hexavalently vaccinated. In this subgroup of the GeSID, 3 cases had died within 2 days of vaccination and an SMR of 2.38 (95% CI 0.77-5.55) was calculated.

The Italian Hera study on the risk of death due to unknown or ill-defined causes during the first 2 years of life was conducted between 1999 and 2003. The results have not yet been reported. The study was performed by the Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute, Istituto Superiore di Sanità, Italy. Vaccinated cases were analysed by a case-series design. Vaccination status was obtained by the Italian Local Health Unit vaccination archives. By means of personal communication, it came to the attention of the TOKEN study group that the Italian study not only investigated the risk period of 0-1 days after vaccination but also a second period of 0-7 days. Some of the main results of the Hera

study were presented at the WHO conference 'Vaccine Safety Evaluation: Post Marketing Surveillance Conference Bethesda' in April 2007 and indicated that the Hera results showed no increased risk of death during 0-1 days following vaccination and no increased risk by dose or in the second year of life. It was further reported that for the risk periods 0-7 and 0-14 days, most relative risk estimates were slightly greater than 1 but not statistically significant, and that at 14 days both hexavalent vaccines had the same estimated relative risk. In addition, it was reported that the relative risks concerning concomitant administration of 6 antigens did not differ from the estimates for the two hexavalent products [76] .

Additional preliminary results were published in 2006 [17] indicating that in the Italian study the risk of sudden unexpected death in the first 2 years was estimated to be higher for the 0-7 day risk period than for the 0-1 day risk period, but that all results were not statistically significant. Thus, the results of the HERA study are not consistent with the TOKEN study. A more detailed comparison of methods and results is hindered by the limited information published so far.

6.2.5. Sudden unexplained death and pentavalent vaccination

Pentavalent vaccines were licensed in December 1997 and April 1998, respectively, in Germany. Only one study has since been conducted in Germany to investigate the risk of uSUD after vaccination. The German case-control study on SIDS (GeSID) was carried out between 1998 and 2001 and revealed a multivariate odds ratio for SIDS of 0.51 (95% CI 0.25-1.00), thus indicating that vaccination was associated with a reduced risk of SIDS, as other studies had already suggested [63]. No temporal association between vaccination and SIDS was found. The exploratory analyses of the TOKEN study indicating towards an increased risk of uSUD after pentavalent vaccination are in contrast to the GeSID study, which enrolled a considerably higher number of cases, had a much higher response proportion, and no obvious selection bias.

After hexavalent vaccines were licensed in Germany, their use was rapidly favoured over pentavalent vaccines. In the TOKEN study only approximately 11% of vaccinated cases and controls were pentavalently vaccinated, whereas the majority was hexavalently vaccinated. Mothers of pentavalently vaccinated children turned out to be older, better educated, and apparently more health conscious (as indicated by a lower prevalence of smoking and a higher prevalence of breast feeding) than mothers of hexavalently vaccinated children. This pattern is plausible considering that suspicion about a potential relationship between hexavalent vaccination and SIDS arose in 2003 and avoidance strategies may have been more prevalent in better educated and more health conscious mothers.

The low number of pentavalently vaccinated cases (n=19) and controls (n=88) impeded stratification by vaccine type. One possible explanation for the unexpected result of the exploratory analysis of pentavalent vaccines – apart from chance – is an even more pronounced self-selection of parents of cases vaccinated shortly prior to death. The presence of such self-selection is supported by the observation that consent could be obtained for all cases who had been pentavalently vaccinated within 3 days prior to death either by case enrolment by the forensic institute (n=1) or already after the *first* letter of invitation (n=3; see Section 5.1.1.3). Pentavalent vaccination may represent a strategy to avoid the perceived SIDS risk of hexavalent vaccines, and a child's death shortly after pentavalent vaccination may have prompted the wish to clarify the reason of its death and a possible relationship to vaccination by means of study participation. The study aim to investigate vaccination as a possible risk factor for uSUD was known to parents invited to participate in the TOKEN

study. The GeSID study, however, had more comprehensive aims and was not focussed on vaccination.

A second mechanism that could have led to an overestimation of risk of uSUD after pentavalent vaccination is confounding by indication. Physicians may have preferentially used pentavalent vaccines for children thought to be at greater risk of SIDS.

6.2.6. Other risk factors and effect modification

Prone sleeping position is one of the best established risk factor for SIDS [77, 78] and its relevance is still high in Germany [40, 51]. Whereas information about sleeping position was not available in controls recruited from the KiGGS survey, an analysis restricted to the prospectively recruited controls showed prone sleeping position to be a significant risk of uSUD also in this study. In the first year of life, 23.7% of cases and 7.5% of controls were put to bed either prone or in varying positions but including the prone position. Within the second study period the relative odds (unconditional analyses, adjusted for the 9 variables of the multivariate models of this study, excluding any variable regarding vaccination) of sleeping prone (or varying including prone) and uSUD was 4.23 (95% CI 2.14-8.36) in cases.

In the SCCS analyses, the risk of uSUD within 3 days after hexavalent vaccination was increased in children whose usual sleeping position was prone (unweighted RR 5.02; 95% CI 1.69-14.87), whereas the relative risk in children not usually sleeping prone was less pronounced (RR 1.92; 95% CI 0.73-5.05). Although attenuated in the weighted analysis, an almost 2-fold risk in prone sleeping children in comparison to non-prone sleeping children remained in the weighted analysis.

This observation is in line with research indicating that several factors potentiate the risk of prone sleeping, whereas these factors do not necessarily increase the risk of SIDS on their own. For example, interaction between prone sleeping and heavy wrapping was found by FLEMING et al. [79] and a high risk of SIDS for the combination of prone sleeping and sleeping on a sheepskin was seen by MITCHELL et al. [80] as well as in the GeSID study [81].

Most interestingly, effect modification has also been reported for infections. While GILBERT et al. reported an odds ratio for SUD in children above the age of 70 days of 3.7 (95% CI 1.03-13.3) for virus infection alone and 13.7 (95% CI 3.2-60.6) for heavy wrapping in healthy children, the risk of SUD in the context of a combination of heavy wrapping and virus infection was estimated at 51.55 (95% CI 5.6-471) [78]. PONSONBY [82] reported that recent illness potentiated the risk of prone sleeping, leading to an odds ratio of 5.7 (95% CI 1.8-19), while recent illness in non-prone sleeping children did not increase the risk of SIDS. Vaccination as well as infections are often accompanied by increased body temperature and sometimes fever. Taking into account the amount of evidence on interaction between prone sleeping and a number of risk factors which are associated with increased body temperature or impaired thermoregulation, the hypothesis that vaccination potentiates the risk of prone sleeping is to be confirmed by future studies.

The investigation of interaction between hexavalent vaccination and additional SIDS risk factors in the TOKEN study also indicated that preterm born infants were at considerably higher risk than maturely born children. This observation is in line with an examination of fatalities subsequent to vaccinations reported to the US 'Vaccine Adverse Event Reporting System' in 2001, where a higher percentage of cases reported were considered 'low-birth weight infants' in comparison to the percentage of 'low-birth weight infants' in the US general population [83]. Other investigations have reported that premature infants may be at higher risk of apnoea or bradycardia after immunisation [84-90]. Together, these

investigations resulted in a recommendation by the EMEA to modify the package inserts of vaccines for infants, such that respiratory monitoring for 48-72 hours following primary immunisation in very premature infants should be considered. Because of the small sample size, the TOKEN study did not stratify risk estimates for prematurely born children any further, but only compared children prematurely born at <38 weeks of gestation to maturely born infants. However, also in the light of the additional amount of evidence indicating a higher risk of prematurely born infants after immunisation, the results of the TOKEN study seem plausible and care should be taken to avoid any well-known SIDS risk factor after vaccination (sleeping position, maternal smoking, heating of the bedroom, thick beddings etc.).

The TOKEN data indicate that any uSUD within 3 days after hexavalent vaccination most frequently occurred in children having additional risk factors. All but one child dying within 3 days after a hexavalent vaccination had several additional modifiable SIDS risk factors, such as prone sleeping position, a smoking mother, or extra heating during sleeping. Five out of the 11 deaths in the first 3 days after a hexavalent vaccination had been left unattended (and subsequently had not been fed) for more than 9 hours, 3 of them even for more than 12 hours).

Taken together, whereas the TOKEN study results did not show an increased risk of uSUD within 1 week after hexavalent vaccination, they are consistent with the hypothesis that vaccination may temporarily modify the known risks of prone sleeping and prematurity.

The TOKEN study revealed that 23.7% of cases occurring within the first year of life but only 7.5% of control children had been usually put to bed in prone position, or in a varying position including prone. Half the mothers of cases but only 20.2% of the mothers of controls were smokers. Only 59.4% of cases but 84.3% of the controls had been breast fed. Overall, these results re-emphasise the importance to further strive for implementation of current recommendations of SIDS prevention.

7. Conclusions

The TOKEN study was prompted by spontaneous reports on cases of uSUD that had occurred shortly after hexavalent vaccination. Suspicion about a possible relationship between hexavalent vaccination and risk of uSUD in the 2nd year of life arose from a statistical analysis of these spontaneous reports by VON KRIES [1]. Consequently, the main study question of the TOKEN study focussed on the first few days after vaccination and the 2nd year of life. By implementing a nationwide active surveillance system in the context of a standardised epidemiological study over a period of 3 years, this study was expected to overcome the methodological and sample size limitations of the first evaluation.

Unfortunately, however, the response proportion of parents was low (37,6%) despite all attempts towards better study participation. In particular, only one child who had died in its 2nd year of life in close temporal relationship to vaccination could be enrolled, although additional cases came to the attention of the study team but could not be included for various reasons. The number of enrolled children who received non-hexavalent vaccines was also low (n=19). The greatest study limitations were, however, the self-selection of parents whose child had died shortly after a vaccination as well as preferential enrolment of recently vaccinated infants by the participating forensic institutes, both of which introduced important selection bias into the TOKEN study. Whereas the latter source of bias could be at least partially accounted for in the analyses by inverse-probability weighting, the former source was uncontrollable and probably led to an overestimation of the risk in the studied population. However, for the same reason, it can be assumed that the true risk will most likely not exceed the estimates calculated in the TOKEN study.

Within these limitations, the risk of uSUD in the studied population within 1 week after hexavalent vaccination is concluded to be not different from the risk of uSUD more than 1 week after vaccination (SCCS analysis; weighted RR 0.59; 95% CI 0.26-1.33; unweighted RR 0.96; 95%, 0.49-1.86). This conclusion is supported by the case-control analyses which yielded similar results.

The TOKEN study results indicate that the risk of uSUD may not be equally distributed over the first week after hexavalent vaccination. The SCCS results are compatible with a higher risk of uSUD within the first 3 days (unweighted RR 1.92; 95% CI 0.94-3.93; weighted RR 1.26; 95% CI 0.54-2.97), followed by a lower risk between the 4th and 7th day (unweighted RR 0.27; 95% CI 0.06-1.12; weighted RR 0.11; 95% CI 0.01-1.01). This pattern was observed also in the case-control analyses.

However, considering the very small numbers of cases especially for the first risk period, the significant methodological limitations of the TOKEN study, and the results of other studies that consistently reported a decreased risk even in the immediate post-immunisation period, the pattern observed in the TOKEN study may well be coincidental and should be interpreted with caution.

Although the rigorous methodology of the TOKEN study would have provided more robust results than the statistical evaluation of spontaneous reports that triggered it, the TOKEN study suffered from similar sample size limitations. Study size and low response proportion were of particular relevance when stratified analyses were necessary. Only 1 of the 13 cases enrolled in the TOKEN study who had died within 7 days after hexavalent vaccination was older than one year at the time of death. Risk stratification by age was thus not meaningful.

In the TOKEN study, just over 10% of the enrolled children were pentavalently vaccinated, hindering reliable risk estimation for pentavalently vaccinated children and risk comparisons

between types of vaccines. Nonetheless, the weighted SCCS and the case-control analyses, both exploratory analyses, indicated an elevated uSUD risk after pentavalent vaccination but not after hexavalent vaccination. Although this difference should be cautiously interpreted in light of the limitations of this study and is most likely an artifact, it does support the view that a higher risk of uSUD after hexavalent vaccination in comparison to pentavalent vaccination is improbable.

The study question whether the absolute risk of vaccinated children may differ from unvaccinated children was approached by the case-control analysis, which yielded a weighted multivariate odds ratio for uSUD during the first year of life of 1.20 (95% CI 0.60-2.40; unweighted multivariate OR 1.34; 95% CI 0.70-2.53). Thus, there is no indication that the risk of uSUD during the first year of life is different between vaccinated and unvaccinated children. Because almost all children above the age of 1 year were vaccinated, no conclusive statistical analysis was possible for older children.

The study results suggest that the established risk factors for SIDS, particularly prone sleeping and maternal smoking, are still important and should be strictly avoided in the first years of life.

The pathological study part focussed on the question whether *post mortem* investigations can identify findings indicating a common pathological mechanism of sudden deaths after vaccination. Prior observations have suspected brain oedema to occur frequently in deaths shortly after vaccination. However, the brain-body-ratios measured in this study do not support the view that vaccination may be associated with severe brain oedema. Neither the extensive investigations of the immune system nor the morphological, immunological and genetic investigations revealed a common pattern of findings.

The TOKEN study specifically examined only cases of *unexplained* sudden death. Protective effects of vaccination on infant mortality from *explained* death such as lethal *Haemophilus influenzae*- or Pertussis infections were not investigated and are not reflected in the calculated risk estimates. Thus, the statistics produced in the TOKEN study do not provide an overall estimate of the effect of vaccination on infant mortality.

Given the significant limitations of this study, most of the study questions posed cannot be answered with certainty. The public health importance of the topic should prompt development of strategies to verify the actual association. Taking into account that a qualitatively and quantitatively sufficient data base could not be established despite high motivation, adequate funding, and governmental and local support, it is concluded that these study questions can only be answered in Germany if a vaccination register is established that is linkable to a mortality register on a case-by-case basis.

It is an accomplishment of the TOKEN study to have identified vulnerable subgroups in which vaccination may modify the effect of established risk factors for SIDS. Prone sleeping position and maternal smoking are such avoidable risk factors, and as for any infant during its first year of life, recently vaccinated children should be prevented from these risks.

The most probably overestimated initial risk increase within 3 days after (hexavalent) vaccination was limited to children with additional risk factors for SIDS. Despite all study limitations, it is concluded that the risk of uSUD within 1 week after (hexavalent) vaccination was not increased.

8. Tables

Table 1: Sample size calculation of the minimum number of cases required to detect a relative incidence of 2, 4 or 8 (power 80%, alpha 0.05)

Relative incidence	Dose 1	Dose 2	Dose 3	Dose 4	Total
2	110-120	100-110	270-280	250	150-160
4	25-30	25-30	50-60	50-60	30-35
8	10	10	20	20	15-17

Table 2: Results of the 4 sequential analyses (H_0 = null hypothesis)

	Stage 1	Stage 2	Stage 3	Stage 4
Critical value, reject H_0	2.6700	2.1240	1.9190	1.8330
Information rate	0.2220	0.5550	0.8330	1.0000
alpha spent	0.0038	0.0192	0.0369	0.0500
Observed p-value (one-sided)	0.2442	0.1370	0.7104	0.1748
Inverse normal	0.6930	1.2860	0.7290	1.0480

Table 3: Results of the capture-recapture analysis in SUD cases ≥ 9 months; 2006

Age group	Number of observed SIDS/SUD cases			Estimated completeness of data source		Estimated total cases*
	LHA	Forensic institutes	Matches	LHA	Forensic institutes	
Months	n	n	n	% (95% CI)	% (95% CI)	
9-11	27	20	14	70.0 (54.4-85.6)	51.9 (34.8-68.9)	38.6
12-23	61	65	50	76.9 (67.5-86.4)	82.0 (73.3-90.6)	79.3
Total	88	85	64	75.3 (67.2-83.4)	72.7 (64.4-81.1)	116.9

* The sum of age-specific CRA estimates does not sum up to the overall CRA estimate.

Table 4: Classification of the underlying cause of death according to the case conference

Case conference decision	Brighton level of diagnosis certainty	Autopsy protocol	Number of cases
R95	1 or 2	'Standard' or complete and 'normal'	23
R98-99* (*indicated as R95 but age >1 year)	1 or 2	'Standard' or complete and 'normal'	7
R98-99 (with autopsy)	2	Incomplete	174
R98-99 (without autopsy)	3 or less	Absent	54
Explained cause of death		Present	48
Total			306

Table 5: Response proportion of cases by age at death (1st or 2nd year of life)

Age at death		Consent	Declined	No address available	No answer case enrolment unsuccessfully finished	Initial consent withdrawn	Consent but no data	Total
1st year of life	n	215	118	27	230	1	3	594
		36.2%	19.9%	4.5%	38.7%	0.2%	0.5%	100.0%
2nd year of life	n	39	18	3	22	0	0	82
		47.6%	22.0%	3.7%	26.8%	0.0%	0.0%	100.0%
Total	n	254	136	30	252	1	3	676
		37.6%	20.1%	4.4%	37.3%	0.1%	0.4%	100.0%

Table 6: Response proportion of cases by age at death (<9 months or ≥9 months)

Age at death		Consent	Declined	No address available	No answer case enrolment unsuccessfully finished	Initial consent withdrawn	Consent but no data	Total
2nd to 9th month	n	190	109	25	216	1	2	543
		35.0%	20.1%	4.6%	39.8%	0.2%	0.4%	100.0%
10th to 24th month	n	64	27	5	36	0	1	133
		48.1%	20.3%	3.8%	27.1%	0.0%	0.8%	100.0%
Total	n	254	136	30	252	1	3	676
		37.6%	20.1%	4.4%	37.3%	0.1%	0.4%	100.0%

Table 7: Response proportion of cases by age at death (<9 months or ≥9 months) and by initiator of case enrolment

Age at death	First case enrolment step initiated by		Consent	Declined	No address available	No answer case enrolment unsuccessfully finished	Initial consent withdrawn	Consent but no data	Total
2nd to 9th month	LHA	n	178	109	25	214	0	2	528
			33.7%	20.6%	4.7%	40.5%	0.0%	0.4%	100.0%
	Forensic Institute	n	12	0	0	2	1	0	15
			80.0%	0.0%	0.0%	13.3%	6.7%	0.0%	100.0%
	Total	n	190	109	25	216	1	2	543
			35.0%	20.1%	4.6%	39.8%	0.2%	0.4%	100.0%
10th to 24th month	LHA	n	43	19	2	27		1	92
			46.7%	20.7%	2.2%	29.3%		1.1%	100.0%
	Forensic Institute	n	21	8	3	9		0	41
			51.2%	19.5%	7.3%	22.0%		0.0%	100.0%
	Total	n	64	27	5	36		1	133
			48.1%	20.3%	3.8%	27.1%		0.8%	100.0%

Table 8: Response proportion of cases by study period and by initiator of case enrolment (cases aged 2nd-9th months only)

Study period	Initiator of case enrolment		Consent	Declined	No address available	No answer case enrolment unsuccessfully finished	Initial consent withdrawn	Consent but no data	Total
Before study protocol amendment	LHA	n	42	23	7	35			107
			39.3%	21.5%	6.5%	32.7%			100.0%
After study protocol amendment	LHA	n	136	86	18	179	0	2	421
			32.3%	20.4%	4.3%	42.5%	0.0%	0.5%	100.0%
	Forensic Institutes	n	12	0	0	2	1	0	15
			80.0%	0.0%	0.0%	13.3%	6.7%	0.0%	100.0%
	Total	n	148	86	18	181	1	2	436
			33.9%	19.7%	4.1%	41.5%	0.2%	0.5%	100.0%

Table 9: Participation of cases by hexavalent risk period and step of case enrolment

		Hexavalent risk class					
Consent after		Risk I	Risk II	Risk III	≥15 days	No hexavalent vaccination	Total
First contact by Forensic institute	n	6	2	2	6	2	18
		54.5%	100.0%	14.3%	4.7%	2.0%	7.1%
First letter by LHA	n	3	0	7	58	43	111
		27.3%	0.0%	50.0%	45.3%	43.4%	43.7%
Second letter by LHA	n	1	0	0	38	22	61
		9.1%	0.0%	0.0%	29.7%	22.2%	24.0%
Phone contact by LHA	n	0	0	3	13	15	31
		0.0%	0.0%	21.4%	10.2%	15.2%	12.2%
Third letter by LHA	n	1	0	2	13	17	33
		9.1%	0.0%	14.3%	10.2%	17.2%	13.0%
Total	n	11	2	14	128	99	254
		100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 10: Participation of cases by pentavalent risk period and step of case enrolment

		Pentavalent risk class				
Consent after		Risk I	Risk II	≥15 days	No penta- and no hexavalent vaccination	Total
First contact by Forensic institute	n	1	0	0	1	2
		25.0%	0.0%	0.0%	1.3%	2.0%
First letter by LHA	n	3	0	8	32	43
		75.0%	0.0%	57.1%	40.0%	43.4%
Second letter by LHA	n	0	1	3	18	22
		0.0%	100.0%	21.4%	22.5%	22.2%
Third letter by LHA	n	0	0	1	16	17
		0.0%	0.0%	7.1%	20.0%	17.2%
Phone contact by LHA	n	0	0	2	13	15
		0.0%	0.0%	14.3%	16.3%	15.2%
Total	n	4	1	14	80	99
		100.0%	100.0%	100.0%	100.0%	100.0%

Table 11: Recruitment efficacy proportion of cases by age (1st or 2nd year of life)

Age at death		Consent	Declined	No answer case enrolment unsuccessfully finished	Initial consent withdrawn	Consent but no data	Total
1st year of life	n	215	118	230	1	3	567
		37.9%	20.8%	40.6%	0.2%	0.5%	100.0%
2nd year of life	n	39	18	22	0	0	79
		49.4%	22.8%	27.8%	0.0%	0.0%	100.0%
Total	n	254	136	252	1	3	646
		39.3%	21.1%	39.0%	0.2%	0.5%	100.0%

Table 12: Comparison of responders and non-responders – cases

	Responders		Non-responders with questionnaire		Non-responders without questionnaire	
Characteristic	n	%*	n	%*	n	%*
Gender						
Male	167	65.0	23	56.1	242	64.0
Female	90	35.0	18	43.9	136	36.0
Age						
1st year of life	218	84.8	34	82.9	342	90.5
2nd year of life	39	15.2	7	17.1	36	9.5
Place of residence						
West	215	83.7	36	87.8	325	86.0
East	42	16.3	5	12.2	53	14.0
Nationality						
German	208	80.9	31	75.6		
Other	30	11.7	5	12.2		
Missing	19	7.4	5	12.2		
Maternal age						
<21	32	12.5	6	14.6		
21 - 25	70	27.2	10	24.4		
26 - 30	47	18.3	9	22		
31 - 35	52	20.2	6	14.6		
≥ 36	40	15.5	6	17		
Missing	16	6.2	3	7.3		
Maternal education						
Low	97	37.7	18	43.9		
Medium	83	32.3	12	29.3		
High	55	21.4	3	7.3		
Missing	22	8.6	8	19.5		
Maternal Smoking						
Yes	121	47.1	19	46.3		
No	117	45.5	18	43.9		
Missing	19	7.4	4	9.8		
last hexavalent vaccination						
Risk period I	11	4.3	2	4.9		
Risk period II	2	0.8	2	4.9		
Risk period III	14	5.4	0	0.0		
15-183 days	102	39.7	7	17.1		
≥184 days	26	10.1	0	0.0		
No hexavalent vaccination	99	38.5	18	43.9		
Missing	3	1.2	12	29.3		

*) Percentages indicate the prevalence of each characteristic in the groups of responders and non-responders (with or without non-responder questionnaire)

Table 13: Response proportion of controls by age at death of the corresponding case

Age at death		Consent	Declined	No address available	No contact enrolment un-successfully finished	Consent but no data	Total
1st year of life	n	671	273	31	355	40	1 370
		49.0%	19.9%	2.3%	25.9%	2.9%	100.0%
2nd year of life	n	112	56	4	66	14	252
		44.4%	22.2%	1.6%	26.2%	5.6%	100.0%
Total	n	783	329	35	421	54	1 622
		48.3%	20.3%	2.2%	26.0%	3.3%	100.0%

Table 14: Response proportion of controls by age at death of the corresponding case (< 9 months or ≥ 9 months)

Age at death		Consent	Declined	No address available	No contact enrolment unsuccess-fully finished	Consent but no data	Total
2nd to 9th months of life	n	602	245	28	320	38	1 233
		48.8%	19.9%	2.3%	26.0%	3.1%	100.0%
10th to 23rd month of life	n	181	84	7	101	16	389
		46.5%	21.6%	1.8%	26.0%	4.1%	100.0%
Total	n	783	329	35	421	54	1 622
		48.3%	20.3%	2.2%	26.0%	3.3%	100.0%

Table 15: Recruitment efficacy proportion of controls by age of the corresponding case (1st or 2nd year of life)

Age at death		Consent	Declined	No contact enrolment unsuccess-fully finished	Consent but no data	Total
1st year of life	n	671	273	355	40	1 339
		50.1%	20.4%	26.5%	3.0%	100.0%
2nd year of life	n	112	56	66	14	248
		45.2%	22.6%	26.6%	5.6%	100.0%
Total	n	783	329	421	54	1 587
		49.3%	20.7%	26.5%	3.4%	100.0%

Table 16: Number of controls per case (entire study)

Number of controls (x) per case	Number of cases with x controls	Percent	Cumulative percent
1	14	5.5	5.5
2	25	9.8	15.4
3	40	15.7	31.1
4	51	20.1	51.2
5	50	19.7	70.9
6	33	13.0	83.9
7	18	7.1	90.9
8	6	2.4	93.3
9	8	3.1	96.5
10	5	2.0	98.4
11	2	0.8	99.2
12	1	0.4	99.6
14	1	0.4	100.0
Total	254	100.0	100.0

Table 17: Number of controls per case (study period before May 2006)

Number of controls (x) per case	Number of cases with x controls	Percent	Cumulative percent
1	6	7.7	7.7
2	11	14.1	21.8
3	9	11.5	33.3
4	13	16.7	50.0
5	8	10.3	60.3
6	10	12.8	73.1
7	7	9.0	82.1
8	2	2.6	84.6
9	3	3.8	88.5
10	5	6.4	94.9
11	2	2.6	97.4
12	1	1.3	98.7
14	1	1.3	100.0
Total	78	100.0	100.0

Table 18: Number of enrolled controls per case (study period after April 2006)

Number of controls (x) per case	Number of cases with x controls	Percent	Cumulative percent
2	1	0.6	0.6
4	1	0.6	1.1
5	5	2.8	4.0
6	5	2.8	6.8
7	10	5.7	12.5
8	13	7.4	19.9
9	23	13.1	33.0
10	118	67.0	100.0
Total	176	100.0	100.0

Table 19: Number of participating controls per case (study period after April 2006)

Number of controls (x) per case	Number of cases with x controls	Percent	Cumulative percent
1	8	4.5	4.5
2	14	8.0	12.5
3	31	17.6	30.1
4	38	21.6	51.7
5	42	23.9	75.6
6	23	13.1	88.6
7	11	6.3	94.9
8	4	2.3	97.2
9	5	2.8	100.0
Total	176	100.0	100.0

Table 20: Comparison between responders and non-responders – controls

	Responders		Non-responders with questionnaire		Non-responders without questionnaire	
Characteristic	n	%*	n	%*	n	%*
Gender						
Male	419	53.5	39	48.8	405	53.4
Female	364	46.5	41	51.3	354	46.6
Missing						
Age						
1st year of life	671	85.7	73	91.3	626	82.5
2nd year of life	112	14.3	7	8.8	133	17.5
Place of residence						
West	551	70.4	44	55.0	529	69.7
East	232	29.6	36	45.0	230	30.3
Nationality						
German	705	90.0	59	73.8		
Other	78	10.0	15	18.8		
Missing			6	7.5		
Maternal age (actual)						
<21	12	1.5	7	8.8		
21 - 25	89	11.4	13	16.3		
26 - 30	205	26.2	16	20.0		
31 - 35	288	36.8	24	30.0		
≥ 36	189	24.1	18	22.6		
Missing	0	0.0	2	2.5		
Maternal education						
Low	87	11.1	28	35.0		
Medium	320	40.9	32	40.0		
High	374	47.8	15	18.8		
Missing	2	0.3	5	6.3		
Maternal Smoking						
Yes	142	18.1	14	17.5		
No	638	81.5	63	78.8		
Missing	3	0.4	3	3.8		
Hexavalent vaccination						
Risk period I	20	2.6	3	3.8		
Risk period II	32	4.1	4	5.0		
Risk period III	43	5.5	5	6.3		
15-183 days	297	37.9	18	22.5		
≥184 days	48	6.1	0	0.0		
No hexavalent vaccination	343	43.8	27	33.8		
Missing			23	28.8		

*) Percentages indicate the prevalence of each characteristic in the groups of responders and non-responders (with or without non-responder questionnaire)

Table 21: Characteristics of hexavalently vaccinated cases included in the SCCS analyses

			Hexavalent vaccination within							
	Total		Risk period I		Risk period II		Risk period III		Control period	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	98		11		2		14		71	
Region of residence										
Eastern part of Germany	17	17.3%	1	9.1%	0	0.0%	1	7.1%	15	21.1%
Western part of Germany	81	82.7%	10	90.9%	2	100.0%	13	92.9%	56	78.9%
Gender										
Female	32	32.7%	3	27.3%	1	50.0%	3	21.4%	25	35.2%
Male	66	67.3%	8	72.7%	1	50.0%	11	78.6%	46	64.8%
Age [days]										
30.0 - 60	1	1.0%	1	9.1%	0	0.0%	0	0.0%	0	0.0%
>60.0 - 91	8	8.2%	3	27.3%	0	0.0%	3	21.4%	2	2.8%
>91.0 - 152	27	27.6%	6	54.5%	1	50.0%	4	28.6%	16	22.5%
>152.0 - 183	9	9.2%	0	0.0%	0	0.0%	1	7.1%	8	11.3%
>183.0 - 274	27	27.6%	0	0.0%	1	50.0%	4	28.6%	22	31.0%
>274.0 - 365	15	15.3%	0	0.0%	0	0.0%	1	7.1%	14	19.7%
>365.0 - 456	3	3.1%	1	9.1%	0	0.0%	0	0.0%	2	2.8%
>456.0 - 730	8	8.2%	0	0.0%	0	0.0%	1	7.1%	7	9.9%
Maternal age at birth										
0-20	17	17.3%	1	9.1%	1	50.0%	5	35.7%	10	14.1%
21-25	27	27.6%	6	54.5%	0	0.0%	1	7.1%	20	28.2%
26-30	16	16.3%	2	18.2%	1	50.0%	4	28.6%	9	12.7%
>30	32	32.7%	2	18.2%	0	0.0%	3	21.4%	27	38.0%
Missing	6	6.1%	0	0.0%	0	0.0%	1	7.1%	5	7.0%
Number of siblings										
No sibling	32	32.7%	4	36.4%	1	50.0%	5	35.7%	22	31.0%
1-2 sibling(s)	43	43.9%	6	54.5%	1	50.0%	6	42.9%	30	42.3%
≥3 siblings	12	12.2%	0	0.0%	0	0.0%	1	7.1%	11	15.5%
Missing	11	11.2%	1	9.1%	0	0.0%	2	14.3%	8	11.3%
Maternal smoking (current)										
Yes	44	44.9%	7	63.6%	1	50.0%	6	42.9%	30	42.3%
No	47	48.0%	4	36.4%	1	50.0%	6	42.9%	36	50.7%
Missing	7	7.1%	0	0.0%	0	0.0%	2	14.3%	5	7.0%
Smoking during pregnancy										
Yes	31	31.6%	4	36.4%	1	50.0%	3	21.4%	23	32.4%
No	55	56.1%	6	54.5%	1	50.0%	9	64.3%	39	54.9%
Missing	12	12.2%	1	9.1%	0	0.0%	2	14.3%	9	12.7%
Breast feeding (ever)										
Yes	50	51.0%	5	45.5%	1	50.0%	6	42.9%	38	53.5%
No	36	36.7%	5	45.5%	1	50.0%	6	42.9%	24	33.8%
Missing	12	12.2%	1	9.1%	0	0.0%	2	14.3%	9	12.7%
Gestational age <38 wks										
Yes	21	21.4%	3	27.3%	0	0.0%	1	7.1%	17	23.9%
No	76	77.6%	8	72.7%	2	100.0%	12	85.7%	54	76.1%
Missing	1	1.0%	0	0.0%	0	0.0%	1	7.1%	0	0.0%
Maternal education										
Low	35	35.7%	7	63.6%	2	100.0%	5	35.7%	21	29.6%
Medium	39	39.8%	3	27.3%	0	0.0%	6	42.9%	30	42.3%
High	16	16.3%	1	9.1%	0	0.0%	1	7.1%	14	19.7%
Family status										

			Hexavalent vaccination within							
	Total		Risk period I		Risk period II		Risk period III		Control period	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Both parents	73	74.5%	9	81.8%	1	50.0%	9	64.3%	54	76.1%
Single parent with new partner	2	2.0%	0	0.0%	1	50.0%	0	0.0%	1	1.4%
Single parent	15	15.3%	2	18.2%	0	0.0%	3	21.4%	10	14.1%
Missing	8	8.2%	0	0.0%	0	0.0%	2	14.3%	6	8.5%
Favorite position when put to sleep (last 4 wks)										
Supine	49	50.0%	3	27.3%	1	50.0%	9	64.3%	36	50.7%
Prone or varying including prone	20	20.4%	5	45.5%	0	0.0%	1	7.1%	14	19.7%
Side	11	11.2%	1	9.1%	1	50.0%	1	7.1%	8	11.3%
Varying but never prone	4	4.1%	1	9.1%	0	0.0%	0	0.0%	3	4.2%
Missing	14	14.3%	1	9.1%	0	0.0%	3	21.4%	10	14.1%
Position put to last sleep										
Supine	51	52.0%	3	27.3%	1	50.0%	7	50.0%	40	56.3%
Prone	19	19.4%	6	54.5%	0	0.0%	2	14.3%	11	15.5%
Side	11	11.2%	0	0.0%	1	50.0%	2	14.3%	8	11.3%
Missing	17	17.3%	2	18.2%	0	0.0%	3	21.4%	12	16.9%
Position when found dead										
Supine	27	27.6%	3	27.3%	1	50.0%	5	35.7%	18	25.4%
Prone	53	54.1%	7	63.6%	1	50.0%	6	42.9%	39	54.9%
Side	3	3.1%	0	0.0%	0	0.0%	0	0.0%	3	4.2%
Other	1	1.0%	0	0.0%	0	0.0%	0	0.0%	1	1.4%
Missing	14	14.3%	1	9.1%	0	0.0%	3	21.4%	10	14.1%

Table 22: Unweighted SCCS analysis, relative risk of uSUD after hexavalent vaccination (1st and 2nd year of life) n=98

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	11	4-28/183	2.26	0.022	1.13 - 4.51
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	11	8-28/183	1.92	0.073	0.94 - 3.93
II: [4-7]	2	8-28/183	0.27	0.071	0.06 - 1.12
I+II: [0-7]	13	8-28/183	0.96	0.896	0.49 - 1.86

Table 23: Unweighted SCCS analysis, relative risk of uSUD after hexavalent vaccination (1st year of life) n=87

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	10	4-28/183	2.07	0.050	1.00 - 4.30
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	10	8-28/183	1.75	0.145	0.82 - 3.72
II: [4-7]	2	8-28/183	0.27	0.076	0.07 - 1.15
I+II: [0-7]	12	8-28/183	0.89	0.746	0.44 - 1.79

Table 24: Unweighted SCCS analysis, relative risk of uSUD after hexavalent vaccination (2nd year of life) n=11

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	1	4-28/183	5.59	0.125	0.62 - 50.18
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	1	8-28/183	5.25	0.140	0.58 - 47.51
II: [4-7]	0	8-28/183	No estimate		
I+II: [0-7]	1	8-28/183	2.15	0.493	0.24 - 19.05

Table 25: Unweighted SCCS analysis, relative risk of uSUD after hexavalent vaccination in cases with available information on sleeping position during the last 4 weeks (1st and 2nd year of life) n=84

Risk period[days]/ sleeping position	Cases in risk period	Cases in control period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days						
I: [0-3]/ all cases	10	74	4-28/183	2.76	0.006	1.34 - 5.67
I: [0-3]/ non prone	5	59	4-28/183	1.92	0.189	0.73 - 5.05
I: [0-3]/ prone	5	15	4-28/183	5.02	0.004	1.69 - 14.87
Model II: Risk period I and II versus control period 8-28/183 days						
I +II:[0-7]/ all cases	12	72	8-28/183	1.25	0.526	0.63 - 2.48
I +II:[0-7]/ non prone	7	57	8-28/183	1.03	0.948	0.44 - 2.43
I +II:[0-7]/ prone	5	15	8-28/183	1.80	0.291	0.61 - 5.33

Age classes >30 to 60 days and >60 to 91 days were combined. Age classes >274 days were combined

Table 26: Unweighted SCCS analysis, relative risk of uSUD after hexavalent vaccination in cases with available information on sleeping position during the last 4 weeks and maternal smoking (1st and 2nd year of life) n=84

Risk period[days]/ presence of maternal smoking or prone sleeping position	Number of cases in risk period	Number of cases in control period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days						
I: [0-3]/ all cases	10	74	4-28/183	2.76	0.006	1.34 - 5.67
I: [0-3]/ No	1	31	4-28/183	0.89	0.910	0.12 - 6.83
I: [0-3]/ Yes	9	43	4-28/183	3.63	0.001	1.66 - 7.93
Model II: Risk period I and II versus control period 8-28/183 days						
I +II:[0-7]/ all cases	12	72	8-28/183	1.25	0.526	0.63 - 2.48
I +II:[0-7]/ No	2	30	8-28/183	0.69	0.636	0.15 - 3.14
I +II:[0-7]/ Yes	10	42	8-28/183	1.49	0.302	0.70 - 3.20

Age classes >30 to 60 days and >60 to 91 days were combined. Age classes >274 days were combined.

Table 27: Weighted SCCS analysis, relative risk of uSUD after hexavalent vaccination (1st and 2nd year of life) n= 98; weighted n=92.1 (weight 0.41)

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	6.87	4-28/183	1.54	0.311	0.67 - 3.54
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	6.87	8-28/183	1.26	0.597	0.54 - 2.97
II: [4-7]	0.82	8-28/183	0.11	0.051	0.01 - 1.01
I+II: [0-7]	7.69	8-28/183	0.59	0.206	0.26 - 1.33

Table 28: Weighted SCCS analysis, relative risk of uSUD after hexavalent vaccination (1st year of life) n=87; weighted n=81.1 (weight 0.41)

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	5.87	4-28/183	1.33	0.540	0.54 - 3.26
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	5.87	8-28/183	1.06	0.900	0.42 - 2.69
II: [4-7]	0.82	8-28/183	0.11	0.053	0.01 - 1.03
I+II: [0-7]	6.69	8-28/183	0.51	0.135	0.21 - 1.23

Table 29: Weighted SCCS analysis, relative risk of uSUD after hexavalent vaccination in cases with available information on sleeping position during the last 4 weeks (1st and 2nd year of life) n=84, weighted n=78.7 (weight 0.41)

Risk period[days]/ sleeping position	Number of cases in risk period	Number of cases in control period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days						
I: [0-3]/ all cases	6.46	72.23	4-28/183	1.91	0.140	0.81 - 4.53
I: [0-3]/ non prone	3.82	57.23	4-28/183	1.58	0.413	0.53 - 4.70
I: [0-3]/ prone	2.64	15	4-28/183	2.78	0.145	0.70 - 10.98
Model II: Risk period I and II versus control period 8-28/183 days						
I +II:[0-7]/ all cases	7.28	71.41	8-28/183	0.78	0.553	0.34 - 1.79
I +II:[0-7]/ non prone	4.64	56.41	8-28/183	0.69	0.480	0.25 - 1.92
I +II:[0-7]/ prone	2.64	15	8-28/183	0.99	0.986	0.25 - 3.89

Age classes >30 to 60 days and >60 to 91 days were combined. Age classes >274 days were combined.

Table 30: Weighted SCCS analysis, relative risk of uSUD after hexavalent vaccination in cases with available information onsleeping position during the last 4 weeks and maternal smoking (1st and 2nd year of life) n=84, weighted n=78.69 (weight=0.41)

Risk period[days]/presence of maternal smoking or prone sleeping position	Number of cases in risk period	Number of cases in control period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days						
I: [0-3]/ all cases	6.46	72.23	4-28/183	1.91	0.140	0.81 - 4.53
I: [0-3]/ No	1	30.41	4-28/183	0.94	0.954	0.12 - 7.28
I: [0-3]/ Yes	5.46	41.82	4-28/183	2.37	0.075	0.92 - 6.12
Model II: Risk period I and II versus control period 8-28/183 days						
I +II:[0-7]/ all cases	7.28	71.41	8-28/183	0.78	0.553	0.34 - 1.79
I +II:[0-7]/ No	1.41	30	8-28/183	0.48	0.420	0.08 - 2.83
I +II:[0-7]/ Yes	5.87	41.41	8-28/183	0.91	0.843	0.36 - 2.31

Age classes >30 to 60 days and >60 to 91 days were combined. Age classes >274 days were combined.

Table 31: Unweighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination (1st and 2nd year of life) n=112

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	15	4-28/183	2.98	0.001	1.61 - 5.52
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	15	8-28/183	2.63	0.003	1.40 - 4.97
II: [4-7]	3	8-28/183	0.40	0.130	0.12 - 1.31
I+II: [0-7]	18	8-28/183	1.33	0.345	0.74 - 2.39

Table 32: Unweighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination (1st year of life) n=98

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	13	4-28/183	2.56	0.005	1.32 - 4.93
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	13	8-28/183	2.23	0.021	1.13 - 4.40
II: [4-7]	3	8-28/183	0.40	0.132	0.12 - 1.32
I+II: [0-7]	16	8-28/183	1.17	0.627	0.63 - 2.18

Table 33: Unweighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination (2nd year of life) n=14

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	2	4-28/183	13.86	0.002	2.55 - 75.23
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	2	8-28/183	13.20	0.003	2.41 - 72.15
II: [4-7]	0	8-28/183	no estimate		
I+II: [0-7]	2	8-28/183	5.27	0.052	0.99 - 28.17

Table 34: Unweighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination in cases with available information on sleeping position during the last 4 weeks (1st and 2nd year of life) n=94

Risk period [days]/ sleeping position	Number of cases in risk period	Number of cases in control period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days						
I: [0-3]/ all cases	13	81	4-28/183	3.49	<0.001	1.81 -6.73
I: [0-3]/ non prone	7	65	4-28/183	2.61	0.026	1.12 - 6.08
I: [0-3]/ prone	6	16	4-28/183	5.91	0.001	2.12 - 16.44
Model II: Risk period I and II versus control period 8-28/183 days						
I +II:[0-7]/ all cases	15	79	8-28/183	1.52	0.197	0.8 - 2.86
I +II:[0-7]/ non prone	9	63	8-28/183	1.28	0.534	0.59 - 2.8
I +II:[0-7]/ prone	6	16	8-28/183	2.12	0.150	0.76 - 5.92

Age classes >30 to 60 days and >60 to 91 days were combined. Age classes >274 days were combined.

Table 35: Unweighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination in cases with available information on sleeping position during the last 4 weeks and maternal smoking (1st and 2nd year of life) n=94

Risk period[days]/ presence of maternal smoking or prone sleeping position	Number of cases in risk period	Number of cases in control period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days						
I: [0-3]/ all cases	13	81	4-28/183	3.49	<0.001	1.81 - 6.73
I: [0-3]/ No	2	35	4-28/183	1.63	0.521	0.37 - 7.18
I: [0-3]/ Yes	11	46	4-28/183	4.45	<0.001	2.15 - 9.23
Model II: Risk period I and II versus control period 8-28/183 days						
I +II:[0-7]/ all cases	15	79	8-28/183	1.52	0.197	0.80 - 2.86
I +II:[0-7]/ No	3	34	8-28/183	0.94	0.928	0.27 - 3.34
I +II:[0-7]/ Yes	12	45	8-28/183	1.80	0.108	0.88 - 3.69

Age classes >30 to 60 days and >60 to 91 days were combined.

Table 36: Weighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination (1st and 2nd year of life) n=112, weighted n=105.5

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	10.28	4-28/183	2.19	0.031	1.08 - 4.45
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	10.28	8-28/183	1.85	0.097	0.89 - 3.84
II: [4-7]	1.82	8-28/183	0.25	0.067	0.06 - 1.10
I+II: [0-7]	12.1	8-28/183	0.92	0.808	0.47 - 1.81

Table 37: Weighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination (1st year of life) n=98, weighted n=91.5

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	8.28	4-28/183	1.72	0.176	0.78 - 3.75
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	8.28	8-28/183	1.42	0.393	0.63 - 3.19
II: [4-7]	1.82	8-28/183	0.24	0.064	0.05 - 1.09
I+II: [0-7]	10.1	8-28/183	0.74	0.428	0.35 - 1.55

Table 38: Weighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination in cases for whom information about the usual sleeping position during the last 4 weeks was available (1st and 2nd year of life) n=94, weighted n=88.1 (weight: 0.41)

Risk period[days]/ sleeping position	Number of cases in risk period	Number of cases in control period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days						
I: [0-3]/ all cases	8.87	79.23	4-28/183	2.57	0.015	1.20 - 5.49
I: [0-3]/ non prone	5.82	63.23	4-28/183	2.34	0.070	0.93 - 5.85
I: [0-3]/ prone	3.05	16	4-28/183	3.17	0.082	0.86 - 11.63
Model II: Risk period I and II versus control period 8-28/183 days						
I +II:[0-7]/ all cases	9.69	78.41	8-28/183	1.01	0.980	0.48 - 2.13
I +II:[0-7]/ non prone	6.64	62.41	8-28/183	0.96	0.930	0.40 - 2.32
I +II:[0-7]/ prone	3.05	16	8-28/183	1.13	0.850	0.31 - 4.15

Age classes >30 to 60 days and >60 to 91 days were combined. Age classes >274 days were combined.

Table 39: Weighted SCCS analysis, relative risk of uSUD after hexa- or pentavalent vaccination in cases for whom information about the usual sleeping position during the last 4 weeks and maternal smoking was available (1st and 2nd year of life) n=94, weighted n=88.1 (weight: 0.41)

Risk period[days]/ presence of maternal smoking or prone sleeping position	Number of cases in risk period	Number of cases in control period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days						
I: [0-3]/ all cases	8.87	79.23	4-28/183	2.57	0.015	1.20 - 5.49
I: [0-3]/ No	2	34.41	4-28/183	1.73	0.471	0.39 - 7.67
I: [0-3]/ Yes	6.87	44.82	4-28/183	3.00	0.013	1.26 - 7.15
Model II: Risk period I and II versus control period 8-28/183 days						
I +II:[0-7]/ all cases	9.69	78.41	8-28/183	1.01	0.980	0.48 - 2.13
I +II:[0-7]/ No	2.41	34	8-28/183	0.76	0.696	0.19 - 3.04
I +II:[0-7]/ Yes	7.28	44.41	8-28/183	1.14	0.771	0.48 - 2.68

Age classes >30 to 60 days and >60 to 91 days were combined.

Table 40: Unweighted SCCS analysis, relative risk of uSUD after pentavalent vaccination (1st and 2nd year of life) n=14

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	4	4-28/183	9.08	0.003	2.17 - 37.96
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	4	8-28/183	10.51	0.002	2.32 - 47.54
II: [4-7]	1	8-28/183	2.14	0.508	0.23 - 20.29
I+II: [0-7]	5	8-28/183	5.75	0.016	1.38 - 23.97

Table 41: Weighted SCCS analysis, relative risk of uSUD after pentavalent vaccination (1st and 2nd year of life) n=14, weighted n=13.41

Risk period [days]	Cases in risk period	Control period [days]	Relative risk	p-value	95% CI
Model I: Risk period I versus control period 4-28/183 days					
I: [0-3]	3.41	4-28/183	8.11	0.006	1.81 - 36.24
Model II: Risk period I and II versus control period 8-28/183 days					
I: [0-3]	3.41	8-28/183	9.48	0.005	1.97 - 45.51
II: [4-7]	1	8-28/183	2.29	0.469	0.24 - 21.68
I+II: [0-7]	4.41	8-28/183	5.40	0.024	1.25 - 23.33

Table 42: Case-control analysis, characteristics of cases – part I

			Hexavalent vaccination within									
	Total		Risk period I		Risk period II		Risk period III		Control period or outside control period		No hexavalent vaccination	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	254		11		2		14		128		99	
Region of residence												
Eastern part of German	42	16.5%	1	9.1%	0	0.0%	1	7.1%	28	21.9%	12	12.1%
Western part of German	212	83.5%	10	90.9%	2	100.0%	13	92.9%	100	78.1%	87	87.9%
Gender												
Female	90	35.4%	3	27.3%	1	50.0%	3	21.4%	46	35.9%	37	37.4%
Male	164	64.6%	8	72.7%	1	50.0%	11	78.6%	82	64.1%	62	62.6%
Age [days]												
30.0 - 60	33	13.0%	1	9.1%	0	0.0%	0	0.0%	0	0.0%	32	32.3%
>60.0 - 91	42	16.5%	3	27.3%	0	0.0%	3	21.4%	2	1.6%	34	34.3%
>91.0 - 152	54	21.3%	6	54.5%	1	50.0%	4	28.6%	28	21.9%	15	15.2%
>152.0 - 183	16	6.3%	0	0.0%	0	0.0%	1	7.1%	12	9.4%	3	3.0%
>183.0 - 274	45	17.7%	0	0.0%	1	50.0%	4	28.6%	33	25.8%	7	7.1%
>274.0 - 365	25	9.8%	0	0.0%	0	0.0%	1	7.1%	21	16.4%	3	3.0%
>365.0 - 456	11	4.3%	1	9.1%	0	0.0%	0	0.0%	10	7.8%	0	0.0%
>456.0 - 730	28	11.0%	0	0.0%	0	0.0%	1	7.1%	22	17.2%	5	5.1%
Maternal age at birth												
0-20	37	14.6%	1	9.1%	1	50.0%	5	35.7%	18	14.1%	12	12.1%
21-25	67	26.4%	6	54.5%	0	0.0%	1	7.1%	35	27.3%	25	25.3%
26-30	48	18.9%	2	18.2%	1	50.0%	4	28.6%	19	14.8%	22	22.2%
>30	88	34.6%	2	18.2%	0	0.0%	3	21.4%	46	35.9%	37	37.4%
Missing	14	5.5%	0	0.0%	0	0.0%	1	7.1%	10	7.8%	3	3.0%
Number of siblings												
No sibling	89	35.0%	4	36.4%	1	50.0%	5	35.7%	46	35.9%	33	33.3%
1-2 sibling(s)	115	45.3%	6	54.5%	1	50.0%	6	42.9%	52	40.6%	50	50.5%
≥3 siblings	26	10.2%	0	0.0%	0	0.0%	1	7.1%	16	12.5%	9	9.1%
Missing	24	9.4%	1	9.1%	0	0.0%	2	14.3%	14	10.9%	7	7.1%
Maternal smoking (current)												
Yes	120	47.2%	7	63.6%	1	50.0%	6	42.9%	57	44.5%	49	49.5%
No	118	46.5%	4	36.4%	1	50.0%	6	42.9%	61	47.7%	46	46.5%
Missing	16	6.3%	0	0.0%	0	0.0%	2	14.3%	10	7.8%	4	4.0%
Smoking during pregnancy												
Yes	96	37.8%	4	36.4%	1	50.0%	3	21.4%	46	35.9%	42	42.4%
No	131	51.6%	6	54.5%	1	50.0%	9	64.3%	67	52.3%	48	48.5%
Missing	26	10.2%	1	9.1%	0	0.0%	2	14.3%	15	11.7%	9	9.1%
Breast feeding (ever)												
Yes	133	52.4%	5	45.5%	1	50.0%	6	42.9%	69	53.9%	52	52.5%
No	91	35.8%	5	45.5%	1	50.0%	6	42.9%	43	33.6%	36	36.4%
Missing	30	11.8%	1	9.1%	0	0.0%	2	14.3%	16	12.5%	11	11.1%
Gestational age <38 wks												
Yes	59	23.2%	3	27.3%	0	0.0%	1	7.1%	29	22.7%	26	26.3%
No	194	76.4%	8	72.7%	2	100.0%	12	85.7%	99	77.3%	73	73.7%
Missing	1	0.4%	0	0.0%	0	0.0%	1	7.1%	0	0.0%	0	0.0%

Table 43: Case-control analysis, characteristics of controls – part I

			Hexavalent vaccination within									
	Total		Risk period I		Risk period II		Risk period III		Control period or outside control period		No hexavalent vaccination	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	1180		34		49		60		585		452	
Region of residence												
Eastern part of German	367	31.1%	12	35.3%	22	44.9%	16	26.7%	209	35.7%	108	23.9%
Western part of German	813	68.9%	22	64.7%	27	55.1%	44	73.3%	376	64.3%	344	76.1%
Gender												
Female	567	48.1%	11	32.4%	28	57.1%	27	45.0%	299	51.1%	202	44.7%
Male	613	51.9%	23	67.6%	21	42.9%	33	55.0%	286	48.9%	250	55.3%
Age [days]												
30.0 - 60	139	11.8%	0	0.0%	0	0.0%	0	0.0%	1	0.2%	138	30.5%
>60.0 - 91	153	13.0%	11	32.4%	8	16.3%	9	15.0%	9	1.5%	116	25.7%
>91.0 - 152	258	21.9%	12	35.3%	25	51.0%	32	53.3%	96	16.4%	93	20.6%
>152.0 - 183	90	7.6%	5	14.7%	3	6.1%	8	13.3%	58	9.9%	16	3.5%
>183.0 - 274	227	19.2%	4	11.8%	8	16.3%	9	15.0%	169	28.9%	37	8.2%
>274.0 - 365	119	10.1%	1	2.9%	2	4.1%	0	0.0%	94	16.1%	22	4.9%
>365.0 - 456	44	3.7%	0	0.0%	1	2.0%	0	0.0%	35	6.0%	8	1.8%
>456.0 - 730	150	12.7%	1	2.9%	2	4.1%	2	3.3%	123	21.0%	22	4.9%
Maternal age at birth												
0-20	23	1.9%	0	0.0%	2	4.1%	2	3.3%	13	2.2%	6	1.3%
21-25	181	15.3%	3	8.8%	8	16.3%	14	23.3%	95	16.2%	61	13.5%
26-30	336	28.5%	11	32.4%	17	34.7%	11	18.3%	174	29.7%	123	27.2%
>30	639	54.2%	20	58.8%	22	44.9%	33	55.0%	303	51.8%	261	57.7%
Missing	1	0.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.2%
Number of siblings												
No sibling	585	49.6%	18	52.9%	25	51.0%	29	48.3%	305	52.1%	208	46.0%
1-2 sibling(s)	544	46.1%	13	38.2%	21	42.9%	28	46.7%	253	43.3%	229	50.7%
≥3 siblings	46	3.9%	3	8.8%	3	6.1%	3	5.0%	23	3.9%	14	3.1%
Missing	5	0.4%	0	0.0%	0	0.0%	0	0.0%	4	0.7%	1	0.2%
Maternal smoking (current)												
Yes	237	20.1%	6	17.6%	14	28.6%	19	31.7%	117	20.0%	81	17.9%
No	936	79.3%	27	79.4%	35	71.4%	41	68.3%	464	79.3%	369	81.6%
Missing	7	0.6%	1	2.9%	0	0.0%	0	0.0%	4	0.7%	2	0.4%
Smoking during pregnancy												
Yes	177	15.0%	5	14.7%	9	18.4%	16	26.7%	88	15.0%	59	13.1%
No	995	84.3%	29	85.3%	40	81.6%	44	73.3%	491	83.9%	391	86.5%
Missing	8	0.7%	0	0.0%	0	0.0%	0	0.0%	6	1.0%	2	0.4%
Breast feeding (ever)												
Yes	988	83.7%	31	91.2%	41	83.7%	52	86.7%	483	82.6%	381	84.3%
No	184	15.6%	3	8.8%	8	16.3%	8	13.3%	95	16.2%	70	15.5%
Missing	8	0.7%	0	0.0%	0	0.0%	0	0.0%	7	1.2%	1	0.2%
Gestational age <38 weeks												
Yes	135	11.4%	3	8.8%	5	10.2%	5	8.3%	67	11.5%	55	12.2%
No	1029	87.2%	31	91.2%	44	89.8%	53	88.3%	508	86.8%	393	86.9%
Missing	16	1.4%	0	0.0%	0	0.0%	2	3.3%	10	1.7%	4	0.9%

Table 44: Case-control analysis, characteristics of cases – part II

			Hexavalent vaccination within									
	Total		Risk period I		Risk period II		Risk period III		Control period or outside control period		No hexavalent vaccination	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	254		11		2		14		128		99	
Maternal education												
Low	96	37.8%	7	63.6%	2	100.0%	5	35.7%	45	35.2%	37	37.4%
Medium	84	33.1%	3	27.3%	0	0.0%	6	42.9%	44	34.4%	31	31.3%
High	55	21.7%	1	9.1%	0	0.0%	1	7.1%	28	21.9%	25	25.3%
Missing	19	7.5%	0	0.0%	0	0.0%	2	14.3%	11	8.6%	6	6.1%
Family status												
Both parents	200	78.7%	9	81.8%	1	50.0%	9	64.3%	97	75.8%	84	84.8%
Single parent with new partner	10	3.9%	0	0.0%	1	50.0%	0	0.0%	5	3.9%	4	4.0%
Single parent	26	10.2%	2	18.2%	0	0.0%	3	21.4%	15	11.7%	6	6.1%
Missing	18	7.1%	0	0.0%	0	0.0%	2	14.3%	11	8.6%	5	5.1%
Every vaccination												
No vaccination	79	31.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	79	79.8%
Risk I	17	6.7%	11	100.0%	0	0.0%	0	0.0%	1	50.0%	5	5.1%
Risk II	4	1.6%	0	0.0%	2	100.0%	0	0.0%	1	50.0%	1	1.0%
Risk III	17	6.7%	0	0.0%	0	0.0%	14	100.0%	0	0.0%	3	3.0%
Control period or outside	137	53.9%	0	0.0%	0	0.0%	0	0.0%	126	98.4%	11	11.1%
Favorite position when put to sleep (last 4 weeks)												
Supine	123	48.4%	3	27.3%	1	50.0%	9	64.3%	68	53.1%	42	42.4%
Prone or varying including prone	54	21.3%	5	45.5%	0	0.0%	1	7.1%	23	18.0%	25	25.3%
Side	22	8.7%	1	9.1%	1	50.0%	1	7.1%	12	11.8%	7	7.1%
Varying but never prone	11	4.3%	1	9.1%	0	0.0%	0	0.0%	4	3.9%	6	6.1%
Missing	44	17.3%	1	9.1%	0	0.0%	3	21.4%	21	16.4%	19	19.2%
Position put to last sleep												
Supine	122	48.0%	3	27.3%	1	50.0%	7	50.0%	78	60.9%	33	33.3%
Prone	54	21.3%	6	54.5%	0	0.0%	2	14.3%	18	14.1%	28	28.3%
Side	32	12.6%	0	0.0%	1	50.0%	2	14.3%	11	8.6%	18	18.2%
Missing	46	18.1%	2	18.2%	0	0.0%	3	21.4%	21	16.4%	20	20.2%
Position when found dead												
Supine	59	23.2%	3	27.3%	1	50.0%	5	35.7%	28	21.9%	22	22.2%
Prone	137	53.9%	7	63.6%	1	50.0%	6	42.9%	74	57.8%	49	49.5%
Side	12	4.7%	0	0.0%	0	0.0%	0	0.0%	6	4.7%	6	6.1%
Other	1	0.4%	0	0.0%	0	0.0%	0	0.0%	1	0.8%	0	0.0%
Missing	45	17.7%	1	9.1%	0	0.0%	3	21.4%	19	14.8%	22	22.2%
Only cases who died in their 1st year of life:												
Favorite position when put to sleep (last 4 weeks)												
Total	215		10		2		13		96		94	
Supine	94	43.7%	2	20.0%	1	50.0%	8	61.5%	44	45.8%	39	41.5%
Prone or varying including prone	51	23.7%	5	50.0%	1	50.0%	1	7.7%	21	21.9%	24	25.5%
Side	22	10.2%	1	10.0%	0	0.0%	1	7.7%	12	12.5%	7	7.4%
Varying but never prone	10	4.7%	1	10.0%	0	0.0%	0	0.0%	3	3.1%	6	6.4%
Missing	38	17.7%	1	10.0%	0	0.0%	3	23.1%	16	16.7%	18	19.1%

Table 45: Case-control analysis, characteristics of controls – part II

			Hexavalent vaccination within									
	Total		Risk period I		Risk period II		Risk period III		Control period or outside control period		No hexavalent vaccination	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Total	1180		34		49		60		585		452	
Maternal education												
Low	156	13.2%	4	11.8%	5	10.2%	9	15.0%	83	14.0%	56	12.4%
Medium	505	42.8%	13	38.2%	21	42.9%	33	55.0%	264	45.1%	174	38.5%
High	513	43.5%	17	50.0%	22	44.9%	18	30.0%	236	40.3%	220	48.7%
Missing	6	0.0%	0	0.0%	1	2.0%	0	0.0%	3	0.5%	2	0.4%
Family status												
Both parents	1085	92.0%	31	91.2%	42	85.7%	52	86.7%	535	91.5%	425	94.0%
Single parent with new partner	12	1.0%	1	2.9%	0	0.0%	0	0.0%	8	1.4%	3	0.7%
Single parent	80	6.8%	2	5.9%	7	14.3%	8	13.3%	41	7.0%	22	4.9%
Missing	3	0.3%	0	0.0%	0	0.0%	0	0.0%	1	0.2%	2	0.4%
Every vaccination												
No vaccination	346	29.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	346	76.5%
Risk I	45	3.8%	34	100.0%	0	0.0%	0	0.0%	6	1.0%	5	1.1%
Risk II	66	5.6%	0	0.0%	49	100.0%	0	0.0%	10	1.7%	7	1.5%
Risk III	85	7.2%	0	0.0%	0	0.0%	60	100.0%	13	2.2%	12	2.7%
Control period or outside	638	54.1%	0	0.0%	0	0.0%	0	0.0%	556	95.0%	82	18.1%
Only prospective controls:												
Total	783		20		32		43		345		343	
Favorite position when put to sleep (last 4 weeks)												
Supine	560	71.5%	13	65.0%	21	65.6%	33	76.7%	259	75.1%	234	68.2%
Prone or varying including prone	63	8.0%	0	0.0%	1	3.1%	2	4.7%	24	7.0%	36	10.5%
Side	118	15.1%	5	25.0%	8	25.0%	7	16.3%	47	13.6%	51	14.9%
Varying but never prone	37	4.7%	2	10.0%	2	6.3%	1	2.3%	14	4.1%	18	5.2%
Missing	5	0.6%	0	0.0%	0	0.0%	0	0.0%	1	0.3%	4	1.2%
Position put to reference sleep												
Supine												
Prone							Not available					
Side												
Missing												
Position when awoke after reference sleep												
Supine												
Prone												
Side							Not available					
Other												
Missing												
Only prospective controls in their 1st year of life:												
Favorite position when put to sleep (last 4 weeks)												
Total	671		20		31		42		255		323	
Supine	483	72.0%	13	65.0%	20	64.5%	32	76.2%	200	78.4%	218	67.5%
Prone or varying including prone	50	7.5%	0	0.0%	1	3.2%	2	4.8%	12	4.7%	35	10.8%
Side	100	14.9%	5	25.0%	8	25.8%	7	16.7%	32	12.6%	48	14.9%
Varying but never prone	33	4.9%	2	10.0%	2	6.5%	1	2.4%	10	3.9%	18	5.6%
Missing	5	0.7%	0	0.0%	0	0.0%	0	0.0%	1	0.4%	4	1.2%

Table 46: Case-control analysis, characteristics of hexavalently versus pentavalently vaccinated cases and controls

	Cases				Controls			
	Vaccinated with				Vaccinated with			
	Hexavalent vaccine		Pentavalent vaccine		Hexavalent vaccine		Pentavalent vaccine	
	n	%	n	%	n	%	n	%
Total	155	89.1%	19	10.9% of vaccinated cases	728	89.2%	88	10.8% of vaccinated controls
Region of residence								
Eastern part of Germany	30	19.4%	4	21.1%	259	35.6%	25	28.4%
Western part of Germany	125	80.6%	15	78.9%	469	64.4%	63	71.6%
Gender								
female	53	34.2%	4	21.1%	365	50.1%	40	45.5%
male	102	65.8%	15	78.9%	363	49.9%	48	54.5%
Age [days]								
30.0 - 60	1	0.6%	0	0.0%	1	0.1%	0	0.0%
>60.0 - 91	8	5.2%	2	10.5%	37	5.1%	1	1.1%
>91.0 - 152	39	25.2%	3	15.8%	165	22.7%	23	26.1%
>152.0 - 183	13	8.4%	1	5.3%	74	10.2%	8	9.1%
>183.0 - 274	38	24.5%	5	26.3%	190	26.1%	24	27.3%
>274.0 - 365	22	14.2%	3	15.8%	97	13.3%	14	15.9%
>365.0 - 456	11	7.1%	0	0.0%	36	4.9%	3	3.4%
>456.0 - 730	23	14.8%	5	26.3%	128	17.6%	15	17.0%
Maternal age at birth								
0-20	25	16.1%	2	10.5%	17	2.3%	0	0.0%
21-25	42	27.1%	5	26.3%	120	16.5%	10	11.4%
26-30	26	16.8%	4	21.1%	213	29.3%	22	25.0%
>30	51	32.9%	8	42.1%	378	51.9%	55	62.5%
Missing	11	7.1%	0	0.0%	0	0.0%	1	1.1%
Number of siblings								
No sibling	56	36.1%	9	47.4%	377	51.8%	47	53.4%
1-2 sibling(s)	65	41.9%	6	31.6%	315	43.3%	40	45.5%
≥3 siblings	17	11.0%	4	21.1%	32	4.4%	0	0.0%
Missing	17	11.0%	0	0.0%	4	0.5%	1	1.1%
Maternal smoking (current)								
Yes	71	45.8%	5	26.3%	156	21.4%	14	15.9%
No	72	46.5%	13	68.4%	567	77.9%	73	83.0%
Missing	12	7.7%	1	5.3%	5	0.7%	1	1.1%
Smoking during pregnancy								
Yes	54	34.8%	3	15.8%	118	16.2%	5	5.7%
No	83	53.5%	15	78.9%	604	83.0%	82	93.2%
Missing	18	11.6%	1	5.3%	6	0.8%	1	1.1%
Breast feeding (ever)								
Yes	81	52.3%	16	84.2%	607	83.4%	78	88.6%
No	55	35.5%	3	15.8%	114	15.7%	9	10.2%
Missing	19	12.3%	0	0.0%	7	1.0%	1	1.1%
Gestational age <38 wks								
Yes	33	21.3%	5	26.3%	80	11.0%	12	13.6%
No	121	78.1%	14	73.7%	636	87.4%	75	85.2%
Missing	1	0.6%	0	0.0%	12	1.6%	1	1.1%
Maternal education								
Low	59	38.1%	5	26.3%	100	13.7%	9	10.2%
Medium	53	34.2%	7	36.8%	331	45.5%	24	27.3%
High	30	19.4%	5	26.3%	293	40.2%	54	61.4%
Missing	13	8.4%	2	10.5%	4	0.5%	1	1.1%
Family status								
Both parents	116	74.8%	18	94.7%	660	90.7%	83	94.3%
Single parent with new partner	6	3.9%	0	0.0%	9	1.2%	1	1.1%
Single parent	20	12.9%	1	5.3%	58	8.0%	3	3.4%
Missing	13	8.4%	0	0.0%	1	0.1%	1	1.1%
All cases and only prospective controls								
Favorite position when put to sleep (last 4 wks)								
Supine	81	52.3%	11	57.9%	326	74.1%	43	74.1%
Prone or varying including prone	29	18.7%	3	15.8%	27	6.1%	3	5.2%
Side	15	9.7%	1	5.3%	67	15.2%	9	15.5%
Varying but never prone	5	3.2%	0	0.0%	19	4.3%	3	5.2%
Missing	25	16.1%	4	21.1%	1	0.2%	0	0.0%

Table 47: Unweighted case-control analysis of any vaccination within last 72 hours, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 72 hours										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
No vaccination (reference)	237	93.31	1135	96.19						
Vaccination ≤ 72 hours	17	6.69	45	3.81	**1.68**	(0.89 - 3.15)	0.110	**1.67**	(0.71 - 3.91)	0.238
1st year of life										
No vaccination (reference)	200	93.02	946	95.94						
Vaccination ≤ 72 hours**	15	6.98	40	4.06	**1.58**	(0.81 - 3.07)	0.176	**1.49**	(0.57 - 3.90)	0.412
2nd year of life										
No vaccination (reference)	37	94.87	189	97.42						
Vaccination ≤ 72 hours***	2	5.13	5	2.58	**3.13**	(0.40 - 24.58)	0.277			

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Multivariate analysis is based on a lower number of cases. Only those cases and controls are included for whom all categories were calculable.
*** Multivariate estimate not calculated due to the low number of cases.

Table 48: Unweighted case-control analysis of any vaccination within last 7 days, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 7 days										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
No vaccination (reference)	233	91.73	1069	90.59						
Vaccination ≤ 7 days	21	8.27	111	9.41	**0.86**	(0.51 - 1.46)	0.579	**0.95**	(0.48 - 1.88)	0.873
1st year of life										
No vaccination (reference)	197	91.63	891	90.37						
Vaccination ≤ 7 days**	18	8.37	95	9.63	**0.83**	(0.47 - 1.45)	0.508	**0.83**	(0.40 - 1.73)	0.622
2nd year of life										
No vaccination (reference)	36	92.31	178	91.75						
Vaccination ≤ 7 days***	3	7.69	16	8.25	**1.14**	(0.28 - 4.67)	0.851			

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Multivariate analysis is based on a lower number of cases. Only those cases and controls are included for whom all categories were calculable.
*** Multivariate estimate not calculated due to the low number of cases.

Table 49: Weighted case-control analysis of any vaccination within last 72 hours, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 72 hours										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
No vaccination (reference)	234.6	95.03	1097.2	96.16						
Vaccination ≤ 72 hours	12.3	4.97	43.8	3.84	**1.18**	(0.58 - 2.40)	0.651	**1.28**	(0.50 - 3.28)	0.604
1st year of life										
No vaccination (reference)	197.6	95.06	908.2	95.90						
Vaccination ≤ 72 hours**	10.3	4.94	38.8	4.10	**1.06**	(0.49 - 2.26)	0.885	**1.06**	(0.36 - 3.16)	0.918
2nd year of life										
No vaccination (reference)	37	94.87	189	97.42						
Vaccination ≤ 72 hours***	2	5.13	5	2.58	**3.13**	(0.40 - 24.58)	0.277			

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Multivariate analysis is based on a lower number of cases. Only those cases and controls are included for whom all categories were calculable.
*** Multivariate estimate not calculated due to the low number of cases

Table 50: Weighted case-control analysis of any vaccination within last 7 days, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 7 days										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
No vaccination (reference)	231.8	93.88	1033.6	90.58						
Vaccination ≤ 7 days	15.1	6.12	107.5	9.42	**0.60**	(0.33 - 1.10)	0.100	**0.70**	(0.33 - 1.51)	0.364
1st year of life										
No vaccination (reference)	195.8	94.18	855.6	90.34						
Vaccination ≤ 7 days**	12.1	5.82	91.5	9.66	**0.54**	(0.27 - 1.04)	0.067	**0.46**	(0.18 - 1.16)	0.100
2nd year of life										
No vaccination (reference)	36	92.31	178	91.75						
Vaccination ≤ 7 days***	3	7.69	16	8.25	**1.14**	(0.28 - 4.67)	0.851			

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** This multivariate model was only calculable without the covariables 'siblings' and 'gestational age'
*** Multivariate estimate not calculated due to the low number of cases.

Table 51: Unweighted case-control analysis of hexavalent or non-hexavalent vaccination within last 72 hours, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 72 hours										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
No vaccination (reference)	237	93.31	1135	96.19						
Hexavalent vaccination ≤ 72 hours	11	4.33	34	2.88	**1.54**	(0.73 - 3.23)	0.256	**1.51**	(0.56 - 4.07)	0.418
Non- hexavalent vaccination ≤ 72 hours	6	2.36	11	0.93	**2.06**	(0.69 - 6.10)	0.193	**2.12**	(0.51 - 8.79)	0.301
1st year of life										
No vaccination (reference)	200	93.02	946	95.94						
Hexavalent vaccination ≤ 72 hours**	10	4.65	33	3.35	**1.42**	(0.65 - 3.06)	0.377	**1.15**	(0.38 - 3.41)	0.808
Non- hexavalent vaccination ≤ 72 hours**	5	2.33	7	0.71	**2.19**	(0.63 - 7.59)	0.217	**3.81**	(0.60 - 24.18)	0.156
2nd year of life										
No vaccination (reference)	37	94.87	189	97.42						
Hexavalent vaccination ≤ 72 hours***	1	2.56	1	0.52	**7.38**	(0.30 - 179.91)	0.220			
Non- hexavalent vaccination ≤ 72 hours***	1	2.56	4	2.06	**2.40**	(0.23 - 24.64)	0.463			

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Multivariate analysis is based on a lower number of cases. Only those cases and controls are included for whom all categories were calculable.
*** Multivariate estimate not calculated due to the low number of cases

Table 52: Unweighted case-control analysis of hexavalent or non-hexavalent vaccination within last 7 days, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 7 days										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
No vaccination (reference)	233	91.73	1069	90.59						
Hexavalent vaccination ≤ 7 days	13	5.12	83	7.03	**0.74**	(0.39 - 1.39)	0.348	**0.79**	(0.35 - 1.78)	0.567
Non- hexavalent vaccination ≤ 7 days	8	3.15	28	2.37	**1.21**	(0.52 - 2.84)	0.658	**1.45**	(0.47 - 4.50)	0.523
1st year of life										
No vaccination (reference)	197	91.63	891	90.37						
Hexavalent vaccination ≤ 7 days	12	5.58	79	8.01	**0.70**	(0.36 - 1.35)	0.286	**0.62**	(0.26 - 1.49)	0.283
Non- hexavalent vaccination ≤ 7 days	6	2.79	16	1.62	**1.40**	(0.50 - 3.90)	0.519	**1.42**	(0.31 - 6.60)	0.655
2nd year of life										
No vaccination (reference)	36	92.31	178	91.75						
Hexavalent vaccination ≤ 7 days**	1	2.56	4	2.06	**2.14**	(0.17 - 26.41)	0.554			
Non- hexavalent vaccination ≤ 7 days**	2	5.13	12	6.19	**0.98**	(0.20 - 4.72)	0.981			

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Multivariate estimate not calculated due to the low number of cases.

Table 53: Weighted case-control analysis of hexavalent and non-hexavalent vaccination within last 72 hours, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 72 hours										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
No vaccination (reference)	234.6	95.03	1097.2	96.16						
Hexavalent vaccination ≤ 72 hours	6.9	2.78	32.8	2.88	**0.97**	(0.40 - 2.35)	0.954	**1.11**	(0.36 - 3.43)	0.852
Non- hexavalent vaccination ≤ 72 hours	5.4	2.19	11.0	0.96	**1.70**	(0.55 - 5.27)	0.355	**1.72**	(0.38 - 7.71)	0.481
1st year of life										
No vaccination (reference)	197.6	95.06	908.2	95.90						
Hexavalent vaccination ≤ 72 hours	5.9	2.82	31.8	3.36	**0.84**	(0.33 - 2.16)	0.723	**0.75**	(0.21 - 2.72)	0.665
Non- hexavalent vaccination ≤ 72 hours**	4.4	2.12	7.0	0.74	**1.76**	(0.48 - 6.41)	0.392	**3.10**	(0.42 - 22.61)	0.265
2nd year of life										
No vaccination (reference)	37	94.87	189	97.42						
Hexavalent vaccination ≤ 72 hours***	1	2.56	1	0.52	**7.38**	(0.30 - 179.91)	0.220			
Non- hexavalent vaccination ≤ 72 hours***	1	2.56	4	2.06	**2.40**	(0.23 - 24.64)	0.463			

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Multivariate analyses are based on a lower number of cases. Only those cases and controls are included for whom all categories were calculable.
*** Multivariate estimate not calculated due to the low number of cases.

Table 54: Weighted case-control analysis of hexavalent and non-hexavalent vaccination within last 7 days, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 7 days										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
No vaccination (reference)	231.8	93.88	1033.6	90.58						
Hexavalent vaccination ≤ 7 days	7.7	3.11	80.1	7.02	**0.44**	(0.20 - 0.96)	0.038	**0.53**	(0.20 - 1.37)	0.189
Non- hexavalent vaccination ≤ 7 days	7.4	3.00	27.4	2.40	**1.06**	(0.44 - 2.57)	0.897	**1.22**	(0.37 - 4.02)	0.739
1st year of life										
No vaccination (reference)	197.6	95.06	908.2	95.90						
Hexavalent vaccination ≤ 7 days**	5.9	2.82	31.8	3.36	**0.39**	(0.17 - 0.90)	0.027	**0.36**	(0.12 - 1.05)	0.062
Non- hexavalent vaccination ≤ 7 days**	4.4	2.12	7.0	0.74	**1.17**	(0.40 - 3.46)	0.773	**1.06**	(0.20 - 5.63)	0.949
2nd year of life										
No vaccination (reference)	36	92.31	178	91.75						
Hexavalent vaccination ≤ 7 days***	1	2.56	4	2.06	**2.14**	(0.17 - 26.41)	0.554			
Non- hexavalent vaccination ≤ 7 days***	2	5.13	12	6.19	**0.98**	(0.20 - 4.72)	0.981			

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Multivariate analyses are based on a lower number of cases. Only those cases and controls are included for whom all categories were calculable.
*** Multivariate estimate not calculated due to the low number of cases.

Table 55: Unweighted case-control analysis of pentavalent and non -pentavalent vaccination, number (percentage), univariate and multivariate odds ratios

Number (percentage), uni- and multivariate odds ratios										
Variable	Cases n=254	(%)	Controls n=1080	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
Any age, vaccination ≤ 72 hours										
None (Reference)	237	93.31	1135	96.19						
Pentavalent**	4	1.57	2	0.17	**7.89**	(1.33 - 46.77)	0.023			
Non-pentavalent	13	5.12	43	3.64	**1.33**	(0.66 - 2.68)	0.427	**1.07**	(0.41 - 2.78)	0.889
Any age, vaccination ≤ 7 days										
None (Reference)	233	91.73	1069	90.59						
Pentavalent**	5	1.97	6	0.51	**3.24**	(0.93 - 11.22)	0.064			
Non-pentavalent	16	6.30	105	8.90	**0.70**	(0.39 - 1.25)	0.225	**0.72**	(0.33 - 1.53)	0.390

* 'Univariate' OR are adjusted for oversampling of control children living in the eastern part of Germany
** Multivariate estimate not calculated due to the low number of cases

Table 56: Weighted case-control analysis of pentavalent and non-pentavalent vaccination , number (percentage), univariate and multivariate odds ratios

Number (percentage), uni- and multivariate odds ratios										
Variable	Cases n=254	(%)	Controls n=1080	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
Any age, vaccination ≤ 72 hours										
None (Reference)	234.6	95.03	1097.2	96.16						
Pentavalent**	3.4	1.38	2.0	0.18	**6.16**	(0.98 - 38.85)	0.053			
Non-pentavalent	8.9	3.59	41.8	3.67	**0.88**	(0.39 - 1.99)	0.765	**0.78**	(0.27 - 2.28)	0.647
Any age, vaccination ≤ 7 days										
None (Reference)	231.8	93.88	1033.6	90.58						
Pentavalent**	4.4	1.79	6.0	0.53	**2.66**	(0.73 - 9.67)	0.138			
Non-pentavalent	10.7	4.33	101.5	8.89	**0.45**	(0.22 - 0.91)	0.025	**0.50**	(0.21 - 1.21)	0.124

* 'Univariate' OR are adjusted for oversampling of control children living in the eastern part of Germany
** Multivariate estimate not calculated due to the low number of cases

Table 57: Unweighted case-control analysis of ever vaccinated versus never vaccinated, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 72 hours										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
Never vaccinated (reference)	79	31.10	346	29.32						
Ever vaccinated	175	68.90	834	70.68	**1.37**	(0.84 - 2.23)	0.210	**1.78**	(0.93 - 3.41)	0.084
1st year of life**										
Never vaccinated (reference)	79	36.74	342	34.69						
Ever vaccinated	136	63.26	644	65.31	**1.33**	(0.81 - 2.18)	0.257	**1.34**	(0.70 - 2.53)	0.376
2nd year of life										
Never vaccinated (reference)	0	0.0	4	2.06	uncalculable			uncalculable		
Ever vaccinated	39	100.0	190	97.94						

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Model was only calculable without the variables 'sibling' and 'gestational age'.

Table 58: Weighted case-control analysis of ever vaccinated versus never vaccinated, number (percentage), univariate and multivariate odds ratios

Number (percentage), univariate and multivariate odds ratios for vaccination within last 72 hours										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95% CI)	p-value	Multivariate OR	(95% CI)	p-value
All ages										
Never vaccinated (reference)	78.4	31.76	330.1	28.93						
Ever vaccinated	168.5	68.24	811.0	71.07	**1.20**	(0.73 - 1.97)	0.479	**1.58**	(0.81 - 3.07)	0.181
1st year of life**										
Never vaccinated (reference)	78.4	37.71	326.1	34.43						
Ever vaccinated	129.5	62.29	621.0	65.57	**1.16**	(0.70 - 1.92)	0.568	**1.20**	(0.60 - 2.40)	0.613
2nd year of life										
Never vaccinated (reference)	0	0.0	4	2.06	uncalculable			uncalculable		
Ever vaccinated	39	100.0	190	97.94						

* 'Univariate' ORs are adjusted for oversampling of control children living in the eastern part of Germany.
** Model was only calculable without the variables 'sibling' and 'gestational age'

Table 59: Pathological study part: Underlying cause of death and mean age of children at death

Underlying cause of death	2nd to 9th month of life		10th to 24th month of life	
	n	Mean age [months]	n	Mean age [months]
SIDS (R95)	6	4.3	0	-
Unknown (R96-99)	3	2.5	18	16.0
Explained	3	4	13	15.8
Total	12	-	31	-

Table 60: Pathological study part: Brain weight as percent of body weight in vaccinated children

No	Brain weight [g]	Age in months	Gender	Body weight [g]	Brain weight as percent of body weight
1	1560*	2	male	5580	28%
2	580	2	female	6800	9%
3	632	2	male	6200	10%
4	630	2	female	4500	14%
5	562	3	female	4510	12%
6	711	3	male	5923	12%
8	660	3	female	5700	12%
9	720	4	male	5600	13%
10	790	4	female	6300	13%
11	1050	7	male	8030	13%
12	920	8	male	6570	14%
13	985	11	female	10700	9%
14	570	13	male	6780	8%

* As no very severe brain oedema or other abnormalities were noted, this result was judged to likely be a documentation error.

Table 61: Pathological study part: Brain weight as percent of body weight in unvaccinated children

No	Brain weight	Age in months	Gender	Body weight	Brain weight as percent of body weight
1	986	10	male	10000	10%
2	980	11	male	11200	9%
3	800	11	female	8500	9%
5	1310	12	male	11500	11%
6	1035	12	male	8000	13%
7	985	13	male	8100	12%
8	833	13	female	6800	12%
9	900	13	female	11200	8%
10	1235	13	male	10300	12%
11	570	14	female	6780	8%
12	970	13	female	11900	8%
13	1100	13	female	11230	10%
14	1184	14	male	10000	12%
15	1130	16	female	8600	13%
16	1135	16	male	11000	10%
17	1165	16	male	11000	11%
18	1170	17	male	10000	12%
19	840	18	female	6430	13%
20	1340	19	male	13400	10%
21	555	20	male	9200	6%
22	1360	20	male	11500	12%
23	1295	20	male	12585	10%
24	1120	22	female	10000	11%
25	930	23	female	13200	7%

9. List of abbreviations

CI	Confidence interval
CHMP	Committee for Medical Products for Human Use
CRC	Capture-recapture
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DTP	diphtheria-tetanus-pertussis vaccine
EMEA	European Agency for the Evaluation of Medicinal Products
GeSID	German study on sudden infant death
ICD	International Classification of Diseases
IFSG	Infektionsschutzgesetz - Act on the Prevention and Control of Infectious Diseases in Man
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland - German Health Interview and Examination Survey for Children and Adolescents
LHA	Gesundheitsamt - Local Health Authority
LMU	Institut für Soziale Pädiatrie der Ludwig-Maximilians-Universität München
MHH	Institut für Biometrie Medizinische Hochschule Hannover
NRQ	Non-response questionnaire
OR	Odds ratio
PEI	Paul-Ehrlich-Institute
RKI	Robert Koch Institute
RR	Relative risk
SCCS	Self controlled case series
SIDS	Sudden infant death syndrome
SMR	Standardised mortality ratio
STIKO	Ständige Impfkommission - German Standing Vaccination Committee
SUD	Sudden unexpected death
SUDI	Sudden unexpected death in infancy
uSUD	Unexplained sudden unexpected death
UCD	Underlying cause of death

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Appendix tables (Tables not included in main text of study report)

Appendix Table 1: Any vaccination, unweighted case-control analysis: Uni- and multivariate odds ratios for any vaccination within 72 hours

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination										
none (Reference)	237	93.31	1135	96.19						
Vaccination ≤ 72 hours	17	6.69	45	3.81	**1.68**	(0.89 - 3.15)	0.110	**1.67**	(0.71 - 3.91)	0.238
Region of residence										
Eastern part of Germany (Reference)	42	16.54	367	31.10						
Western part of Germany	212	83.46	813	68.90	2.85	(1.91 - 4.27)	<0.0005	2.65	(1.61 - 4.37)	<0.0005
Gender										
female (Reference)	90	35.43	567	48.05						
male	164	64.57	613	51.95	1.76	(1.31 - 2.37)	<0.0005	2.04	(1.39 - 2.99)	<0.0005
Maternal age (years)										
26-30 (Reference)	48	18.90	336	28.47						
0-20	37	14.57	23	1.95	12.20	(6.25 - 23.83)	<0.0005	10.62	(4.56 - 24.73)	<0.0005
21-25	67	26.38	181	15.34	2.80	(1.79 - 4.36)	<0.0005	2.87	(1.70 - 4.85)	<0.0005
>30	88	34.65	639	54.15	0.85	(0.57 - 1.27)	0.430	0.83	(0.52 - 1.33)	0.433
Missing	14	5.51	1	0.08	107.46	(13.40 - 861.57)	<0.0005	1.70	(0.01 - 219.32)	0.830
Number of siblings										
No sibling (Reference)	89	35.04	585	49.58						
1-2 sibling(s)	115	45.28	544	46.10	1.35	(0.99 - 1.85)	0.062	1.76	(1.16 - 2.67)	0.008
≥3 siblings	26	10.24	46	3.90	3.08	(1.75 - 5.43)	<0.0005	5.54	(2.67 - 11.48)	<0.0005
Missing	24	9.45	5	0.42	35.94	(12.94 - 99.83)	<0.0005	37.71	(1.20 - 1 187.15)	0.039
Maternal smoking (current)										
No (Reference)	118	46.46	936	79.32						
Yes	120	47.24	237	20.08	4.38	(3.16 - 6.08)	<0.0005	1.98	(1.30 - 3.01)	0.001
Missing	16	6.30	7	0.59	19.99	(7.70 - 51.89)	<0.0005	4.28	(0.31 - 59.64)	0.279
Breast feeding (ever)										
Yes (Reference)	133	52.36	988	83.73						
No	91	35.83	184	15.59	3.56	(2.53 - 5.02)	<0.0005	2.12	(1.37 - 3.26)	0.001
Missing	30	11.81	8	0.68	33.39	(14.10 - 79.09)	<0.0005	7.69	(1.44 - 41.17)	0.017
Gestational age <38 wk										
No (Reference)	194	76.38	1029	87.20						
Yes	59	23.23	135	11.44	2.25	(1.57 - 3.22)	<0.0005	2.04	(1.27 - 3.27)	0.003
Missing	1	0.39	16	1.36	0.32	(0.04 - 2.49)	0.279	0.00	(0.00 - 0.06)	0.003
Maternal education										
Medium (Reference)	84	33.07	505	42.80						
Low	96	37.80	156	13.22	3.56	(2.43 - 5.23)	<0.0005	2.02	(1.26 - 3.22)	0.003
High	55	21.65	513	43.47	0.62	(0.42 - 0.92)	0.016	1.20	(0.75 - 1.94)	0.450
Missing	19	7.48	6	0.51	20.58	(7.62 - 55.63)	<0.0005	2.91	(0.49 - 17.40)	0.241
Family status										
Parents (Reference)	200	78.74	1085	91.95						
Single parent with new partner	10	3.94	12	1.02	5.81	(2.34 - 14.43)	<0.0005	2.46	(0.63 - 9.67)	0.198
Single parent	26	10.24	80	6.78	1.94	(1.17 - 3.22)	0.011	0.82	(0.42 - 1.60)	0.565
Missing	18	7.09	3	0.25	46.91	(10.42 - 211.16)	<0.0005	5.84	(0.35 - 97.04)	0.218

* 'Univariate' OR are adusted for oversampling of control children iving in the eastern part of Germany

Appendix Table 2: Any vaccination, unweighted case-control analysis: Uni- and multivariate odds ratios for any vaccination within seven days

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination < 7 days										
None	233	91.73	1069	90.59						
Yes	21	8.27	111	9.41	**0.86**	(0.51 - 1.46)	0.579	**0.95**	(0.48 - 1.88)	0.873
Region of residence										
Eastern part of Germany (Reference)	42	16.54	367	31.10						
Western part of Germany	212	83.46	813	68.90	2.85	(1.91 - 4.27)	<0.0005	2.71	(1.64 - 4.46)	<0.0005
Gender										
female (Reference)	90	35.43	567	48.05						
male	164	64.57	613	51.95	1.76	(1.31 - 2.37)	<0.0005	2.05	(1.40 - 3.01)	<0.0005
Maternal age (years)										
26-30 (Reference)	48	18.90	336	28.47						
0-20	37	14.57	23	1.95	12.20	(6.25 - 23.83)	<0.0005	10.31	(4.46 - 23.83)	<0.0005
21-25	67	26.38	181	15.34	2.80	(1.79 - 4.36)	<0.0005	2.94	(1.74 - 4.96)	<0.0005
>30	88	34.65	639	54.15	0.85	(0.57 - 1.27)	0.430	0.82	(0.51 - 1.32)	0.415
Missing	14	5.51	1	0.08	107.46	(13.40 - 861.57)	<0.0005	1.23	(0.01 - 176.94)	0.935
Number of siblings										
No s bling (Reference)	89	35.04	585	49.58						
1-2 s bling(s)	115	45.28	544	46.10	1.35	(0.99 - 1.85)	0.062	1.74	(1.15 - 2.64)	0.009
≥3 siblings	26	10.24	46	3.90	3.08	(1.75 - 5.43)	<0.0005	5.51	(2.66 - 11.41)	<0.0005
Missing	24	9.45	5	0.42	35.94	(12.94 - 99.83)	<0.0005	38.54	(1.24 - 1 193.85)	0.037
Maternal smoking (current)										
No (Reference)	118	46.46	936	79.32						
Yes	120	47.24	237	20.08	4.38	(3.16 - 6.08)	<0.0005	2.01	(1.32 - 3.04)	0.001
Missing	16	6.30	7	0.59	19.99	(7.70 - 51.89)	<0.0005	7.16	(0.55 - 94.03)	0.134
Breast feeding (ever)										
Yes (Reference)	133	52.36	988	83.73						
No	91	35.83	184	15.59	3.56	(2.53 - 5.02)	<0.0005	2.08	(1.35 - 3.19)	0.001
Missing	30	11.81	8	0.68	33.39	(14.10 - 79.09)	<0.0005	7.21	(1.38 - 37.67)	0.019
Gestational age <38 wk										
No (Reference)	194	76.38	1029	87.20						
Yes	59	23.23	135	11.44	2.25	(1.57 - 3.22)	<0.0005	2.04	(1.27 - 3.27)	0.003
Missing	1	0.39	16	1.36	0.32	(0.04 - 2.49)	0.279	0.00	(0.00 - 0.05)	0.003
Maternal education										
Medium (Reference)	84	33.07	505	42.80						
Low	96	37.80	156	13.22	3.56	(2.43 - 5.23)	<0.0005	2.03	(1.27 - 3.24)	0.003
High	55	21.65	513	43.47	0.62	(0.42 - 0.92)	0.016	1.19	(0.74 - 1.91)	0.481
Missing	19	7.48	6	0.51	20.58	(7.62 - 55.63)	<0.0005	2.91	(0.49 - 17.30)	0.241
Family status										
Parents (Reference)	200	78.74	1085	91.95						
Single parent with new partner	10	3.94	12	1.02	5.81	(2.34 - 14.43)	<0.0005	2.48	(0.63 - 9.79)	0.195
Single parent	26	10.24	80	6.78	1.94	(1.17 - 3.22)	0.011	0.83	(0.43 - 1.61)	0.578
Missing	18	7.09	3	0.25	46.91	(10.42 - 211.16)	<0.0005	5.56	(0.34 - 91.92)	0.000

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 3: Any vaccination, age-stratified unweighted case-control analysis: Uni- and multivariate odds ratios for any vaccination within 72 hours in the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model										
Variable	Cases n=215	(%)	Controls n=986	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination ≤ 72 hours										
None	200	93.02	946	95.94						
Yes	15	6.98	40	4.06	**1.58**	(0.81 - 3.07)	0.176	**1.49**	(0.57 - 3.90)	0.412
Region of residence										
Eastern part of Germany (Reference)	36	16.74	305	30.93						
Western part of Germany	179	83.26	681	69.07	2.86	(1.85 - 4.41)	<0.0005	2.39	(1.38 - 4.13)	0.002
Gender										
female (Reference)	73	33.95	472	47.87						
male	142	66.05	514	52.13	1.90	(1.37 - 2.64)	<0.0005	2.15	(1.37 - 3.38)	0.001
Maternal age (years)										
26-30 (Reference)	40	18.60	279	28.30						
0-20	34	15.81	18	1.83	13.89	(6.62 - 29.14)	<0.0005	12.97	(5.03 - 33.42)	<0.0005
21-25	62	28.84	148	15.01	3.19	(1.96 - 5.17)	<0.0005	3.52	(1.94 - 6.37)	<0.0005
>30	67	31.16	540	54.77	0.76	(0.49 - 1.19)	0.225	0.71	(0.41 - 1.21)	0.210
Missing	12	5.58	1	0.10	79.52	(9.77 - 647.37)	<0.0005	0.42	(0.00 - 194.04)	0.783
Number of siblings										
No s bling (Reference)	73	33.95	486	49.29						
1-2 s bling(s)	99	46.05	457	46.35	1.43	(1.01 - 2.02)	0.046	1.98	(1.22 - 3.21)	0.006
≥3 siblings	22	10.23	40	4.06	2.94	(1.58 - 5.44)	0.001	6.41	(2.80 - 14.69)	<0.0005
Missing	21	9.77	3	0.30	49.07	(13.89 - 173.35)	<0.0005	uncalculable		
Maternal smoking (current)										
No (Reference)	94	43.72	789	80.02						
Yes	107	49.77	192	19.47	5.09	(3.55 - 7.32)	<0.0005	2.00	(1.24 - 3.22)	0.005
Missing	14	6.51	5	0.51	24.14	(8.15 - 71.46)	<0.0005	12.15	(0.40 - 366.45)	0.151
Breast feeding (ever)										
Yes (Reference)	103	47.91	827	83.87						
No	85	39.53	153	15.52	4.29	(2.94 - 6.25)	<0.0005	2.42	(1.49 - 3.93)	<0.0005
Missing	27	12.56	6	0.61	37.92	(14.97 - 96.02)	<0.0005	7.57	(1.18 - 48.39)	0.032
Gestational age <38 wk										
No (Reference)	160	74.42	869	88.13						
Yes	54	25.12	104	10.55	2.65	(1.80 - 3.92)	<0.0005	2.54	(1.48 - 4.33)	0.001
Missing	1	0.47	13	1.32	0.36	(0.05 - 2.81)	0.331	uncalculable		
Maternal education										
Medium (Reference)	72	33.49	425	43.10						
Low	83	38.60	133	13.49	3.36	(2.23 - 5.05)	<0.0005	1.81	(1.08 - 3.04)	0.024
High	43	20.00	424	43.00	0.57	(0.37 - 0.88)	0.011	1.26	(0.72 - 2.18)	0.420
Missing	17	7.91	4	0.41	24.30	(7.68 - 76.87)	<0.0005	5.50	(0.55 - 55.45)	0.148
Family status										
Parents (Reference)	167	77.67	906	91.89						
Single parent with new partner	8	3.72	9	0.91	5.40	(1.94 - 15.03)	0.001	2.33	(0.37 - 14.67)	0.367
Single parent	24	11.16	68	6.90	2.14	(1.25 - 3.67)	0.006	0.84	(0.40 - 1.73)	0.629
Missing	16	7.44	3	0.30	40.44	(8.90 - 183.73)	<0.0005	10.25	(0.42 - 251.97)	0.154

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR only includes cases and controls for whom all categories were calculable

Appendix Table 4: Any vaccination, age-stratified unweighted case-control analysis: Uni- and multivariate odds ratios for any vaccination within seven days in the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model										
Variable	Cases n=215	(%)	Controls n=986	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination < 7 days										
None (Reference)	197	91.63	891	90.37						
Yes	18	8.37	95	9.63	**0.83**	(0.47 - 1.45)	**0.508**	0.83	(0.40 - 1.73)	0.622
Region of residence										
Eastern part of Germany (Reference)	36	16.74	305	30.93						
Western part of Germany	179	83.26	681	69.07	2.86	(1.85 - 4.41)	<0.0005	2.53	(1.51 - 4.25)	<0.0005
Gender										
female (Reference)	73	33.95	472	47.87						
male	142	66.05	514	52.13	1.90	(1.37 - 2.64)	<0.0005	2.10	(1.38 - 3.19)	<0.0005
Maternal age (years)										
26-30 (Reference)	40	18.60	279	28.30						
0-20	34	15.81	18	1.83	13.89	(6.62 - 29.14)	<0.0005	8.67	(3.56 - 21.13)	<0.0005
21-25	62	28.84	148	15.01	3.19	(1.96 - 5.17)	<0.0005	2.70	(1.58 - 4.61)	<0.0005
>30	67	31.16	540	54.77	0.76	(0.49 - 1.19)	0.225	0.93	(0.57 - 1.52)	0.779
Missing	12	5.58	1	0.10	79.52	(9.77 - 647.37)	<0.0005	6.24	(0.05 - 809.45)	0.461
Number of siblings										
No sibling (Reference)	73	33.95	486	49.29						
1-2 sibling(s)	99	46.05	457	46.35	1.43	(1.01 - 2.02)	0.046			
≥3 siblings	22	10.23	40	4.06	2.94	(1.58 - 5.44)	0.001			
Missing	21	9.77	3	0.30	49.07	(13.89 - 173.35)	<0.0005			
Maternal smoking (current)										
No (Reference)	94	43.72	789	80.02						
Yes	107	49.77	192	19.47	5.09	(3.55 - 7.32)	<0.0005	2.30	(1.47 - 3.60)	<0.0005
Missing	14	6.51	5	0.51	24.14	(8.15 - 71.46)	<0.0005	0.28	(0.02 - 4.59)	0.372
Breast feeding (ever)										
Yes (Reference)	103	47.91	827	83.87						
No	85	39.53	153	15.52	4.29	(2.94 - 6.25)	<0.0005	2.63	(1.67 - 4.13)	<0.0005
Missing	27	12.56	6	0.61	37.92	(14.97 - 96.02)	<0.0005	16.28	(4.53 - 58.58)	<0.0005
Gestational age <38 wk										
No (Reference)	160	74.42	869	88.13						
Yes	54	25.12	104	10.55	2.65	(1.80 - 3.92)	<0.0005			
Missing	1	0.47	13	1.32	0.36	(0.05 - 2.81)	0.331			
Maternal education										
Medium (Reference)	72	33.49	425	43.10						
Low	83	38.60	133	13.49	3.36	(2.23 - 5.05)	<0.0005	1.82	(1.12 - 2.95)	0.015
High	43	20.00	424	43.00	0.57	(0.37 - 0.88)	0.011	0.99	(0.59 - 1.67)	0.980
Missing	17	7.91	4	0.41	24.30	(7.68 - 76.87)	<0.0005	5.26	(0.65 - 42.40)	0.119
Family status										
Parents (Reference)	167	77.67	906	91.89						
Single parent with new partner	8	3.72	9	0.91	5.40	(1.94 - 15.03)	0.001	1.67	(0.33 - 8.42)	0.536
Single parent	24	11.16	68	6.90	2.14	(1.25 - 3.67)	0.006	0.98	(0.49 - 1.94)	0.944
Missing	16	7.44	3	0.30	40.44	(8.90 - 183.73)	<0.0005	1.90	(0.11 - 32.05)	0.000

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

**Multivariate model was only calculable without the covariables 'siblings' and 'gestational age'.

Appendix Table 5: Any vaccination, age-stratified unweighted case-control analysis: Univariate odds ratios for any vaccination within 72 hours in the second year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=39	(%)	Controls n=194	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination ≤ 72 hours										
None (Reference)	37	94.87	189	97.42						
Yes	2	5.13	5	2.58	**3.13**	(0.40 - 24.58)	0.277			
Region of residence										
Eastern part of Germany (Reference)	6	15.38	62	31.96						
Western part of Germany	33	84.62	132	68.04	2.82	(0.94 - 8.46)	0.064			
Gender										
female (Reference)	17	43.59	95	48.97						
male	22	56.41	99	51.03	1.26	(0.63 - 2.51)	0.515			
Maternal age (years)										
26-30 (Reference)	8	20.51	57	29.38						
0-20	3	7.69	5	2.58	7.08	(1.22 - 40.91)	0.029			
21-25	5	12.82	33	17.01	1.21	(0.35 - 4.13)	0.760			
>30	21	53.85	99	51.03	1.38	(0.54 - 3.52)	0.502			
Missing	2	5.13	0	0.00	uncalculable					
Number of siblings										
No s bling (Reference)	16	41.03	99	51.03						
1-2 s bling(s)	16	41.03	87	44.85	1.04	(0.48 - 2.24)	0.921			
≥3 siblings	4	10.26	6	3.09	4.09	(0.99 - 16.96)	0.052			
Missing	3	7.69	2	1.03	16.63	(2.12 - 130.42)	0.007			
Maternal smoking (current)										
No (Reference)	24	61.54	147	75.77						
Yes	13	33.33	45	23.20	2.08	(0.93 - 4.66)	0.075			
Missing	2	5.13	2	1.03	11.55	(1.14 - 117.43)	0.039			
Breast feeding (ever)										
Yes (Reference)	30	76.92	161	82.99						
No	6	15.38	31	15.98	1.14	(0.42 - 3.07)	0.795			
Missing	3	7.69	2	1.03	19.70	(1.60 - 242.11)	0.020			
Gestational age <38 wk										
No (Reference)	34	87.18	160	82.47						
Yes	5	12.82	31	15.98	0.84	(0.29 - 2.39)	0.741			
Missing	0	0.00	3	1.55	uncalculable					
Maternal education										
Medium (Reference)	12	30.77	80	41.24						
Low	13	33.33	23	11.86	5.17	(1.63 - 16.39)	0.005			
High	12	30.77	89	45.88	0.94	(0.37 - 2.38)	0.892			
Missing	2	5.13	2	1.03	12.10	(1.15 - 127.56)	0.038			
Family status										
Parents (Reference)	33	84.62	179	92.27						
Single parent with new partner	2	5.13	3	1.55	10.26	(1.26 - 83.38)	0.029			
Single parent	2	5.13	12	6.19	0.90	(0.18 - 4.51)	0.897			
Missing	2	5.13	0	0.00	uncalculable					

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR not calculated due to low number of cases

Appendix Table 6: Any vaccination, age-stratified unweighted case-control analysis: Univariate odds ratios for any vaccination within seven days in the second year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model										
Variable	Cases n=39	(%)	Controls n=194	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination < 7 days										
None (Reference)	36	92.31	178	91.75						
Yes	3	7.69	16	8.25	**1.14**	(0.28 - 4.67)	0.851			
Region of residence										
Eastern part of Germany (Reference)	6	15.38	62	31.96						
Western part of Germany	33	84.62	132	68.04	2.82	(0.94 - 8.46)	0.064			
Gender										
female (Reference)	17	43.59	95	48.97						
male	22	56.41	99	51.03	1.26	(0.63 - 2.51)	0.515			
Maternal age (years)										
26-30 (Reference)	8	20.51	57	29.38						
0-20	3	7.69	5	2.58	7.08	(1.22 - 40.91)	0.029			
21-25	5	12.82	33	17.01	1.21	(0.35 - 4.13)	0.760			
>30	21	53.85	99	51.03	1.38	(0.54 - 3.52)	0.502			
Missing	2	5.13	0	0.00	uncalculable					
Number of siblings										
No sibling (Reference)	16	41.03	99	51.03						
1-2 s bling(s)	16	41.03	87	44.85	1.04	(0.48 - 2.24)	0.921			
≥3 siblings	4	10.26	6	3.09	4.09	(0.99 - 16.96)	0.052			
Missing	3	7.69	2	1.03	16.63	(2.12 - 130.42)	0.007			
Maternal smoking (current)										
No (Reference)	24	61.54	147	75.77						
Yes	13	33.33	45	23.20	2.08	(0.93 - 4.66)	0.075			
Missing	2	5.13	2	1.03	11.55	(1.14 - 117.43)	0.039			
Breast feeding (ever)										
Yes (Reference)	30	76.92	161	82.99						
No	6	15.38	31	15.98	1.14	(0.42 - 3.07)	0.795			
Missing	3	7.69	2	1.03	19.70	(1.60 - 242.11)	0.020			
Gestational age <38 wk										
No (Reference)	34	87.18	160	82.47						
Yes	5	12.82	31	15.98	0.84	(0.29 - 2.39)	0.741			
Missing	0	0.00	3	1.55	uncalculable					
Maternal education										
Medium (Reference)	12	30.77	80	41.24						
Low	13	33.33	23	11.86	5.17	(1.63 - 16.39)	0.005			
High	12	30.77	89	45.88	0.94	(0.37 - 2.38)	0.892			
Missing	2	5.13	2	1.03	12.10	(1.15 - 127.56)	0.038			
Family status										
Parents (Reference)	33	84.62	179	92.27						
Single parent with new partner	2	5.13	3	1.55	10.26	(1.26 - 83.38)	0.029			
Single parent	2	5.13	12	6.19	0.90	(0.18 - 4.51)	0.897			
Missing	2	5.13	0	0.00	uncalculable					

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR not calculated due to low number of cases

Appendix Table 7: Hexavalent and non-hexavalent vaccination, unweighted case-control analysis: Uni- and multivariate odds ratios for hexavalent and non-hexavalent vaccination within 72 hours

Number (percentage), uni- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination ≤ 72 hours										
None (Reference)	237	93.31	1135	96.19						
Hexavalent	11	4.33	34	2.88	**1.54**	(0.73 - 3.23)	0.256	**1.51**	(0.56 - 4.07)	0.418
Non-hexavalent	6	2.36	11	0.93	**2.06**	(0.69 - 6.10)	0.193	**2.12**	(0.51 - 8.79)	0.301
Region of residence										
Eastern part of Germany (Reference)	42	16.54	367	31.10						
Western part of Germany	212	83.46	813	68.90	2.85	(1.91 - 4.27)	<0.0005	2.64	(1.60 - 4.35)	<0.0005
Gender										
female (Reference)	90	35.43	567	48.05						
male	164	64.57	613	51.95	1.76	(1.31 - 2.37)	<0.0005	2.04	(1.39 - 3.00)	<0.0005
Maternal age (years)										
26-30 (Reference)	48	18.90	336	28.47						
0-20	37	14.57	23	1.95	12.20	(6.25 - 23.83)	<0.0005	10.55	(4.53 - 24.57)	<0.0005
21-25	67	26.38	181	15.34	2.80	(1.79 - 4.36)	<0.0005	2.87	(1.70 - 4.85)	<0.0005
>30	88	34.65	639	54.15	0.85	(0.57 - 1.27)	0.430	0.83	(0.52 - 1.34)	0.454
Missing	14	5.51	1	0.08	107.46	(13.40 - 861.57)	<0.0005	1.76	(0.01 - 226.56)	0.820
Number of siblings										
No sibling (Reference)	89	35.04	585	49.58						
1-2 sibling(s)	115	45.28	544	46.10	1.35	(0.99 - 1.85)	0.062	1.76	(1.16 - 2.66)	0.008
≥3 siblings	26	10.24	46	3.90	3.08	(1.75 - 5.43)	<0.0005	5.53	(2.67 - 11.46)	<0.0005
Missing	24	9.45	5	0.42	35.94	(12.94 - 99.83)	<0.0005	38.15	(1.23 - 1 187.90)	0.038
Maternal smoking (current)										
No (Reference)	118	46.46	936	79.32						
Yes	120	47.24	237	20.08	4.38	(3.16 - 6.08)	<0.0005	1.98	(1.30 - 3.00)	0.001
Missing	16	6.30	7	0.59	19.99	(7.70 - 51.89)	<0.0005	3.79	(0.25 - 58.48)	0.339
Breast feeding (ever)										
Yes (Reference)	133	52.36	988	83.73						
No	91	35.83	184	15.59	3.56	(2.53 - 5.02)	<0.0005	2.13	(1.38 - 3.28)	0.001
Missing	30	11.81	8	0.68	33.39	(14.10 - 79.09)	<0.0005	7.54	(1.42 - 39.92)	0.018
Gestational age <38 wk										
No (Reference)	194	76.38	1029	87.20						
Yes	59	23.23	135	11.44	2.25	(1.57 - 3.22)	<0.0005	2.02	(1.26 - 3.25)	0.004
Missing	1	0.39	16	1.36	0.32	(0.04 - 2.49)	0.279	0.00	(0.00 - 0.06)	0.004
Maternal education										
Medium (Reference)	84	33.07	505	42.80						
Low	96	37.80	156	13.22	3.56	(2.43 - 5.23)	<0.0005	2.03	(1.27 - 3.24)	0.003
High	55	21.65	513	43.47	0.62	(0.42 - 0.92)	0.016	1.20	(0.74 - 1.94)	0.454
Missing	19	7.48	6	0.51	20.58	(7.62 - 55.63)	<0.0005	2.91	(0.49 - 17.36)	0.242
Family status										
Parents (Reference)	200	78.74	1085	91.95						
Single parent with new partner	10	3.94	12	1.02	5.81	(2.34 - 14.43)	<0.0005	2.48	(0.63 - 9.74)	0.194
Single parent	26	10.24	80	6.78	1.94	(1.17 - 3.22)	0.011	0.83	(0.42 - 1.61)	0.575
Missing	18	7.09	3	0.25	46.91	(10.42 - 211.16)	<0.0005	6.25	(0.36 - 107.67)	0.207

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 8: Hexavalent and non-hexavalent vaccination, unweighted case-control analysis: Uni- and multivariate odds ratios for hexavalent and non-hexavalent vaccination within seven days

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination < 7 days										
None (Reference)	233	91.73	1069	90.59						
Hexavalent	13	5.12	83	7.03	**0.74**	(0.39 - 1.39)	0.348	**0.79**	(0.35 - 1.78)	0.567
Non-hexavalent	8	3.15	28	2.37	**1.21**	(0.52 - 2.84)	0.658	**1.45**	(0.47 - 4.50)	0.523
Region of residence										
Eastern part of Germany (Reference)	42	16.54	367	31.10						
Western part of Germany	212	83.46	813	68.90	2.85	(1.91 - 4.27)	<0.0005	2.67	(1.62 - 4.39)	<0.0005
Gender										
female (Reference)	90	35.43	567	48.05						
male	164	64.57	613	51.95	1.76	(1.31 - 2.37)	<0.0005	2.05	(1.40 - 3.01)	<0.0005
Maternal age (years)										
26-30 (Reference)	48	18.90	336	28.47						
0-20	37	14.57	23	1.95	12.20	(6.25 - 23.83)	<0.0005	10.13	(4.37 - 23.49)	<0.0005
21-25	67	26.38	181	15.34	2.80	(1.79 - 4.36)	<0.0005	2.92	(1.73 - 4.94)	<0.0005
>30	88	34.65	639	54.15	0.85	(0.57 - 1.27)	0.430	0.83	(0.52 - 1.33)	0.435
Missing	14	5.51	1	0.08	107.46	(13.40 - 861.57)	<0.0005	1.37	(0.01 - 192.32)	0.900
Number of siblings										
No s bling (Reference)	89	35.04	585	49.58						
1-2 s bling(s)	115	45.28	544	46.10	1.35	(0.99 - 1.85)	0.062	1.74	(1.15 - 2.64)	0.009
≥3 siblings	26	10.24	46	3.90	3.08	(1.75 - 5.43)	<0.0005	5.49	(2.66 - 11.37)	<0.0005
Missing	24	9.45	5	0.42	35.94	(12.94 - 99.83)	<0.0005	40.60	(1.30 - 1 265.20)	0.035
Maternal smoking (current)										
No (Reference)	118	46.46	936	79.32						
Yes	120	47.24	237	20.08	4.38	(3.16 - 6.08)	<0.0005	2.01	(1.32 - 3.06)	0.001
Missing	16	6.30	7	0.59	19.99	(7.70 - 51.89)	<0.0005	5.73	(0.39 - 84.48)	0.204
Breast feeding (ever)										
Yes (Reference)	133	52.36	988	83.73						
No	91	35.83	184	15.59	3.56	(2.53 - 5.02)	<0.0005	2.10	(1.36 - 3.22)	0.001
Missing	30	11.81	8	0.68	33.39	(14.10 - 79.09)	<0.0005	6.83	(1.33 - 35.02)	0.021
Gestational age <38 wk										
No (Reference)	194	76.38	1029	87.20						
Yes	59	23.23	135	11.44	2.25	(1.57 - 3.22)	<0.0005	2.00	(1.25 - 3.22)	0.004
Missing	1	0.39	16	1.36	0.32	(0.04 - 2.49)	0.279	0.00	(0.00 - 0.05)	0.003
Maternal education										
Medium (Reference)	84	33.07	505	42.80						
Low	96	37.80	156	13.22	3.56	(2.43 - 5.23)	<0.0005	2.05	(1.28 - 3.28)	0.003
High	55	21.65	513	43.47	0.62	(0.42 - 0.92)	0.016	1.19	(0.74 - 1.92)	0.483
Missing	19	7.48	6	0.51	20.58	(7.62 - 55.63)	<0.0005	2.74	(0.45 - 16.76)	0.274
Family status										
Parents (Reference)	200	78.74	1085	91.95						
Single parent with new partner	10	3.94	12	1.02	5.81	(2.34 - 14.43)	<0.0005	2.49	(0.63 - 9.89)	0.193
Single parent	26	10.24	80	6.78	1.94	(1.17 - 3.22)	0.011	0.85	(0.44 - 1.64)	0.622
Missing	18	7.09	3	0.25	46.91	(10.42 - 211.16)	<0.0005	6.16	(0.36 - 105.45)	0.000

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 9: Hexavalent and non-hexavalent vaccination, age-stratified unweighted case-control analysis: Uni- and multivariate odds ratios for hexavalent and non-hexavalent vaccination within 72 hours in the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model										
Variable	Cases n=215	(%)	Controls n=986	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination ≤ 72 hours										
None(Reference)	200	93.02	946	95.94						
Hexavalent	10	4.65	33	3.35	**1.42**	(0.65 - 3.06)	0.377	**1.15**	(0.38 - 3.41)	0.808
Non-hexavalent	5	2.33	7	0.71	**2.19**	(0.63 - 7.59)	0.217	**3.81**	(0.60 - 24.18)	0.156
Region of residence										
Eastern part of Germany (Reference)	36	16.74	305	30.93						
Western part of Germany	179	83.26	681	69.07	2.86	(1.85 - 4.41)	<0.0005	2.36	(1.37 - 4.06)	0.002
Gender										
female (Reference)	73	33.95	472	47.87						
male	142	66.05	514	52.13	1.90	(1.37 - 2.64)	<0.0005	2.13	(1.36 - 3.35)	0.001
Maternal age (years)										
26-30 (Reference)	40	18.60	279	28.30						
0-20	34	15.81	18	1.83	13.89	(6.62 - 29.14)	<0.0005	12.75	(4.93 - 32.94)	<0.0005
21-25	62	28.84	148	15.01	3.19	(1.96 - 5.17)	<0.0005	3.59	(1.97 - 6.54)	<0.0005
>30	67	31.16	540	54.77	0.76	(0.49 - 1.19)	0.225	0.73	(0.42 - 1.26)	0.259
Missing	12	5.58	1	0.10	79.52	(9.77 - 647.37)	<0.0005	0.37	(0.00 - 204.66)	0.757
Number of siblings										
No s bling (Reference)	73	33.95	486	49.29						
1-2 s bling(s)	99	46.05	457	46.35	1.43	(1.01 - 2.02)	0.046	1.99	(1.23 - 3.23)	0.005
≥3 siblings	22	10.23	40	4.06	2.94	(1.58 - 5.44)	0.001	6.51	(2.84 - 14.92)	<0.0005
Missing	21	9.77	3	0.30	49.07	(13.89 - 173.35)	<0.0005	uncalculable		
Maternal smoking (current)										
No (Reference)	94	43.72	789	80.02						
Yes	107	49.77	192	19.47	5.09	(3.55 - 7.32)	<0.0005	2.02	(1.25 - 3.26)	0.004
Missing	14	6.51	5	0.51	24.14	(8.15 - 71.46)	<0.0005	11.10	(0.35 - 355.77)	0.174
Breast feeding (ever)										
Yes (Reference)	103	47.91	827	83.87						
No	85	39.53	153	15.52	4.29	(2.94 - 6.25)	<0.0005	2.45	(1.51 - 3.98)	<0.0005
Missing	27	12.56	6	0.61	37.92	(14.97 - 96.02)	<0.0005	7.28	(1.19 - 44.63)	0.032
Gestational age <38 wk										
No (Reference)	160	74.42	869	88.13						
Yes	54	25.12	104	10.55	2.65	(1.80 - 3.92)	<0.0005	2.49	(1.46 - 4.26)	0.001
Missing	1	0.47	13	1.32	0.36	(0.05 - 2.81)	0.331	uncalculable		
Maternal education										
Medium (Reference)	72	33.49	425	43.10						
Low	83	38.60	133	13.49	3.36	(2.23 - 5.05)	<0.0005	1.83	(1.09 - 3.06)	0.022
High	43	20.00	424	43.00	0.57	(0.37 - 0.88)	0.011	1.24	(0.71 - 2.17)	0.441
Missing	17	7.91	4	0.41	24.30	(7.68 - 76.87)	<0.0005	4.97	(0.50 - 49.29)	0.171
Family status										
Parents (Reference)	167	77.67	906	91.89						
Single parent with new partner	8	3.72	9	0.91	5.40	(1.94 - 15.03)	0.001	2.34	(0.37 - 14.78)	0.364
Single parent	24	11.16	68	6.90	2.14	(1.25 - 3.67)	0.006	0.84	(0.41 - 1.74)	0.641
Missing	16	7.44	3	0.30	40.44	(8.90 - 183.73)	<0.0005	15.38	(0.46 - 518.22)	0.128

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR only includes cases and controls for whom all categories were calculable

Appendix Table 10: Hexavalent and non-hexavalent vaccination, age-stratified unweighted case-control analysis: Uni- and multivariate odds ratios for hexavalent and non-hexavalent vaccination within seven days in the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=215	(%)	Controls n=986	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination < 7 days										
None (Reference)	197	91.63	891	90.37						
Hexavalent	12	5.58	79	8.01	**0.70**	(0.36 - 1.35)	0.286	**0.62**	(0.26 - 1.49)	0.283
Non-hexavalent	6	2.79	16	1.62	**1.40**	(0.50 - 3.90)	0.519	**1.42**	(0.31 - 6.60)	0.655
Region of residence										
Eastern part of Germany (Reference)	36	16.74	305	30.93						
Western part of Germany	179	83.26	681	69.07	2.86	(1.85 - 4.41)	<0.0005	2.37	(1.37 - 4.09)	0.002
Gender										
female (Reference)	73	33.95	472	47.87						
male	142	66.05	514	52.13	1.90	(1.37 - 2.64)	<0.0005	2.18	(1.39 - 3.41)	0.001
Maternal age (years)										
26-30 (Reference)	40	18.60	279	28.30						
0-20	34	15.81	18	1.83	13.89	(6.62 - 29.14)	<0.0005	12.11	(4.71 - 31.16)	<0.0005
21-25	62	28.84	148	15.01	3.19	(1.96 - 5.17)	<0.0005	3.63	(2.00 - 6.61)	<0.0005
>30	67	31.16	540	54.77	0.76	(0.49 - 1.19)	0.225	0.71	(0.42 - 1.23)	0.222
Missing	12	5.58	1	0.10	79.52	(9.77 - 647.37)	<0.0005	0.27	(0.00 - 174.25)	0.691
Number of siblings										
No sibling (Reference)	73	33.95	486	49.29						
1-2 s bling(s)	99	46.05	457	46.35	1.43	(1.01 - 2.02)	0.046	1.94	(1.20 - 3.15)	0.007
≥3 siblings	22	10.23	40	4.06	2.94	(1.58 - 5.44)	0.001	6.36	(2.78 - 14.59)	<0.0005
Missing	21	9.77	3	0.30	49.07	(13.89 - 173.35)	<0.0005	uncalculable		
Maternal smoking (current)										
No (Reference)	94	43.72	789	80.02						
Yes	107	49.77	192	19.47	5.09	(3.55 - 7.32)	<0.0005	2.04	(1.26 - 3.30)	0.004
Missing	14	6.51	5	0.51	24.14	(8.15 - 71.46)	<0.0005	19.34	(0.63 - 592.83)	0.090
Breast feeding (ever)										
Yes (Reference)	103	47.91	827	83.87						
No	85	39.53	153	15.52	4.29	(2.94 - 6.25)	<0.0005	2.41	(1.48 - 3.91)	<0.0005
Missing	27	12.56	6	0.61	37.92	(14.97 - 96.02)	<0.0005	6.57	(1.10 - 39.36)	0.039
Gestational age <38 wk										
No (Reference)	160	74.42	869	88.13						
Yes	54	25.12	104	10.55	2.65	(1.80 - 3.92)	<0.0005	2.46	(1.44 - 4.20)	0.001
Missing	1	0.47	13	1.32	0.36	(0.05 - 2.81)	0.331	uncalculable		
Maternal education										
Medium (Reference)	72	33.49	425	43.10						
Low	83	38.60	133	13.49	3.36	(2.23 - 5.05)	<0.0005	1.86	(1.11 - 3.13)	0.019
High	43	20.00	424	43.00	0.57	(0.37 - 0.88)	0.011	1.23	(0.71 - 2.15)	0.462
Missing	17	7.91	4	0.41	24.30	(7.68 - 76.87)	<0.0005	5.29	(0.48 - 58.40)	0.174
Family status										
Parents (Reference)	167	77.67	906	91.89						
Single parent with new partner	8	3.72	9	0.91	5.40	(1.94 - 15.03)	0.001	2.23	(0.35 - 14.41)	0.399
Single parent	24	11.16	68	6.90	2.14	(1.25 - 3.67)	0.006	0.87	(0.42 - 1.79)	0.699
Missing	16	7.44	3	0.30	40.44	(8.90 - 183.73)	<0.0005	12.57	(0.42 - 376.53)	0.000

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR only includes cases and controls for whom all categories were calculable

Appendix Table 11: Hexavalent and non-hexavalent vaccination, age-stratified unweighted case-control analysis: Univariate odds ratios for hexavalent and non-hexavalent vaccination within 72 hours in the second year of life

Number (percentage), univariate- and multivariate odds ratios for vaccinationand variables included in the multvariate model										
Variable	Cases n=39	(%)	Controls n=194	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination ≤ 72 hours										
None (Reference)	37	94,87	189	97,42						
Hexavalent	1	2,56	1	0,52	**7,38**	(0,30 - 179,91)	0,220			
Non-hexavalent	1	2,56	4	2,06	**2,40**	(0,23 - 24,64)	0,463			
Region of residence										
Eastern part of Germany (Reference)	6	15,38	62	31,96						
Western part of Germany	33	84,62	132	68,04	2,82	(0,94 - 8,46)	0,064			
Gender										
female (Reference)	17	43,59	95	48,97						
male	22	56,41	99	51,03	1,26	(0,63 - 2,51)	0,515			
Maternal age (years)										
26-30 (Reference)	8	20,51	57	29,38						
0-20	3	7,69	5	2,58	7,08	(1,22 - 40,91)	0,029			
21-25	5	12,82	33	17,01	1,21	(0,35 - 4,13)	0,760			
>30	21	53,85	99	51,03	1,38	(0,54 - 3,52)	0,502			
Missing	2	5,13	0	0,00	uncalculable					
Number of siblings										
No sibling (Reference)	16	41,03	99	51,03						
1-2 s bling(s)	16	41,03	87	44,85	1,04	(0,48 - 2,24)	0,921			
≥3 siblings	4	10,26	6	3,09	4,09	(0,99 - 16,96)	0,052			
Missing	3	7,69	2	1,03	16,63	(2,12 - 130,42)	0,007			
Maternal smoking (current)										
No (Reference)	24	61,54	147	75,77						
Yes	13	33,33	45	23,20	2,08	(0,93 - 4,66)	0,075			
Missing	2	5,13	2	1,03	11,55	(1,14 - 117,43)	0,039			
Breast feeding (ever)										
Yes (Reference)	30	76,92	161	82,99						
No	6	15,38	31	15,98	1,14	(0,42 - 3,07)	0,795			
Missing	3	7,69	2	1,03	19,70	(1,60 - 242,11)	0,020			
Gestational age <38 wk										
No (Reference)	34	87,18	160	82,47						
Yes	5	12,82	31	15,98	0,84	(0,29 - 2,39)	0,741			
Missing	0	0,00	3	1,55	uncalculable					
Maternal education										
Medium (Reference)	12	30,77	80	41,24						
Low	13	33,33	23	11,86	5,17	(1,63 - 16,39)	0,005			
High	12	30,77	89	45,88	0,94	(0,37 - 2,38)	0,892			
Missing	2	5,13	2	1,03	12,10	(1,15 - 127,56)	0,038			
Family status										
Parents (Reference)	33	84,62	179	92,27						
Single parent with new partner	2	5,13	3	1,55	10,26	(1,26 - 83,38)	0,029			
Single parent	2	5,13	12	6,19	0,90	(0,18 - 4,51)	0,897			
Missing	2	5,13	0	0,00	uncalculable					

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR not calculated due to low number of cases

Appendix Table 12: Hexavalent and non-hexavalent vaccination, age-stratified unweighted case-control analysis: Univariate odds ratios for hexavalent and non-hexavalent vaccination within seven days in the second year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=39	(%)	Controls n=194	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination < 7 days										
None (Reference)	36	92.31	178	91.75						
Hexavalent	1	2.56	4	2.06	**2.14**	(0.17 - 26.41)	0.554			
Non-hexavalent	2	5.13	12	6.19	**0.98**	(0.20 - 4.72)	0.981			
Region of residence										
Eastern part of Germany (Reference)	6	15.38	62	31.96						
Western part of Germany	33	84.62	132	68.04	2.82	(0.94 - 8.46)	0.064			
Gender										
female (Reference)	17	43.59	95	48.97						
male	22	56.41	99	51.03	1.26	(0.63 - 2.51)	0.515			
Maternal age (years)										
26-30 (Reference)	8	20.51	57	29.38						
0-20	3	7.69	5	2.58	7.08	(1.22 - 40.91)	0.029			
21-25	5	12.82	33	17.01	1.21	(0.35 - 4.13)	0.760			
>30	21	53.85	99	51.03	1.38	(0.54 - 3.52)	0.502			
Missing	2	5.13	0	0.00	uncalculable					
Number of siblings										
No sibling (Reference)	16	41.03	99	51.03						
1-2 sibling(s)	16	41.03	87	44.85	1.04	(0.48 - 2.24)	0.921			
≥3 siblings	4	10.26	6	3.09	4.09	(0.99 - 16.96)	0.052			
Missing	3	7.69	2	1.03	16.63	(2.12 - 130.42)	0.007			
Maternal smoking (current)										
No (Reference)	24	61.54	147	75.77						
Yes	13	33.33	45	23.20	2.08	(0.93 - 4.66)	0.075			
Missing	2	5.13	2	1.03	11.55	(1.14 - 117.43)	0.039			
Breast feeding (ever)										
Yes (Reference)	30	76.92	161	82.99						
No	6	15.38	31	15.98	1.14	(0.42 - 3.07)	0.795			
Missing	3	7.69	2	1.03	19.70	(1.60 - 242.11)	0.020			
Gestational age <38 wk										
No (Reference)	34	87.18	160	82.47						
Yes	5	12.82	31	15.98	0.84	(0.29 - 2.39)	0.741			
Missing	0	0.00	3	1.55	uncalculable		0.990			
Maternal education										
Medium (Reference)	12	30.77	80	41.24						
Low	13	33.33	23	11.86	5.17	(1.63 - 16.39)	0.005			
High	12	30.77	89	45.88	0.94	(0.37 - 2.38)	0.892			
Missing	2	5.13	2	1.03	12.10	(1.15 - 127.56)	0.038			
Family status										
Parents (Reference)	33	84.62	179	92.27						
Single parent with new partner	2	5.13	3	1.55	10.26	(1.26 - 83.38)	0.029			
Single parent	2	5.13	12	6.19	0.90	(0.18 - 4.51)	0.897			
Missing	2	5.13	0	0.00	uncalculable		0.986			

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multvariate OR not calculated due to low number of cases

Appendix Table 13: Pentavalent and non-pentavalent vaccination, unweighted case-control analysis: Uni- and multivariate odds ratios for pentavalent and non-pentavalent vaccination within 72 hours

Number (percentage), uni- and multivariate odds ratios for vaccination within the last 72 hours and variables included in the multvariate model										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination ≤ 72 hours										
None (Reference)	237	93,31	1135	96,19						
Pentavalent**	4	1,57	2	0,17	**7,894**	(1,33 - 46,77)	0,0230			
Non-pentavalent	13	5,12	43	3,64	**1,329**	(0,66 - 2,68)	0,4270	**1,070**	(0,41 - 2,78)	0,8890
Region of residence										
Eastern part of Germany (Reference)	42	16,54	367	31,10						
Western part of Germany	212	83,46	813	68,90	2,853	(1,91 - 4,27)	<0.0005	2,539	(1,54 - 4,17)	<0.0005
Gender										
female (Reference)	90	35,43	567	48,05						
male	164	64,57	613	51,95	1,763	(1,31 - 2,37)	<0.0005	2,015	(1,37 - 2,97)	<0.0005
Maternal age (years)										
26-30 (Reference)	48	18,90	336	28,47						
0-20	37	14,57	23	1,95	12,199	(6,25 - 23,83)	<0.0005	10,397	(4,47 - 24,18)	<0.0005
21-25	67	26,38	181	15,34	2,795	(1,79 - 4,36)	<0.0005	2,925	(1,72 - 4,98)	<0.0005
>30	88	34,65	639	54,15	0,851	(0,57 - 1,27)	0,4300	0,853	(0,53 - 1,37)	0,5150
Missing	14	5,51	1	0,08	107,464	(13,40 - 861,57)	<0.0005	1,170	(0,01 - 218,42)	0,9530
Number of siblings										
No sibling (Reference)	89	35,04	585	49,58						
1-2 s bling(s)	115	45,28	544	46,10	1,351	(0,99 - 1,85)	0,0620	1,776	(1,17 - 2,70)	0,0070
≥3 siblings	26	10,24	46	3,90	3,082	(1,75 - 5,43)	<0.0005	5,674	(2,73 - 11,78)	<0.0005
Missing	24	9,45	5	0,42	35,938	(12,94 - 99,83)	<0.0005	42,039	(1,24 - 1.430,86)	0,0380
Maternal smoking (current)										
No (Reference)	118	46,46	936	79,32						
Yes	120	47,24	237	20,08	4,383	(3,16 - 6,08)	<0.0005	1,982	(1,30 - 3,02)	0,0010
Missing	16	6,30	7	0,59	19,986	(7,70 - 51,89)	<0.0005	3,620	(0,22 - 59,30)	0,3670
Breast feeding (ever)										
Yes (Reference)	133	52,36	988	83,73						
No	91	35,83	184	15,59	3,561	(2,53 - 5,02)	<0.0005	2,147	(1,39 - 3,31)	0,0010
Missing	30	11,81	8	0,68	33,390	(14,10 - 79,09)	<0.0005	7,224	(1,41 - 37,02)	0,0180
Gestational age <38 wk										
No (Reference)	194	76,38	1029	87,20						
Yes	59	23,23	135	11,44	2,248	(1,57 - 3,22)	<0.0005	1,975	(1,23 - 3,18)	0,0050
Missing	1	0,39	16	1,36	0,324	(0,04 - 2,49)	0,2790	0,000	(0,00 - 0,06)	0,0040
Maternal education										
Medium (Reference)	84	33,07	505	42,80						
Low	96	37,80	156	13,22	3,565	(2,43 - 5,23)	<0.0005	2,121	(1,32 - 3,41)	0,0020
High	55	21,65	513	43,47	0,619	(0,42 - 0,92)	0,0160	1,204	(0,74 - 1,95)	0,4490
Missing	19	7,48	6	0,51	20,583	(7,62 - 55,63)	<0.0005	2,444	(0,41 - 14,57)	0,3270
Family status										
Parents (Reference)	200	78,74	1085	91,95						
Single parent with new partner	10	3,94	12	1,02	5,814	(2,34 - 14,43)	<0.0005	2,525	(0,63 - 10,05)	0,1890
Single parent	26	10,24	80	6,78	1,939	(1,17 - 3,22)	0,0110	0,828	(0,42 - 1,62)	0,5810
Missing	18	7,09	3	0,25	46,913	(10,42 - 211,16)	<0.0005	14,547	(0,52 - 408,78)	0,1160

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 14: Pentavalent and non-pentavalent vaccination, unweighted case-control analysis: Uni- and multivariate odds ratios for pentavalent and non-pentavalent vaccination within seven days

Number (percentage), uni- and multivariate odds ratios for vaccination within the last 7 days and variables included in the multvariate model										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination ≤ 7 days										
None (Reference)	233	91,73	1069	90,59						
Pentavalent**	5	1,97	6	0,51	**3,237**	(0,93 - 11,22)	0,0640			
Non-pentavalent	16	6,30	105	8,90	**0,695**	(0,39 - 1,25)	0,2250	**0,717**	(0,33 - 1,53)	0,3900
Region of residence										
Eastern part of Germany (Reference)	42	16,54	367	31,10						
Western part of Germany	212	83,46	813	68,90	2,853	(1,91 - 4,27)	<0.0005	2,605	(1,58 - 4,29)	<0.0005
Gender										
female (Reference)	90	35,43	567	48,05						
male	164	64,57	613	51,95	1,763	(1,31 - 2,37)	<0.0005	2,058	(1,40 - 3,03)	<0.0005
Maternal age (years)										
26-30 (Reference)	48	18,90	336	28,47						
0-20	37	14,57	23	1,95	12,199	(6,25 - 23,83)	<0.0005	10,057	(4,34 - 23,29)	<0.0005
21-25	67	26,38	181	15,34	2,795	(1,79 - 4,36)	<0.0005	2,889	(1,70 - 4,90)	<0.0005
>30	88	34,65	639	54,15	0,851	(0,57 - 1,27)	0,4300	0,833	(0,52 - 1,34)	0,4510
Missing	14	5,51	1	0,08	107,464	(13,40 - 861,57)	<0.0005	1,117	(0,01 - 189,26)	0,9660
Number of siblings										
No sibling (Reference)	89	35,04	585	49,58						
1-2 sibling(s)	115	45,28	544	46,10	1,351	(0,99 - 1,85)	0,0620	1,751	(1,16 - 2,66)	0,0080
≥3 siblings	26	10,24	46	3,90	3,082	(1,75 - 5,43)	<0.0005	5,558	(2,68 - 11,52)	<0.0005
Missing	24	9,45	5	0,42	35,938	(12,94 - 99,83)	<0.0005	45,343	(1,24 - 1.663,81)	0,0380
Maternal smoking (current)										
No (Reference)	118	46,46	936	79,32						
Yes	120	47,24	237	20,08	4,383	(3,16 - 6,08)	<0.0005	1,996	(1,31 - 3,04)	0,0010
Missing	16	6,30	7	0,59	19,986	(7,70 - 51,89)	<0.0005	6,365	(0,44 - 92,16)	0,1750
Breast feeding (ever)										
Yes (Reference)	133	52,36	988	83,73						
No	91	35,83	184	15,59	3,561	(2,53 - 5,02)	<0.0005	2,077	(1,35 - 3,20)	0,0010
Missing	30	11,81	8	0,68	33,390	(14,10 - 79,09)	<0.0005	6,834	(1,35 - 34,60)	0,0200
Gestational age <38 wk										
No (Reference)	194	76,38	1029	87,20						
Yes	59	23,23	135	11,44	2,248	(1,57 - 3,22)	<0.0005	1,953	(1,22 - 3,13)	0,0060
Missing	1	0,39	16	1,36	0,324	(0,04 - 2,49)	0,2790	0,000	(0,00 - 0,05)	0,0030
Maternal education										
Medium (Reference)	84	33,07	505	42,80						
Low	96	37,80	156	13,22	3,565	(2,43 - 5,23)	<0.0005	2,124	(1,32 - 3,41)	0,0020
High	55	21,65	513	43,47	0,619	(0,42 - 0,92)	0,0160	1,193	(0,74 - 1,93)	0,4710
Missing	19	7,48	6	0,51	20,583	(7,62 - 55,63)	<0.0005	2,062	(0,32 - 13,46)	0,4490
Family status										
Parents (Reference)	200	78,74	1085	91,95						
Single parent with new partner	10	3,94	12	1,02	5,814	(2,34 - 14,43)	<0.0005	2,393	(0,60 - 9,57)	0,2170
Single parent	26	10,24	80	6,78	1,939	(1,17 - 3,22)	0,0110	0,850	(0,44 - 1,66)	0,6340
Missing	18	7,09	3	0,25	46,913	(10,42 - 211,16)	<0.0005	9,934	(0,45 - 217,37)	0,1450

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 15: Ever vaccinated versus never vaccinated, unweighted case-control analysis: Uni and multivariate odds ratios for any vaccination at any point in time

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=254	(%)	Controls n=1180	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Ever vaccinated										
No	79	31.10	346	29.32						
Yes	175	68.90	834	70.68	**1.37**	(0.84 - 2.23)	0.210	**1.78**	(0.93 - 3.41)	0.084
Region of residence										
Eastern part of Germany (Reference)	42	16.54	367	31.10						
Western part of Germany	212	83.46	813	68.90	2.85	(1.91 - 4.27)	<0.0005	2.87	(1.73 - 4.77)	<0.0005
Gender										
female (Reference)	90	35.43	567	48.05						
male	164	64.57	613	51.95	1.76	(1.31 - 2.37)	<0.0005	2.05	(1.40 - 3.00)	<0.0005
Maternal age (years)										
26-30 (Reference)	48	18.90	336	28.47						
0-20	37	14.57	23	1.95	12.20	(6.25 - 23.83)	<0.0005	10.58	(4.57 - 24.52)	<0.0005
21-25	67	26.38	181	15.34	2.80	(1.79 - 4.36)	<0.0005	2.83	(1.67 - 4.79)	<0.0005
>30	88	34.65	639	54.15	0.85	(0.57 - 1.27)	0.430	0.81	(0.51 - 1.31)	0.393
Missing	14	5.51	1	0.08	107.46	(13.40 - 861.57)	<0.0005	1.87	(0.01 - 292.71)	0.809
Number of siblings										
No s bling (Reference)	89	35.04	585	49.58						
1-2 s bling(s)	115	45.28	544	46.10	1.35	(0.99 - 1.85)	0.062	1.77	(1.17 - 2.69)	0.007
≥3 siblings	26	10.24	46	3.90	3.08	(1.75 - 5.43)	<0.0005	5.67	(2.72 - 11.81)	<0.0005
Missing	24	9.45	5	0.42	35.94	(12.94 - 99.83)	<0.0005	43.36	(1.16 - 1 624.44)	0.041
Maternal smoking (current)										
No (Reference)	118	46.46	936	79.32						
Yes	120	47.24	237	20.08	4.38	(3.16 - 6.08)	<0.0005	2.04	(1.34 - 3.10)	0.001
Missing	16	6.30	7	0.59	19.99	(7.70 - 51.89)	<0.0005	6.24	(0.49 - 79.55)	0.159
Breast feeding (ever)										
Yes (Reference)	133	52.36	988	83.73						
No	91	35.83	184	15.59	3.56	(2.53 - 5.02)	<0.0005	2.05	(1.33 - 3.16)	0.001
Missing	30	11.81	8	0.68	33.39	(14.10 - 79.09)	<0.0005	7.62	(1.47 - 39.34)	0.015
Gestational age <38 wk										
No (Reference)	194	76.38	1029	87.20						
Yes	59	23.23	135	11.44	2.25	(1.57 - 3.22)	<0.0005	2.15	(1.33 - 3.45)	0.002
Missing	1	0.39	16	1.36	0.32	(0.04 - 2.49)	0.279	0.00	(0.00 - 0.04)	0.003
Maternal education										
Medium (Reference)	84	33.07	505	42.80						
Low	96	37.80	156	13.22	3.56	(2.43 - 5.23)	<0.0005	2.03	(1.27 - 3.25)	0.003
High	55	21.65	513	43.47	0.62	(0.42 - 0.92)	0.016	1.21	(0.75 - 1.96)	0.426
Missing	19	7.48	6	0.51	20.58	(7.62 - 55.63)	<0.0005	2.29	(0.38 - 13.78)	0.367
Family status										
Parents (Reference)	200	78.74	1085	91.95						
Single parent with new partner	10	3.94	12	1.02	5.81	(2.34 - 14.43)	<0.0005	2.54	(0.64 - 10.01)	0.183
Single parent	26	10.24	80	6.78	1.94	(1.17 - 3.22)	0.011	0.82	(0.42 - 1.61)	0.565
Missing	18	7.09	3	0.25	46.91	(10.42 - 211.16)	<0.0005	5.83	(0.34 - 101.08)	0.226

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 16: Ever vaccinated versus never vaccinated, age-stratified, unweighted case-control analysis: Uni and multivariate odds ratios for any vaccination at any point in time during the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model**										
Variable	Cases n=215	(%)	Controls n=986	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Ever vaccinated										
No (Reference)	79	36.74	342	34.69						
Yes	136	63.26	644	65.31	**1.33**	(0.81 - 2.18)	0.257	**1.34**	(0.70 - 2.53)	0.376
Region of residence										
Eastern part of Germany (Reference)	36	16.74	305	30.93						
Western part of Germany	179	83.26	681	69.07	2.86	(1.85 - 4.41)	<0.0005	2.63	(1.55 - 4.47)	<0.0005
Gender										
female (Reference)	73	33.95	472	47.87						
male	142	66.05	514	52.13	1.90	(1.37 - 2.64)	<0.0005	2.09	(1.38 - 3.18)	0.001
Maternal age (years)										
26-30 (Reference)	40	18.60	279	28.30						
0-20	34	15.81	18	1.83	13.89	(6.62 - 29.14)	<0.0005	8.74	(3.56 - 21.42)	<0.0005
21-25	62	28.84	148	15.01	3.19	(1.96 - 5.17)	<0.0005	2.63	(1.54 - 4.49)	<0.0005
>30	67	31.16	540	54.77	0.76	(0.49 - 1.19)	0.225	0.94	(0.57 - 1.53)	0.791
Missing	12	5.58	1	0.10	79.52	(9.77 - 647.37)	<0.0005	6.75	(0.05 - 917.06)	0.446
Number of siblings										
No sibling (Reference)	73	33.95	486	49.29						
1-2 s bling(s)	99	46.05	457	46.35	1.43	(1.01 - 2.02)	0.046			
≥3 siblings	22	10.23	40	4.06	2.94	(1.58 - 5.44)	0.001			
Missing	21	9.77	3	0.30	49.07	(13.89 - 173.35)	<0.0005			
Maternal smoking (current)										
No (Reference)	94	43.72	789	80.02						
Yes	107	49.77	192	19.47	5.09	(3.55 - 7.32)	<0.0005	2.32	(1.48 - 3.64)	<0.0005
Missing	14	6.51	5	0.51	24.14	(8.15 - 71.46)	<0.0005	0.29	(0.02 - 4.64)	0.382
Breast feeding (ever)										
Yes (Reference)	103	47.91	827	83.87						
No	85	39.53	153	15.52	4.29	(2.94 - 6.25)	<0.0005	2.64	(1.68 - 4.16)	<0.0005
Missing	27	12.56	6	0.61	37.92	(14.97 - 96.02)	<0.0005	16.71	(4.67 - 59.79)	<0.0005
Gestational age <38 wk										
No (Reference)	160	74.42	869	88.13						
Yes	54	25.12	104	10.55	2.65	(1.80 - 3.92)	<0.0005			
Missing	1	0.47	13	1.32	0.36	(0.05 - 2.81)	0.331			
Maternal education										
Medium (Reference)	72	33.49	425	43.10						
Low	83	38.60	133	13.49	3.36	(2.23 - 5.05)	<0.0005	1.79	(1.11 - 2.91)	0.018
High	43	20.00	424	43.00	0.57	(0.37 - 0.88)	0.011	1.00	(0.60 - 1.67)	0.989
Missing	17	7.91	4	0.41	24.30	(7.68 - 76.87)	<0.0005	4.31	(0.54 - 34.22)	0.167
Family status										
Parents (Reference)	167	77.67	906	91.89						
Single parent with new partner	8	3.72	9	0.91	5.40	(1.94 - 15.03)	0.001	1.72	(0.34 - 8.66)	0.510
Single parent	24	11.16	68	6.90	2.14	(1.25 - 3.67)	0.006	0.96	(0.48 - 1.91)	0.897
Missing	16	7.44	3	0.30	40.44	(8.90 - 183.73)	<0.0005	2.06	(0.12 - 34.78)	0.617

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Model was only calculable without the variables 'sibling' and 'gestational age'

Appendix Table 17: Any vaccination, weighted case-control analysis: Uni- and multivariate odds ratios for any vaccination within 72 hours

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases	(%)	Controls	(%)		(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
	n=246.9		n=1141.1		Univariate OR*					
Vaccination										
none (Reference)	234.6	95.03	1097.2	96.16						
Vaccination ≤ 72 hours	12.3	4.97	43.8	3.84	**1.18**	(0.58 - 2.40)	0.651	**1.28**	(0.50 - 3.28)	0.604
Region of residence										
Eastern part of Germany (Reference)	41.4	16.77	350.5	30.72						
Western part of Germany	205.5	83.23	790.6	69.28	2.74	(1.82 - 4.12)	<0.0005	2.56	(1.54 - 4.26)	<0.0005
Gender										
female (Reference)	87.6	35.49	546.9	47.93						
male	159.3	64.51	594.1	52.07	1.75	(1.29 - 2.36)	<0.0005	2.02	(1.37 - 2.97)	<0.0005
Maternal age (years)										
26-30 (Reference)	46.2	18.72	323.6	28.36						
0-20	36.4	14.75	21.8	1.91	12.88	(6.50 - 25.51)	<0.0005	11.05	(4.70 - 25.97)	<0.0005
21-25	64.1	25.94	176.3	15.45	2.73	(1.74 - 4.29)	<0.0005	2.91	(1.70 - 4.96)	<0.0005
>30	86.2	34.92	618.4	54.19	0.85	(0.57 - 1.28)	0.448	0.83	(0.52 - 1.35)	0.457
Missing	14.0	5.67	1.0	0.09	105.88	(13.22 - 848.13)	<0.0005	1.49	(0.01 - 208.18)	0.874
Number of siblings										
No s bling (Reference)	86.1	34.85	565.5	49.56						
1-2 s bling(s)	111.5	45.14	525.7	46.07	1.36	(0.99 - 1.88)	0.058	1.76	(1.15 - 2.68)	0.009
≥3 siblings	26.0	10.53	44.8	3.93	3.20	(1.81 - 5.66)	<0.0005	5.69	(2.74 - 11.82)	<0.0005
Missing	23.4	9.48	5.0	0.44	35.10	(12.60 - 97.79)	<0.0005	36.24	(1.15 - 1 144.72)	0.042
Maternal smoking (current)										
No (Reference)	115.6	46.83	903.6	79.19						
Yes	115.3	46.69	230.5	20.20	4.28	(3.07 - 5.97)	<0.0005	1.97	(1.29 - 3.01)	0.002
Missing	16.0	6.48	7.0	0.61	19.62	(7.57 - 50.88)	<0.0005	5.40	(0.37 - 78.13)	0.216
Breast feeding (ever)										
Yes (Reference)	130.1	52.67	956.7	83.85						
No	87.5	35.42	176.9	15.50	3.51	(2.48 - 4.97)	<0.0005	2.12	(1.37 - 3.28)	0.001
Missing	29.4	11.91	7.4	0.65	34.68	(14.21 - 84.61)	<0.0005	8.12	(1.48 - 44.68)	0.016
Gestational age <38 wk										
No (Reference)	189.3	76.66	994.2	87.13						
Yes	56.6	22.94	131.5	11.52	2.18	(1.51 - 3.13)	<0.0005	2.02	(1.25 - 3.25)	0.004
Missing	1.0	0.40	15.4	1.35	0.34	(0.04 - 2.63)	0.303	0.00	(0.00 - 0.05)	0.003
Maternal education										
Medium (Reference)	82.2	33.30	489.7	42.91						
Low	91.9	37.21	153.6	13.46	3.47	(2.35 - 5.11)	<0.0005	1.94	(1.21 - 3.12)	0.006
High	53.8	21.80	491.8	43.10	0.63	(0.42 - 0.93)	0.022	1.22	(0.75 - 1.98)	0.414
Missing	19.0	7.69	6.0	0.53	20.25	(7.50 - 54.69)	<0.0005	2.83	(0.47 - 16.94)	0.255
Family status										
Parents (Reference)	194.7	78.85	1050.2	92.04						
Single parent with new partner	8.8	3.57	12.0	1.05	5.25	(2.06 - 13.43)	0.001	2.30	(0.57 - 9.27)	0.241
Single parent	25.4	10.29	75.9	6.65	2.02	(1.21 - 3.39)	0.007	0.84	(0.43 - 1.65)	0.607
Missing	18.0	7.29	3.0	0.26	46.53	(10.36 - 209.04)	<0.0005	5.84	(0.35 - 96.80)	0.218

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 18: Any vaccination, weighted case-control analysis: Uni- and multivariate odds ratios for any vaccination within seven days

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination < 7 days										
None	231.8	93.88	1033.6	90.58						
Yes	15.1	6.12	107.5	9.42	**0.60**	(0.33 - 1.10)	0.100	**0.70**	(0.33 - 1.51)	0.364
Region of residence										
Eastern part of Germany (Reference)	41.4	16.77	350.5	30.72						
Western part of Germany	205.5	83.23	790.6	69.28	2.74	(1.82 - 4.12)	<0.0005	2.56	(1.54 - 4.26)	<0.0005
Gender										
female (Reference)	87.6	35.49	546.9	47.93						
male	159.3	64.51	594.1	52.07	1.75	(1.29 - 2.36)	<0.0005	2.02	(1.37 - 2.98)	<0.0005
Maternal age (years)										
26-30 (Reference)	46.2	18.72	323.6	28.36						
0-20	36.4	14.75	21.8	1.91	12.88	(6.50 - 25.51)	<0.0005	10.88	(4.64 - 25.52)	<0.0005
21-25	64.1	25.94	176.3	15.45	2.73	(1.74 - 4.29)	<0.0005	2.96	(1.73 - 5.06)	<0.0005
>30	86.2	34.92	618.4	54.19	0.85	(0.57 - 1.28)	0.448	0.83	(0.51 - 1.33)	0.433
Missing	14.0	5.67	1.0	0.09	105.88	(13.22 - 848.13)	<0.0005	1.04	(0.01 - 169.84)	0.987
Number of siblings										
No sibling (Reference)	86.1	34.85	565.5	49.56						
1-2 sibling(s)	111.5	45.14	525.7	46.07	1.36	(0.99 - 1.88)	0.058	1.74	(1.14 - 2.65)	0.010
≥3 siblings	26.0	10.53	44.8	3.93	3.20	(1.81 - 5.66)	<0.0005	5.67	(2.73 - 11.79)	<0.0005
Missing	23.4	9.48	5.0	0.44	35.10	(12.60 - 97.79)	<0.0005	35.41	(1.21 - 1 034.70)	0.038
Maternal smoking (current)										
No (Reference)	115.6	46.83	903.6	79.19						
Yes	115.3	46.69	230.5	20.20	4.28	(3.07 - 5.97)	<0.0005	1.97	(1.29 - 3.02)	0.002
Missing	16.0	6.48	7.0	0.61	19.62	(7.57 - 50.88)	<0.0005	8.76	(0.65 - 118.57)	0.103
Breast feeding (ever)										
Yes (Reference)	130.1	52.67	956.7	83.85						
No	87.5	35.42	176.9	15.50	3.51	(2.48 - 4.97)	<0.0005	2.08	(1.34 - 3.21)	0.001
Missing	29.4	11.91	7.4	0.65	34.68	(14.21 - 84.61)	<0.0005	7.50	(1.39 - 40.49)	0.019
Gestational age <38 wk										
No (Reference)	189.3	76.66	994.2	87.13						
Yes	56.6	22.94	131.5	11.52	2.18	(1.51 - 3.13)	<0.0005	2.02	(1.25 - 3.24)	0.004
Missing	1.0	0.40	15.4	1.35	0.34	(0.04 - 2.63)	0.303	0.00	(0.00 - 0.04)	0.002
Maternal education										
Medium (Reference)	82.2	33.30	489.7	42.91						
Low	91.9	37.21	153.6	13.46	3.47	(2.35 - 5.11)	<0.0005	1.95	(1.21 - 3.13)	0.006
High	53.8	21.80	491.8	43.10	0.63	(0.42 - 0.93)	0.022	1.21	(0.75 - 1.97)	0.438
Missing	19.0	7.69	6.0	0.53	20.25	(7.50 - 54.69)	<0.0005	3.04	(0.51 - 18.27)	0.223
Family status										
Parents (Reference)	194.7	78.85	1050.2	92.04						
Single parent with new partner	8.8	3.57	12.0	1.05	5.25	(2.06 - 13.43)	0.001	2.22	(0.54 - 9.08)	0.267
Single parent	25.4	10.29	75.9	6.65	2.02	(1.21 - 3.39)	0.007	0.84	(0.43 - 1.66)	0.623
Missing	18.0	7.29	3.0	0.26	46.53	(10.36 - 209.04)	<0.0005	5.56	(0.33 - 92.41)	0.232

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 19: Any vaccination, age-stratified weighted case-control analysis: Uni- and multivariate odds ratios for any vaccination within 72 hours in the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination within the last 72 hours and variables included in the multvariate model										
Variable	Cases	(%)	Controls	(%)		(95%CI)	p-value	Multivariate	(95%CI)	p-value
	n=207.9		n=947.1		Univariate OR*			OR**		
Vaccination										
none (Reference)	197.6	95.06	908.2	95.90						
Vaccination ≤ 72 hours	10.3	4.94	38.8	4.10	**1.06**	(0.49 - 2.26)	0.885	**1.06**	(0.36 - 3.16)	0.918
Region of residence										
Eastern part of Germany (Reference)	35.4	17.03	288.5	30.46						
Western part of Germany	172.5	82.97	658.6	69.54	2.72	(1.76 - 4.23)	<0.0005	2.28	(1.30 - 4.00)	0.004
Gender										
female (Reference)	70.6	33.97	451.9	47.72						
male	137.3	66.03	495.1	52.28	1.88	(1.35 - 2.63)	<0.0005	2.14	(1.35 - 3.38)	0.001
Maternal age (years)										
26-30 (Reference)	38.2	18.39	266.6	28.15						
0-20	33.4	16.07	16.8	1.78	14.96	(6.98 - 32.07)	<0.0005	13.92	(5.31 - 36.54)	<0.0005
21-25	59.1	28.40	143.3	15.13	3.13	(1.91 - 5.13)	<0.0005	3.63	(1.97 - 6.68)	<0.0005
>30	65.2	31.37	519.4	54.84	0.76	(0.48 - 1.20)	0.235	0.71	(0.41 - 1.23)	0.229
Missing	12.0	5.77	1.0	0.11	77.99	(9.60 - 633.81)	<0.0005	0.35	(0.00 - 198.36)	0.747
Number of siblings										
No sibling (Reference)	70.1	33.69	466.5	49.26						
1-2 s bling(s)	95.5	45.91	438.7	46.32	1.45	(1.01 - 2.06)	0.042	1.98	(1.21 - 3.24)	0.006
≥3 siblings	22.0	10.58	38.8	4.10	3.07	(1.65 - 5.72)	<0.0005	6.66	(2.89 - 15.33)	<0.0005
Missing	20.4	9.82	3.0	0.32	47.85	(13.51 - 169.52)	<0.0005	uncalculable		<0.0005
Maternal smoking (current)										
No (Reference)	91.6	44.07	756.6	79.88						
Yes	102.3	49.19	185.5	19.59	4.98	(3.44 - 7.20)	<0.0005	1.98	(1.21 - 3.22)	0.006
Missing	14.0	6.73	5.0	0.53	23.83	(8.06 - 70.47)	<0.0005	16.82	(0.53 - 532.93)	0.109
Breast feeding (ever)										
Yes (Reference)	100.1	48.12	795.7	84.02						
No	81.5	39.18	145.9	15.41	4.24	(2.89 - 6.21)	<0.0005	2.45	(1.50 - 4.00)	<0.0005
Missing	26.4	12.70	5.4	0.57	39.89	(15.16 - 104.95)	<0.0005	8.07	(1.23 - 52.89)	0.030
Gestational age <38 wk										
No (Reference)	155.3	74.68	834.2	88.08						
Yes	51.6	24.84	100.5	10.61	2.57	(1.73 - 3.82)	<0.0005	2.52	(1.47 - 4.34)	0.001
Missing	1.0	0.48	12.4	1.31	0.39	(0.05 - 3.01)	0.363	uncalculable		.
Maternal education										
Medium (Reference)	70.2	33.78	409.7	43.26						
Low	78.9	37.93	130.6	13.79	3.25	(2.15 - 4.91)	<0.0005	1.73	(1.03 - 2.93)	0.040
High	41.8	20.11	402.8	42.53	0.58	(0.37 - 0.90)	0.015	1.29	(0.73 - 2.26)	0.379
Missing	17.0	8.18	4.0	0.42	23.92	(7.57 - 75.63)	<0.0005	5.30	(0.53 - 53.51)	0.157
Family status										
Parents (Reference)	161.7	77.77	871.2	91.99						
Single parent with new partner	6.8	3.28	9.0	0.95	4.73	(1.63 - 13.72)	0.004	2.13	(0.32 - 14.23)	0.436
Single parent	23.4	11.26	63.9	6.74	2.25	(1.30 - 3.91)	0.004	0.86	(0.41 - 1.80)	0.683
Missing	16.0	7.70	3.0	0.32	40.23	(8.87 - 182.41)	<0.0005	10.36	(0.42 - 254.42)	0.152

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR only includes cases and controls for whom all categories were calculable

Appendix Table 20: Any vaccination, age-stratified weighted case-control analysis: Uni- and multivariate odds ratios for any vaccination within seven days in the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model										
Variable	Cases n=207.9	(%)	Controls n=947.1	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination < 7 days										
None	195.8	94.18	855.6	90.34						
Yes	12.1	5.82	91.5	9.66	**0.54**	(0.27 - 1.04)	0.067	**0.46**	(0.18 - 1.16)	0.100
Region of residence										
Eastern part of Germany (Reference)	35.4	17.03	288.5	30.46						
Western part of Germany	172.5	82.97	658.6	69.54	2.72	(1.76 - 4.23)	<0.0005	2.22	(1.27 - 3.88)	0.005
Gender										
female (Reference)	70.6	33.97	451.9	47.72						
male	137.3	66.03	495.1	52.28	1.88	(1.35 - 2.63)	<0.0005	2.17	(1.37 - 3.44)	0.001
Maternal age (years)										
26-30 (Reference)	38.2	18.39	266.6	28.15						
0-20	33.4	16.07	16.8	1.78	14.96	(6.98 - 32.07)	<0.0005	13.79	(5.24 - 36.28)	<0.0005
21-25	59.1	28.40	143.3	15.13	3.13	(1.91 - 5.13)	<0.0005	3.78	(2.04 - 6.99)	<0.0005
>30	65.2	31.37	519.4	54.84	0.76	(0.48 - 1.20)	0.235	0.71	(0.41 - 1.23)	0.222
Missing	12.0	5.77	1.0	0.11	77.99	(9.60 - 633.81)	<0.0005	0.21	(0.00 - 186.65)	0.651
Number of siblings										
No sibling (Reference)	70.1	33.69	466.5	49.26						
1-2 s bling(s)	95.5	45.91	438.7	46.32	1.45	(1.01 - 2.06)	0.042	1.94	(1.19 - 3.18)	0.008
≥3 siblings	22.0	10.58	38.8	4.10	3.07	(1.65 - 5.72)	<0.0005	6.63	(2.87 - 15.31)	<0.0005
Missing	20.4	9.82	3.0	0.32	47.85	(13.51 - 169.52)	<0.0005	uncalculable		<0.0005
Maternal smoking (current)										
No (Reference)	91.6	44.07	756.6	79.88						
Yes	102.3	49.19	185.5	19.59	4.98	(3.44 - 7.20)	<0.0005	1.97	(1.21 - 3.23)	0.007
Missing	14.0	6.73	5.0	0.53	23.83	(8.06 - 70.47)	<0.0005	27.68	(0.90 - 854.31)	0.058
Breast feeding (ever)										
Yes (Reference)	100.1	48.12	795.7	84.02						
No	81.5	39.18	145.9	15.41	4.24	(2.89 - 6.21)	<0.0005	2.42	(1.48 - 3.95)	<0.0005
Missing	26.4	12.70	5.4	0.57	39.89	(15.16 - 104.95)	<0.0005	6.97	(1.10 - 44.09)	0.039
Gestational age <38 wk										
No (Reference)	155.3	74.68	834.2	88.08						
Yes	51.6	24.84	100.5	10.61	2.57	(1.73 - 3.82)	<0.0005	2.50	(1.45 - 4.29)	0.001
Missing	1.0	0.48	12.4	1.31	0.39	(0.05 - 3.01)	0.363	uncalculable		.
Maternal education										
Medium (Reference)	70.2	33.78	409.7	43.26						
Low	78.9	37.93	130.6	13.79	3.25	(2.15 - 4.91)	<0.0005	1.75	(1.03 - 2.98)	0.037
High	41.8	20.11	402.8	42.53	0.58	(0.37 - 0.90)	0.015	1.27	(0.72 - 2.24)	0.407
Missing	17.0	8.18	4.0	0.42	23.92	(7.57 - 75.63)	<0.0005	7.07	(0.67 - 74.65)	0.104
Family status										
Parents (Reference)	161.7	77.77	871.2	91.99						
Single parent with new partner	6.8	3.28	9.0	0.95	4.73	(1.63 - 13.72)	0.004	1.94	(0.28 - 13.50)	0.505
Single parent	23.4	11.26	63.9	6.74	2.25	(1.30 - 3.91)	0.004	0.88	(0.42 - 1.84)	0.726
Missing	16.0	7.70	3.0	0.32	40.23	(8.87 - 182.41)	<0.0005	10.04	(0.39 - 255.53)	0.162

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany
** Multivariate OR only includes cases and controls for whom all categories were calculable

Appendix Table 21: Hexavalent and non-hexavalent vaccination, weighted case-control analysis: Uni- and multivariate odds ratios for hexavalent and non-hexavalent vaccination within 72 hours

Number (percentage), uni- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination ≤ 72 hours										
None (Reference)	234.6	95.03	1097.2	96.16						
Hexavalent	6.9	2.78	32.8	2.88	**0.97**	(0.40 - 2.35)	0.954	**1.11**	(0.36 - 3.43)	0.852
Non-hexavalent	5.4	2.19	11.0	0.96	**1.70**	(0.55 - 5.27)	0.355	**1.72**	(0.38 - 7.71)	0.481
Region of residence										
Eastern part of Germany (Reference)	41.4	16.77	350.5	30.72						
Western part of Germany	205.5	83.23	790.6	69.28	2.74	(1.82 - 4.12)	<0.0005	2.55	(1.53 - 4.24)	<0.0005
Gender										
female (Reference)	87.6	35.49	546.9	47.93						
male	159.3	64.51	594.1	52.07	1.75	(1.29 - 2.36)	<0.0005	2.02	(1.37 - 2.98)	<0.0005
Maternal age (years)										
26-30 (Reference)	46.2	18.72	323.6	28.36						
0-20	36.4	14.75	21.8	1.91	12.88	(6.50 - 25.51)	<0.0005	10.97	(4.66 - 25.80)	<0.0005
21-25	64.1	25.94	176.3	15.45	2.73	(1.74 - 4.29)	<0.0005	2.91	(1.70 - 4.97)	<0.0005
>30	86.2	34.92	618.4	54.19	0.85	(0.57 - 1.28)	0.448	0.84	(0.52 - 1.36)	0.482
Missing	14.0	5.67	1.0	0.09	105.88	(13.22 - 848.13)	<0.0005	1.55	(0.01 - 216.65)	0.861
Number of siblings										
No sibling (Reference)	86.1	34.85	565.5	49.56						
1-2 sibling(s)	111.5	45.14	525.7	46.07	1.36	(0.99 - 1.88)	0.058	1.76	(1.15 - 2.67)	0.009
≥3 siblings	26.0	10.53	44.8	3.93	3.20	(1.81 - 5.66)	<0.0005	5.68	(2.74 - 11.78)	<0.0005
Missing	23.4	9.48	5.0	0.44	35.10	(12.60 - 97.79)	<0.0005	36.73	(1.18 - 1 144.95)	0.040
Maternal smoking (current)										
No (Reference)	115.6	46.83	903.6	79.19						
Yes	115.3	46.69	230.5	20.20	4.28	(3.07 - 5.97)	<0.0005	1.96	(1.28 - 3.00)	0.002
Missing	16.0	6.48	7.0	0.61	19.62	(7.57 - 50.88)	<0.0005	4.65	(0.29 - 75.72)	0.280
Breast feeding (ever)										
Yes (Reference)	130.1	52.67	956.7	83.85						
No	87.5	35.42	176.9	15.50	3.51	(2.48 - 4.97)	<0.0005	2.14	(1.38 - 3.30)	0.001
Missing	29.4	11.91	7.4	0.65	34.68	(14.21 - 84.61)	<0.0005	7.94	(1.46 - 43.15)	0.016
Gestational age <38 wk										
No (Reference)	189.3	76.66	994.2	87.13						
Yes	56.6	22.94	131.5	11.52	2.18	(1.51 - 3.13)	<0.0005	2.00	(1.24 - 3.23)	0.004
Missing	1.0	0.40	15.4	1.35	0.34	(0.04 - 2.63)	0.303	0.00	(0.00 - 0.06)	0.003
Maternal education										
Medium (Reference)	82.2	33.30	489.7	42.91						
Low	91.9	37.21	153.6	13.46	3.47	(2.35 - 5.11)	<0.0005	1.95	(1.21 - 3.13)	0.006
High	53.8	21.80	491.8	43.10	0.63	(0.42 - 0.93)	0.022	1.22	(0.75 - 1.98)	0.423
Missing	19.0	7.69	6.0	0.53	20.25	(7.50 - 54.69)	<0.0005	2.81	(0.47 - 16.85)	0.257
Family status										
Parents (Reference)	194.7	78.85	1050.2	92.04						
Single parent with new partner	8.8	3.57	12.0	1.05	5.25	(2.06 - 13.43)	0.001	2.32	(0.58 - 9.35)	0.236
Single parent	25.4	10.29	75.9	6.65	2.02	(1.21 - 3.39)	0.007	0.84	(0.43 - 1.66)	0.622
Missing	18.0	7.29	3.0	0.26	46.53	(10.36 - 209.04)	<0.0005	6.32	(0.37 - 109.05)	0.204

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 22: Hexavalent and non-hexavalent vaccination, weighted case-control analysis: Uni- and multivariate odds ratios for hexavalent and non-hexavalent vaccination within seven days

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination < 7 days										
None (Reference)	231.8	93.88	1033.6	90.58						
Hexavalent	7.7	3.11	80.1	7.02	**0.44**	(0.20 - 0.96)	0.038	**0.53**	(0.20 - 1.37)	0.189
Non-hexavalent	7.4	3.00	27.4	2.40	**1.06**	(0.44 - 2.57)	0.897	**1.22**	(0.37 - 4.02)	0.739
Region of residence										
Eastern part of Germany (Reference)	41.4	16.77	350.5	30.72						
Western part of Germany	205.5	83.23	790.6	69.28	2.74	(1.82 - 4.12)	<0.0005	2.51	(1.51 - 4.18)	<0.0005
Gender										
female (Reference)	87.6	35.49	546.9	47.93						
male	159.3	64.51	594.1	52.07	1.75	(1.29 - 2.36)	<0.0005	2.02	(1.37 - 2.98)	<0.0005
Maternal age (years)										
26-30 (Reference)	46.2	18.72	323.6	28.36						
0-20	36.4	14.75	21.8	1.91	12.88	(6.50 - 25.51)	<0.0005	10.69	(4.54 - 25.18)	<0.0005
21-25	64.1	25.94	176.3	15.45	2.73	(1.74 - 4.29)	<0.0005	2.94	(1.72 - 5.04)	<0.0005
>30	86.2	34.92	618.4	54.19	0.85	(0.57 - 1.28)	0.448	0.83	(0.52 - 1.35)	0.459
Missing	14.0	5.67	1.0	0.09	105.88	(13.22 - 848.13)	<0.0005	1.21	(0.01 - 188.70)	0.941
Number of siblings										
No sibling (Reference)	86.1	34.85	565.5	49.56						
1-2 sibling(s)	111.5	45.14	525.7	46.07	1.36	(0.99 - 1.88)	0.058	1.74	(1.14 - 2.65)	0.010
≥3 siblings	26.0	10.53	44.8	3.93	3.20	(1.81 - 5.66)	<0.0005	5.63	(2.71 - 11.70)	<0.0005
Missing	23.4	9.48	5.0	0.44	35.10	(12.60 - 97.79)	<0.0005	37.93	(1.29 - 1 118.59)	0.035
Maternal smoking (current)										
No (Reference)	115.6	46.83	903.6	79.19						
Yes	115.3	46.69	230.5	20.20	4.28	(3.07 - 5.97)	<0.0005	1.97	(1.29 - 3.02)	0.002
Missing	16.0	6.48	7.0	0.61	19.62	(7.57 - 50.88)	<0.0005	6.56	(0.42 - 102.82)	0.181
Breast feeding (ever)										
Yes (Reference)	130.1	52.67	956.7	83.85						
No	87.5	35.42	176.9	15.50	3.51	(2.48 - 4.97)	<0.0005	2.09	(1.35 - 3.23)	0.001
Missing	29.4	11.91	7.4	0.65	34.68	(14.21 - 84.61)	<0.0005	7.01	(1.33 - 37.01)	0.022
Gestational age <38 wk										
No (Reference)	189.3	76.66	994.2	87.13						
Yes	56.6	22.94	131.5	11.52	2.18	(1.51 - 3.13)	<0.0005	1.97	(1.22 - 3.18)	0.005
Missing	1.0	0.40	15.4	1.35	0.34	(0.04 - 2.63)	0.303	0.00	(0.00 - 0.05)	0.003
Maternal education										
Medium (Reference)	82.2	33.30	489.7	42.91						
Low	91.9	37.21	153.6	13.46	3.47	(2.35 - 5.11)	<0.0005	1.97	(1.22 - 3.17)	0.005
High	53.8	21.80	491.8	43.10	0.63	(0.42 - 0.93)	0.022	1.21	(0.74 - 1.97)	0.444
Missing	19.0	7.69	6.0	0.53	20.25	(7.50 - 54.69)	<0.0005	2.79	(0.45 - 17.25)	0.269
Family status										
Parents (Reference)	194.7	78.85	1050.2	92.04						
Single parent with new partner	8.8	3.57	12.0	1.05	5.25	(2.06 - 13.43)	0.001	2.23	(0.54 - 9.16)	0.267
Single parent	25.4	10.29	75.9	6.65	2.02	(1.21 - 3.39)	0.007	0.87	(0.44 - 1.71)	0.686
Missing	18.0	7.29	3.0	0.26	46.53	(10.36 - 209.04)	<0.0005	6.33	(0.37 - 109.59)	

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 23: Hexavalent and non-hexavalent vaccination, age-stratified weighted case-control analysis: Uni- and multivariate odds ratios for hexavalent and non-hexavalent vaccination within 72 hours in the first year of life

Number (percentage), uni- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=207.9	(%)	Controls n=947.1	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination ≤ 72 hours										
None (Reference)	197.6	95.06	908.2	95.90						
Hexavalent	5.9	2.82	31.8	3.36	**0.84**	(0.33 - 2.16)	0.723	**0.75**	(0.21 - 2.72)	0.665
Non-hexavalent	4.4	2.12	7.0	0.74	**1.76**	(0.48 - 6.41)	0.392	**3.10**	(0.42 - 22.61)	0.265
Region of residence										
Eastern part of Germany (Reference)	35.4	17.03	288.5	30.46						
Western part of Germany	172.5	82.97	658.6	69.54	2.72	(1.76 - 4.23)	<0.0005	2.25	(1.29 - 3.93)	0.005
Gender										
female (Reference)	70.6	33.97	451.9	47.72						
male	137.3	66.03	495.1	52.28	1.88	(1.35 - 2.63)	<0.0005	2.11	(1.33 - 3.33)	0.001
Maternal age (years)										
26-30 (Reference)	38.2	18.39	266.6	28.15						
0-20	33.4	16.07	16.8	1.78	14.96	(6.98 - 32.07)	<0.0005	13.75	(5.21 - 36.27)	<0.0005
21-25	59.1	28.40	143.3	15.13	3.13	(1.91 - 5.13)	<0.0005	3.73	(2.02 - 6.91)	<0.0005
>30	65.2	31.37	519.4	54.84	0.76	(0.48 - 1.20)	0.235	0.74	(0.42 - 1.28)	0.282
Missing	12.0	5.77	1.0	0.11	77.99	(9.60 - 633.81)	<0.0005	0.30	(0.00 - 215.03)	0.720
Number of siblings										
No sibling (Reference)	70.1	33.69	466.5	49.26						
1-2 sibling(s)	95.5	45.91	438.7	46.32	1.45	(1.01 - 2.06)	0.042	2.00	(1.23 - 3.28)	0.006
≥3 siblings	22.0	10.58	38.8	4.10	3.07	(1.65 - 5.72)	<0.0005	6.75	(2.94 - 15.53)	<0.0005
Missing	20.4	9.82	3.0	0.32	47.85	(13.51 - 169.52)	<0.0005	uncalculable		
Maternal smoking (current)										
No (Reference)	91.6	44.07	756.6	79.88						
Yes	102.3	49.19	185.5	19.59	4.98	(3.44 - 7.20)	<0.0005	1.99	(1.22 - 3.24)	0.006
Missing	14.0	6.73	5.0	0.53	23.83	(8.06 - 70.47)	<0.0005	15.42	(0.45 - 533.05)	0.130
Breast feeding (ever)										
Yes (Reference)	100.1	48.12	795.7	84.02						
No	81.5	39.18	145.9	15.41	4.24	(2.89 - 6.21)	<0.0005	2.48	(1.52 - 4.05)	<0.0005
Missing	26.4	12.70	5.4	0.57	39.89	(15.16 - 104.95)	<0.0005	7.76	(1.24 - 48.73)	0.029
Gestational age <38 wk										
No (Reference)	155.3	74.68	834.2	88.08						
Yes	51.6	24.84	100.5	10.61	2.57	(1.73 - 3.82)	<0.0005	2.50	(1.45 - 4.31)	0.001
Missing	1.0	0.48	12.4	1.31	0.39	(0.05 - 3.01)	0.363	uncalculable		
Maternal education										
Medium (Reference)	70.2	33.78	409.7	43.26						
Low	78.9	37.93	130.6	13.79	3.25	(2.15 - 4.91)	<0.0005	1.74	(1.03 - 2.94)	0.040
High	41.8	20.11	402.8	42.53	0.58	(0.37 - 0.90)	0.015	1.27	(0.72 - 2.23)	0.411
Missing	17.0	8.18	4.0	0.42	23.92	(7.57 - 75.63)	<0.0005	4.68	(0.47 - 46.61)	0.188
Family status										
Parents (Reference)	161.7	77.77	871.2	91.99						
Single parent with new partner	6.8	3.28	9.0	0.95	4.73	(1.63 - 13.72)	0.004	2.13	(0.32 - 14.25)	0.434
Single parent	23.4	11.26	63.9	6.74	2.25	(1.30 - 3.91)	0.004	0.86	(0.41 - 1.82)	0.698
Missing	16.0	7.70	3.0	0.32	40.23	(8.87 - 182.41)	<0.0005	16.41	(0.47 - 577.93)	0.124

Univariate OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR only includes cases and controls for whom all categories were calculable

Appendix Table 24: Hexavalent and non-hexavalent vaccination, age-stratified weighted case-control analysis: Uni- and multivariate odds ratios for hexavalent and non-hexavalent vaccination within seven days in the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multivariate model										
Variable	Cases n=207.9	(%)	Controls n=947.1	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Vaccination < 7 days										
None (Reference)	197.6	95.06	908.2	95.90						
Hexavalent	5.9	2.82	31.8	3.36	**0.39**	(0.17 - 0.90)	0.027	**0.36**	(0.12 - 1.05)	0.062
Non-hexavalent	4.4	2.12	7.0	0.74	**1.17**	(0.40 - 3.46)	0.773	**1.06**	(0.20 - 5.63)	0.949
Region of residence										
Eastern part of Germany (Reference)	35.4	17.03	288.5	30.46						
Western part of Germany	172.5	82.97	658.6	69.54	2.72	(1.76 - 4.23)	<0.0005	2.18	(1.25 - 3.83)	0.006
Gender										
female (Reference)	70.6	33.97	451.9	47.72						
male	137.3	66.03	495.1	52.28	1.88	(1.35 - 2.63)	<0.0005	2.15	(1.36 - 3.41)	0.001
Maternal age (years)										
26-30 (Reference)	38.2	18.39	266.6	28.15						
0-20	33.4	16.07	16.8	1.78	14.96	(6.98 - 32.07)	<0.0005	13.40	(5.05 - 35.54)	<0.0005
21-25	59.1	28.40	143.3	15.13	3.13	(1.91 - 5.13)	<0.0005	3.77	(2.03 - 7.00)	<0.0005
>30	65.2	31.37	519.4	54.84	0.76	(0.48 - 1.20)	0.235	0.72	(0.42 - 1.25)	0.243
Missing	12.0	5.77	1.0	0.11	77.99	(9.60 - 633.81)	<0.0005	0.20	(0.00 - 197.84)	0.649
Number of siblings										
No s bling (Reference)	70.1	33.69	466.5	49.26						
1-2 s bling(s)	95.5	45.91	438.7	46.32	1.45	(1.01 - 2.06)	0.042	1.95	(1.19 - 3.20)	0.008
≥3 siblings	22.0	10.58	38.8	4.10	3.07	(1.65 - 5.72)	<0.0005	6.62	(2.87 - 15.29)	<0.0005
Missing	20.4	9.82	3.0	0.32	47.85	(13.51 - 169.52)	<0.0005	uncalculable		
Maternal smoking (current)										
No (Reference)	91.6	44.07	756.6	79.88						
Yes	102.3	49.19	185.5	19.59	4.98	(3.44 - 7.20)	<0.0005	1.98	(1.21 - 3.25)	0.007
Missing	14.0	6.73	5.0	0.53	23.83	(8.06 - 70.47)	<0.0005	26.05	(0.76 - 887.08)	0.070
Breast feeding (ever)										
Yes (Reference)	100.1	48.12	795.7	84.02						
No	81.5	39.18	145.9	15.41	4.24	(2.89 - 6.21)	<0.0005	2.42	(1.48 - 3.96)	<0.0005
Missing	26.4	12.70	5.4	0.57	39.89	(15.16 - 104.95)	<0.0005	6.75	(1.09 - 41.62)	0.040
Gestational age <38 wk										
No (Reference)	155.3	74.68	834.2	88.08						
Yes	51.6	24.84	100.5	10.61	2.57	(1.73 - 3.82)	<0.0005	2.45	(1.42 - 4.22)	0.001
Missing	1.0	0.48	12.4	1.31	0.39	(0.05 - 3.01)	0.363	uncalculable		
Maternal education										
Medium (Reference)	70.2	33.78	409.7	43.26						
Low	78.9	37.93	130.6	13.79	3.25	(2.15 - 4.91)	<0.0005	1.77	(1.04 - 3.01)	0.036
High	41.8	20.11	402.8	42.53	0.58	(0.37 - 0.90)	0.015	1.27	(0.72 - 2.24)	0.417
Missing	17.0	8.18	4.0	0.42	23.92	(7.57 - 75.63)	<0.0005	5.70	(0.49 - 66.64)	0.165
Family status										
Parents (Reference)	161.7	77.77	871.2	91.99						
Single parent with new partner	6.8	3.28	9.0	0.95	4.73	(1.63 - 13.72)	0.004	1.84	(0.26 - 13.05)	0.541
Single parent	23.4	11.26	63.9	6.74	2.25	(1.30 - 3.91)	0.004	0.90	(0.42 - 1.90)	0.776
Missing	16.0	7.70	3.0	0.32	40.23	(8.87 - 182.41)	<0.0005	13.68	(0.43 - 437.91)	0.000

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

** Multivariate OR only includes cases and controls for whom all categories were calculable

Appendix Table 25: Pentavalent and non-pentavalent vaccination, weighted case-control analysis: Uni- and multivariate odds ratios for pentavalent and non-pentavalent vaccination within 72 hours

Number (percentage), uni- and multivariate odds ratios for vaccination within the last 72 hours and variables included in the multvariate model										
Variable	Cases n=246,92	(%)	Controls n=1141,06	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination ≤ 72 hours										
None (Reference)	234,6	95,03	1097,2	96,16						
Pentavalent**	3,4	1,38	2,0	0,18	**6,161**	(0,98 - 38,85)	0,0530			
Non-pentavalent	8,9	3,59	41,8	3,67	**0,884**	(0,39 - 1,99)	0,7650	**0,778**	(0,27 - 2,28)	0,6470
Region of residence										
Eastern part of Germany (Reference)	41,4	16,77	350,5	30,72						
Western part of Germany	205,5	83,23	790,6	69,28	2,738	(1,82 - 4,12)	<0.0005	2,456	(1,48 - 4,08)	0,0010
Gender										
female (Reference)	87,6	35,49	546,9	47,93						
male	159,3	64,51	594,1	52,07	1,748	(1,29 - 2,36)	<0.0005	1,979	(1,34 - 2,92)	0,0010
Maternal age (years)										
26-30 (Reference)	46,2	18,72	323,6	28,36						
0-20	36,4	14,75	21,8	1,91	12,878	(6,50 - 25,51)	<0.0005	10,991	(4,68 - 25,83)	<0.0005
21-25	64,1	25,94	176,3	15,45	2,733	(1,74 - 4,29)	<0.0005	2,992	(1,74 - 5,14)	<0.0005
>30	86,2	34,92	618,4	54,19	0,854	(0,57 - 1,28)	0,4480	0,859	(0,53 - 1,39)	0,5390
Missing	14,0	5,67	1,0	0,09	105,876	(13,22 - 848,13)	<0.0005	1,012	(0,00 - 212,84)	0,9960
Number of siblings										
No s bling (Reference)	86,1	34,85	565,5	49,56						
1-2 s bling(s)	111,5	45,14	525,7	46,07	1,364	(0,99 - 1,88)	0,0580	1,791	(1,17 - 2,73)	0,0070
≥3 siblings	26,0	10,53	44,8	3,93	3,201	(1,81 - 5,66)	<0.0005	5,812	(2,80 - 12,08)	<0.0005
Missing	23,4	9,48	5,0	0,44	35,103	(12,60 - 97,79)	<0.0005	40,505	(1,18 - 1.395,13)	0,0400
Maternal smoking (current)										
No (Reference)	115,6	46,83	903,6	79,19						
Yes	115,3	46,69	230,5	20,20	4,277	(3,07 - 5,97)	<0.0005	1,955	(1,28 - 2,99)	0,0020
Missing	16,0	6,48	7,0	0,61	19,621	(7,57 - 50,88)	<0.0005	4,545	(0,26 - 79,18)	0,2990
Breast feeding (ever)										
Yes (Reference)	130,1	52,67	956,7	83,85						
No	87,5	35,42	176,9	15,50	3,509	(2,48 - 4,97)	<0.0005	2,145	(1,39 - 3,32)	0,0010
Missing	29,4	11,91	7,4	0,65	34,675	(14,21 - 84,61)	<0.0005	7,731	(1,46 - 41,06)	0,0160
Gestational age <38 wk										
No (Reference)	189,3	76,66	994,2	87,13						
Yes	56,6	22,94	131,5	11,52	2,177	(1,51 - 3,13)	<0.0005	1,984	(1,23 - 3,20)	0,0050
Missing	1,0	0,40	15,4	1,35	0,342	(0,04 - 2,63)	0,3030	0,000	(0,00 - 0,05)	0,0040
Maternal education										
Medium (Reference)	82,2	33,30	489,7	42,91						
Low	91,9	37,21	153,6	13,46	3,465	(2,35 - 5,11)	<0.0005	2,030	(1,26 - 3,28)	0,0040
High	53,8	21,80	491,8	43,10	0,629	(0,42 - 0,93)	0,0220	1,215	(0,75 - 1,98)	0,4330
Missing	19,0	7,69	6,0	0,53	20,247	(7,50 - 54,69)	<0.0005	2,329	(0,39 - 13,97)	0,3550
Family status										
Parents (Reference)	194,7	78,85	1050,2	92,04						
Single parent with new partner	8,8	3,57	12,0	1,05	5,254	(2,06 - 13,43)	0,0010	2,348	(0,58 - 9,58)	0,2340
Single parent	25,4	10,29	75,9	6,65	2,024	(1,21 - 3,39)	0,0070	0,841	(0,43 - 1,66)	0,6190
Missing	18,0	7,29	3,0	0,26	46,530	(10,36 - 209,04)	<0.0005	15,088	(0,52 - 435,52)	0,1140

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 26: Pentavalent and non-pentavalent vaccination, weighted case-control analysis: Uni- and multivariate odds ratios for pentavalent and non-pentavalent vaccination within seven days

Number (percentage), uni- and multivariate odds ratios for vaccination within the last 7 days and variables included in the multvariate model										
Variable	Cases n=246,92	(%)	Controls n=1141,06	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Vaccination ≤ 7 days										
None (Reference)	231,8	93,88	1033,6	90,58						
Pentavalent**	4,4	1,79	6,0	0,53	**2,658**	(0,73 - 9,67)	0,1380			
Non-pentavalent	10,7	4,33	101,5	8,89	**0,449**	(0,22 - 0,91)	0,0250	**0,502**	(0,21 - 1,21)	0,1240
Region of residence										
Eastern part of Germany (Reference)	41,4	16,77	350,5	30,72						
Western part of Germany	205,5	83,23	790,6	69,28	2,738	(1,82 - 4,12)	<0.0005	2,470	(1,48 - 4,12)	0,0010
Gender										
female (Reference)	87,6	35,49	546,9	47,93						
male	159,3	64,51	594,1	52,07	1,748	(1,29 - 2,36)	<0.0005	2,020	(1,37 - 2,98)	<0.0005
Maternal age (years)										
26-30 (Reference)	46,2	18,72	323,6	28,36						
0-20	36,4	14,75	21,8	1,91	12,878	(6,50 - 25,51)	<0.0005	10,764	(4,57 - 25,33)	<0.0005
21-25	64,1	25,94	176,3	15,45	2,733	(1,74 - 4,29)	<0.0005	2,930	(1,71 - 5,03)	<0.0005
>30	86,2	34,92	618,4	54,19	0,854	(0,57 - 1,28)	0,4480	0,837	(0,52 - 1,35)	0,4680
Missing	14,0	5,67	1,0	0,09	105,876	(13,22 - 848,13)	<0.0005	0,952	(0,00 - 184,69)	0,9850
Number of siblings										
No sibling (Reference)	86,1	34,85	565,5	49,56						
1-2 s bling(s)	111,5	45,14	525,7	46,07	1,364	(0,99 - 1,88)	0,0580	1,764	(1,16 - 2,69)	0,0080
≥3 siblings	26,0	10,53	44,8	3,93	3,201	(1,81 - 5,66)	<0.0005	5,697	(2,74 - 11,84)	<0.0005
Missing	23,4	9,48	5,0	0,44	35,103	(12,60 - 97,79)	<0.0005	42,538	(1,20 - 1.503,43)	0,0390
Maternal smoking (current)										
No (Reference)	115,6	46,83	903,6	79,19						
Yes	115,3	46,69	230,5	20,20	4,277	(3,07 - 5,97)	<0.0005	1,952	(1,27 - 2,99)	0,0020
Missing	16,0	6,48	7,0	0,61	19,621	(7,57 - 50,88)	<0.0005	7,947	(0,52 - 120,80)	0,1350
Breast feeding (ever)										
Yes (Reference)	130,1	52,67	956,7	83,85						
No	87,5	35,42	176,9	15,50	3,509	(2,48 - 4,97)	<0.0005	2,057	(1,33 - 3,19)	0,0010
Missing	29,4	11,91	7,4	0,65	34,675	(14,21 - 84,61)	<0.0005	7,177	(1,36 - 37,81)	0,0200
Gestational age <38 wk										
No (Reference)	189,3	76,66	994,2	87,13						
Yes	56,6	22,94	131,5	11,52	2,177	(1,51 - 3,13)	<0.0005	1,953	(1,21 - 3,14)	0,0060
Missing	1,0	0,40	15,4	1,35	0,342	(0,04 - 2,63)	0,3030	0,000	(0,00 - 0,05)	0,0030
Maternal education										
Medium (Reference)	82,2	33,30	489,7	42,91						
Low	91,9	37,21	153,6	13,46	3,465	(2,35 - 5,11)	<0.0005	2,029	(1,26 - 3,28)	0,0040
High	53,8	21,80	491,8	43,10	0,629	(0,42 - 0,93)	0,0220	1,211	(0,74 - 1,97)	0,4420
Missing	19,0	7,69	6,0	0,53	20,247	(7,50 - 54,69)	<0.0005	2,038	(0,31 - 13,43)	0,4590
Family status										
Parents (Reference)	194,7	78,85	1050,2	92,04						
Single parent with new partner	8,8	3,57	12,0	1,05	5,254	(2,06 - 13,43)	0,0010	2,123	(0,51 - 8,82)	0,3000
Single parent	25,4	10,29	75,9	6,65	2,024	(1,21 - 3,39)	0,0070	0,865	(0,44 - 1,71)	0,6770
Missing	18,0	7,29	3,0	0,26	46,530	(10,36 - 209,04)	<0.0005	10,185	(0,46 - 227,02)	0,1430

Univariate OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 27: Ever vaccinated versus never vaccinated, weighted case-control analysis: Uni and multivariate odds ratios for any vaccination at any point in time

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=246.9	(%)	Controls n=1141.1	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR	(95%CI)	p-value
Ever vaccinated										
No	78.4	31.76	330.1	28.93						
Yes	168.5	68.24	811.0	71.07	**1.20**	(0.73 - 1.97)	0.479	**1.58**	(0.81 - 3.07)	0.181
Region of residence										
Eastern part of Germany (Reference)	41.4	16.77	350.5	30.72						
Western part of Germany	205.5	83.23	790.6	69.28	2.74	(1.82 - 4.12)	<0.0005	2.71	(1.62 - 4.54)	<0.0005
Gender										
female (Reference)	87.6	35.49	546.9	47.93						
male	159.3	64.51	594.1	52.07	1.75	(1.29 - 2.36)	<0.0005	2.02	(1.37 - 2.97)	<0.0005
Maternal age (years)										
26-30 (Reference)	46.2	18.72	323.6	28.36						
0-20	36.4	14.75	21.8	1.91	12.88	(6.50 - 25.51)	<0.0005	11.02	(4.70 - 25.83)	<0.0005
21-25	64.1	25.94	176.3	15.45	2.73	(1.74 - 4.29)	<0.0005	2.85	(1.67 - 4.88)	<0.0005
>30	86.2	34.92	618.4	54.19	0.85	(0.57 - 1.28)	0.448	0.82	(0.51 - 1.33)	0.429
Missing	14.0	5.67	1.0	0.09	105.88	(13.22 - 848.13)	<0.0005	1.75	(0.01 - 275.30)	0.828
Number of siblings										
No sibling (Reference)	86.1	34.85	565.5	49.56						
1-2 sibling(s)	111.5	45.14	525.7	46.07	1.36	(0.99 - 1.88)	0.058	1.77	(1.17 - 2.70)	0.008
≥3 siblings	26.0	10.53	44.8	3.93	3.20	(1.81 - 5.66)	<0.0005	5.79	(2.78 - 12.06)	<0.0005
Missing	23.4	9.48	5.0	0.44	35.10	(12.60 - 97.79)	<0.0005	39.98	(1.10 - 1 448.50)	0.044
Maternal smoking (current)										
No (Reference)	115.6	46.83	903.6	79.19						
Yes	115.3	46.69	230.5	20.20	4.28	(3.07 - 5.97)	<0.0005	2.01	(1.31 - 3.08)	0.001
Missing	16.0	6.48	7.0	0.61	19.62	(7.57 - 50.88)	<0.0005	6.29	(0.49 - 80.61)	0.158
Breast feeding (ever)										
Yes (Reference)	130.1	52.67	956.7	83.85						
No	87.5	35.42	176.9	15.50	3.51	(2.48 - 4.97)	<0.0005	2.08	(1.35 - 3.21)	0.001
Missing	29.4	11.91	7.4	0.65	34.68	(14.21 - 84.61)	<0.0005	8.19	(1.51 - 44.32)	0.015
Gestational age <38 wk										
No (Reference)	189.3	76.66	994.2	87.13						
Yes	56.6	22.94	131.5	11.52	2.18	(1.51 - 3.13)	<0.0005	2.10	(1.30 - 3.39)	0.002
Missing	1.0	0.40	15.4	1.35	0.34	(0.04 - 2.63)	0.303	0.00	(0.00 - 0.04)	0.003
Maternal education										
Medium (Reference)	82.2	33.30	489.7	42.91						
Low	91.9	37.21	153.6	13.46	3.47	(2.35 - 5.11)	<0.0005	1.95	(1.21 - 3.15)	0.006
High	53.8	21.80	491.8	43.10	0.63	(0.42 - 0.93)	0.022	1.24	(0.76 - 2.01)	0.391
Missing	19.0	7.69	6.0	0.53	20.25	(7.50 - 54.69)	<0.0005	2.35	(0.39 - 14.26)	0.354
Family status										
Parents (Reference)	194.7	78.85	1050.2	92.04						
Single parent with new partner	8.8	3.57	12.0	1.05	5.25	(2.06 - 13.43)	0.001	2.36	(0.58 - 9.50)	0.228
Single parent	25.4	10.29	75.9	6.65	2.02	(1.21 - 3.39)	0.007	0.84	(0.42 - 1.65)	0.608
Missing	18.0	7.29	3.0	0.26	46.53	(10.36 - 209.04)	<0.0005	5.91	(0.34 - 101.35)	0.221

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany

Appendix Table 28: Ever vaccinated versus never vaccinated, age-stratified, weighted case-control analysis: Uni and multivariate odds ratios for any vaccination at any point in time during the first year of life

Number (percentage), univariate- and multivariate odds ratios for vaccination and variables included in the multvariate model										
Variable	Cases n=207.9	(%)	Controls n=947.1	(%)	Univariate OR*	(95%CI)	p-value	Multivariate OR**	(95%CI)	p-value
Ever vaccinated										
No	78.4	37.71	326.1	34.43						
Yes	129.5	62.29	621.0	65.57	**1.16**	(0.70 - 1.92)	0.568	**1.20**	(0.60 - 2.40)	0.613
Region of residence										
Eastern part of Germany (Reference)	35.4	17.03	288.5	30.46						
Western part of Germany	172.5	82.97	658.6	69.54	2.72	(1.76 - 4.23)	<0.0005	2.34	(1.32 - 4.12)	0.003
Gender										
female (Reference)	70.6	33.97	451.9	47.72						
male	137.3	66.03	495.1	52.28	1.88	(1.35 - 2.63)	<0.0005	2.14	(1.35 - 3.37)	0.001
Maternal age (years)										
26-30 (Reference)	38.2	18.39	266.6	28.15						
0-20	33.4	16.07	16.8	1.78	14.96	(6.98 - 32.07)	<0.0005	13.78	(5.26 - 36.12)	<0.0005
21-25	59.1	28.40	143.3	15.13	3.13	(1.91 - 5.13)	<0.0005	3.58	(1.94 - 6.60)	<0.0005
>30	65.2	31.37	519.4	54.84	0.76	(0.48 - 1.20)	0.235	0.71	(0.41 - 1.23)	0.225
Missing	12.0	5.77	1.0	0.11	77.99	(9.60 - 633.81)	<0.0005	0.39	(0.00 - 227.95)	0.772
Number of siblings										
No sibling (Reference)	70.1	33.69	466.5	49.26						
1-2 sibling(s)	95.5	45.91	438.7	46.32	1.45	(1.01 - 2.06)	0.042	1.99	(1.22 - 3.24)	0.006
≥3 siblings	22.0	10.58	38.8	4.10	3.07	(1.65 - 5.72)	<0.0005	6.67	(2.89 - 15.37)	<0.0005
Missing	20.4	9.82	3.0	0.32	47.85	(13.51 - 169.52)	<0.0005	uncalculable		
Maternal smoking (current)										
No (Reference)	91.6	44.07	756.6	79.88						
Yes	102.3	49.19	185.5	19.59	4.98	(3.44 - 7.20)	<0.0005	2.00	(1.22 - 3.26)	0.006
Missing	14.0	6.73	5.0	0.53	23.83	(8.06 - 70.47)	<0.0005	17.02	(0.62 - 471.06)	0.094
Breast feeding (ever)										
Yes (Reference)	100.1	48.12	795.7	84.02						
No	81.5	39.18	145.9	15.41	4.24	(2.89 - 6.21)	<0.0005	2.43	(1.49 - 3.97)	<0.0005
Missing	26.4	12.70	5.4	0.57	39.89	(15.16 - 104.95)	<0.0005	8.11	(1.25 - 52.65)	0.028
Gestational age <38 wk										
No (Reference)	155.3	74.68	834.2	88.08						
Yes	51.6	24.84	100.5	10.61	2.57	(1.73 - 3.82)	<0.0005	2.55	(1.48 - 4.40)	0.001
Missing	1.0	0.48	12.4	1.31	0.39	(0.05 - 3.01)	0.363	uncalculable		
Maternal education										
Medium (Reference)	70.2	33.78	409.7	43.26						
Low	78.9	37.93	130.6	13.79	3.25	(2.15 - 4.91)	<0.0005	1.73	(1.03 - 2.93)	0.040
High	41.8	20.11	402.8	42.53	0.58	(0.37 - 0.90)	0.015	1.29	(0.74 - 2.28)	0.369
Missing	17.0	8.18	4.0	0.42	23.92	(7.57 - 75.63)	<0.0005	4.86	(0.48 - 49.61)	0.183
Family status										
Parents (Reference)	161.7	77.77	871.2	91.99						
Single parent with new partner	6.8	3.28	9.0	0.95	4.73	(1.63 - 13.72)	0.004	2.16	(0.32 - 14.46)	0.428
Single parent	23.4	11.26	63.9	6.74	2.25	(1.30 - 3.91)	0.004	0.86	(0.41 - 1.80)	0.682
Missing	16.0	7.70	3.0	0.32	40.23	(8.87 - 182.41)	<0.0005	10.45	(0.42 - 261.58)	0.153

* 'Univariate' OR are adusted for oversampling of control children living in the eastern part of Germany
** Multivariate OR only includes cases and controls for whom all categories were calculable