Annex to the study report of the

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

(TOKEN Study)

CONTENT

Study protocol

Robert Koch Institute

Study Protocol

Study on deaths in young children (2. - 24th month of life)

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Confidential

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Study on deaths in young children (2.- 24th month of life)

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4 Background

From spontaneous notifications, the PEI learnt of (several) cases of death in young children in close (temporal) relation to the administration of hexavalent vaccines. Since licensing of hexavalent vaccines in 2000 up to the end of November 2004 23 cases were reported including four children in the second year of life. All had died suddenly and unexpectedly within two days of receiving a hexavalent vaccine.

A statistical analysis of these cases, undertaken by von Kries, et al. (von Kries 2003) – in which observed deaths were compared with the number of expected cases – revealed no statistically significant increased standardised mortality ratio (SMR) for children under the age of one. For children between one and two years of age, however, a statistically significant increased SMR ($SMR>1$; $p<0.05$) was calculated for one of the two licensed hexavalent vaccines. The 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 one and two years of age.

This initial analysis, however, contains various degrees of uncertainty. In relying on a very low number of cases, especially for the second year of life (n=4), the outcome might be substantially affected by a single misclassified case. General practise in determinating the cause of death involves a wide range of non-standardised procedures. Interpretation of results from post-mortem examinations are likely to differ between pathologists. Exclusion of defined natural causes of death remains inconclusive for some deaths in temporal association with vaccination. Brain oedema should be regarded as a feature repeatedly detected in cases of death associated with vaccination and should be investigated in a standardised manner. Because the cases were reported spontaneously, and thus collected unsystematically, they could show a biased picture of reality. Observed versus expected calculations performed for the first year of life indicate a considerable degree of underreporting. Furthermore, 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, so the denominators of the SMRs have to be deemed somewhat unreliable.

Therefore, this prospective study will systematically examine a potential association between deaths (especially sudden and unexpected cases) in children deceased within the second to 24th month of life (i.e. from the first *completed* month of life to the end of the 24th *completed* month) and the administration of vaccines for the next three years..

This study has two branches: An ‘epidemiological approach’ and a ‘pathological approach’. Within the scope of the ‘epidemiological approach’ local health authorities (LHA ‘*Gesundheitsamt*’) will be asked on a monthly basis to select all death certificates of children deceased within the second to 24^{th} month of life (active surveillance).
Informed consent will be obtained from parents or legal guardians and questionnaires will be send to parents and the doctor responsible for the treatment of the deceased child. The ques-

tionnaires ask for a comprehensive vaccination history and other data relevant to health (including autopsies), for data related to the development of the child and to socio-demographic features (see parents' and doctor's questionnaires Annex 1 and 2).

The 'pathological approach' will include all cases of sudden death deceased within the tenth to 24th month of life for which standardised post mortem examinations were undertaken. All institutes of legal medicine and pathology in Germany will be queried on a monthly basis (active surveillance) whether post mortem examinations have been carried out in children deceased within the tenth to 24th month of life during the past month. Parents or guardians of cases will be asked to give informed consent that all autopsy data may be used in this study. The same standardised questionnaires as used in the 'epidemiological approach' will be send to parents and physicians.'

5 Objective

To clarify a potential temporal association between vaccination and sudden cases of death in young children deceased within the second to 24th months of life in Germany and to investigate whether the risk of sudden death in vaccinated children is different from that of unvaccinated children within the second to 24th months of life.
To facilitate comprehensive assessment of a possible causal association between vaccination and sudden death.

6 Study questions

1. Is there a temporal association between vaccination and risk of sudden death in the first two years of life?
2. For what length of time after vaccination is the risk of death potentially increased?
3. Is this potential association qualitatively and quantitatively the same at different stages of life?
4. Has this potential association the same magnitude across different –hexavalent– vaccines?
5. Is there a common pathological mechanism for cases of sudden death following vaccination (autopsied cases only)?
6. Is the risk of sudden death in vaccinated children different from unvaccinated children?

7 Study region

The territory of the Federal Republic of Germany.

8 Duration of the Study

The duration of the field phase is three years.
Scheduled start: Third quarter of 2005.

9 Methods

An ideal study design would have the following properties: non-selective, prospective case ascertainment, standardised autopsies in all cases, full information on outcome, exposure and confounders and adequate selection of controls.

For obvious reasons, all desirable properties cannot be achieved by a single study approach. In-depths analyses by autopsies of patho-mechanism cannot be performed in all deaths of children in the second to 24th month and these data would not provide any information on the strength of a possible association. Strength of association, however, can be evaluated by epidemiological methods if a high number of cases is available, but imply disadvantages in terms of diagnostic certainty.
This is why this study has two approaches which complement each other.

The path of the data flow is illustrated in Figure 1 (see 9.9.4).

9.1 Epidemiological approach

In the 'epidemiological approach' local health authorities (LHA) will identify all cases of death in children deceased within the second to 24th months of life. With institutional approval from federal authorities, the RKI will query all collaborating LHA's on a monthly basis (active surveillance) whether any such cases have occurred in the previous month. The LHAs will answer this request by sending either a negative reply or photocopies of the relevant death certificates, on which the name, gender and address are to be blacked out for reasons of data protection.

These photocopies will be checked at the RKI for meeting the entrance criteria and to make sure that the case has not already been enrolled in the pathological approach (see below).

- If the case has already been enrolled in the pathological approach (see below) and informed consent of a parent or guardian has been obtained, the project partner in Magdeburg (MD) can then gather the relevant medical data from doctors and the parent or guardian (see below).
- If the case has not been enrolled via the pathological approach, informed consent of a parent or guardian must first be obtained.

In such cases, the RKI will ask the LHA involved to identify the parents or guardians, to inform them about the study and to obtain consent for study participation. This consent will extend to the release of the child's doctors from their obligations concerning patient confidentiality. The LHA will receive written material for that purpose from the RKI, and the parent or guardian will send their response (consenting or withholding consent in a freepost envelope) to the LHA which transmit the informed consent to the RKI. If there is no response after 10 days, a second letter will be sent by the LHA. If there is still no response after another 10 days have passed, the LHA will make additional attempts to contact them by telephone or personally. All attempts to contact parents and to obtain informed consent will be recorded on a form for evaluation. Should the parents or guardians withhold informed consent, they will be sent a freepost non-responder questionnaire, asking for reasons of non-participation, socio-economic status, the age of the mother, single parent status, number of children, smoking status and the vaccination status of the deceased child.

Following consent, the RKI will give the project team at MD all necessary information to contact the parents and the child's doctor, in order to obtain comprehensive data that allow for analyses according to the recommendations of the Brighton Collaboration Work Group on SIDS. These data will be obtained by standardised questionnaires (see parents' and doctor's questionnaires Annex 1 and 2) which comprise information on vaccination history (time and

form of the vaccination, information on the vaccine product), data on infant and mother, information on the event and other data relevant to health.

All information available from the death certificate, from the parents and physicians questionnaires, from potential clinical reports and any available autopsy reports will be used to perform a best possible classification of the cause of death by a paediatrician expert at the RKI who will be blinded against history of exposure and specially trained on ICD-10 classification. An independent second classification will be performed by another trained physician at the RKI. If one or both of these experts classify the cause of death to ICD-10 R95-99, the death certificate will be send to the DIMDI (Deutsches Institut für Medizinische Dokumentation und Information). At the DIMDI the national expert for ICD-10 classification will also perform ICD-10 classification. Complete data and assessment of all three coding experts will be provided to a multi-disciplinary case conference. Decision on classification to ICD-10 R95-R99 will be performed by this case conference. Every death classified to R95-R99 will be defined as case. All persons involved in case ascertainment, reporting and coding of diagnoses or causes of death will be blinded to any exposure history in the epidemiological part of the study.

Data of the epidemiological approach will be statistically analysed by two methods: Analyses of a possible temporal association will be performed by a self-controlled case series design. Estimates of relative risks of sudden unexplained death associated with vaccination will be performed by a case-control design.

9.1.1 Self-Controlled Case Series design (SCCS)

In order to answer the first four study questions, deaths subsequent to vaccinations will be analysed using a self-controlled case series analysis to examine whether the time of death in these cases is in conspicuous proximity to the time of vaccination. The analysis is to be carried out according to the method published by Farrington in 1995 for very rare, non-recurring events.

A self-controlled case series analysis has the advantage of an implicit control of any potential confounders, even when unknown, which are stable over time and can also control for age effects. For unique events, this method requires the additional assumption that the cumulative incidence of events in the population over the observed period is low. Ascertainment of cases must be independent of vaccination status (Farrington 1995). Data analyses can be performed early and time efficiently. Compared to cohort or case-control studies, a self-controlled case series analysis tends to be faster and less expensive when examining rare events, as only information on cases is required.

Besides these strengths, the SCCS method has some limitations. Like cohort or case-control studies even the self-controlled case series method remains susceptible to some bias if vaccination is timed to minimize the risk of an adverse event. Eliminating the effect of time constant covariables is equivalent to eliminating the analyses of the effect of any time-constant covariables. This means that such covariables cannot be studies in a SCCS analyses. In principle the case series method is able to estimate relative risks, but this is not true with non-recurrent events like death. Therefore, the case series method is unable to estimate the magnitude of any potential effect of vaccination on risk of death. Even if there were a general, but delayed protective effect of a vaccination, this may result in an accumulation of events shortly after vaccination. To overcome these limitations and to study the effect of vaccination on risk

of death, additional analyses using a case-control design will be performed to complement the self-controlled case series method.

9.1.2 Case-Control Study

By a case-control study, vaccination histories of cases (deceased children)and controls (children at live) will be compared in order to study the effect of vaccination on risk of death (study question 6) and to study the effects of covariables. This method allows for detection and assessment of risk factors and identification of vulnerable subgroups. In comparison with a cohort study, it has the advantage of lower cost and is ideal for rare events.

A prospective approach is necessary to ensure a standardised case ascertainment independently of vaccination status. Using the case-control approach in rare events, relative risk can be reliably estimated by odds ratios. Odds ratios can be adjusted for potential confounders by multivariate logistic regression. It is important to select controls appropriately, since selection bias in controls can potentially compromise representativeness and introduce a systematic error in effect estimates. Particularly in studies on vaccination, one has to expect potential confounding by health awareness of parents, e. g. if children from low educated parents are more or less likely to be immunised. In studies unable to adjust for such effects, odds ratios for immunisation effects may systematically over- or under-estimate any true association.

9.1.3 Sequential Analyses

Since the results from this study are of particular importance to public health, data analyses should not be left to the end of the study. This is why a sequential data analysis of the SCCS data is intended as a monitoring instrument while the study is running. Ongoing monitoring using the one sided open Sequential Probability Ratio Tests (SPRT) of Wald will be undertaken. For this purpose, a warning line will be defined in the graph with the number of cases on the x-axis and the cumulated test results on the y-axis. Should the path of test points cross the warning line, a full interim analysis (SCCS and case-control analyses) will be performed.

The sequential analyses will be performed after each new case with the SCCS method and can only give rough hints because age, season or any other confounder cannot be controlled for.

9.2 Pat hological approach

The pathological approach of this study is intended to maximise the diagnostic validity in cases to detect natural causes of death that can be taken as sufficient explanations.

Complete ascertainment of sudden and unexpected deaths occurring during the tenth to 24th month of life for which post mortem examinations have been carried out is aspired.
All institutes of legal medicine and pathology in Germany will be informed in advance and agreement for collaboration will be sought. Study protocol, informed consent forms and case report forms will be provided to collaborating institutes of legal medicine and pathology. This collaboration requires that children deceased between the tenth and 24th month of life will be autopsied and specimens processed according to the study-protocol. With the aim to exclude any natural cause of death and detect possibly unknown patho-mechanism, there will be additional neuropathological, immuno-histochemical, bacteriological, virological and immunological investigations and also investigations for predisposing genetic factors. The institutes will identify eligible cases, ask parents for informed consent and pass the case report form and the informed consent to the RKI.

When informed consent of the parents or guardians could be obtained, data and additional samples will be made available to the Institute of Forensic Medicine of the University of Essen. All data from this part of the study will be stored and analysed at the LMU.

At this stage the case will be identified by a so called 'institutsinterne Sektionsnummer' (autopsy identifying number of the local institutes 'internal autopsy number'). This number fits the regular collection system of the institute's of legal medicine and pathology. RKI will allocate a study case number. For reasons of data protection, LMU will receive no information on names or addresses of cases and will process all data on the basis of the 'institutsinterne Sektionsnummer'.
In addition all institutes of legal medicine and pathology will be queried by LMU on a monthly basis (active surveillance) whether any post mortem examinations have been carried out in children deceased within the tenth and 24th month of life during the past month. The institutes will answer this request by sending either a negative reply or by a brief report form, on which initials, birth date, death date and the 'institutsinterne Sektionsnummer' are stated. In addition, there it will be stated whether the post mortem examination has been performed according to the Standardized Auopsy Protocol (SAP). Information on former reporting of this case will be also included.
LMU will match these short reports upon request with case reports received spontaneously from collaborating institutes. If a case reported on request has not already been included in the study and the post mortem examination had been performed according to the study protocol, the institute of legal medicine or pathology will be asked to contact parents or legal guardians for their informed consent for study enrolment and different parts of the study (e. g. use of autopsy data, special pathological examinations, questionnaires etc.). This informed consent will make sure that all autopsy data and additional microbiological and molecular-genetic investigation data can be used in this study. In addition, this consent will extend to the release of the child's doctors from their obligations concerning patient confidentiality and to the questionnaires sent by the project team at MD. Vaccination history will be obtained by standardised questionnaires analogously to the epidemiological approach.
Consent and complete personal data will be transmitted to the RKI. Collaborating institutes of legal medicine and pathology will perform all post mortem examinations according to the 'Standard Autopsy Protocol' (SAP) (Annex 3) and the 'Additional Investigation' (Annex 4) as specified in the 'Manual related to the Standard Autopsy Protocol' (Annex 5). Data deriving from the autopsies will be collected and processed at the Institute of Forensic Medicine of the University of Essen. All reports, data and specimens will be labelled by internal autopsy numbers. In addition plausibility check and verification of data completeness will be performed. Interdisciplinary case conferences will be held under the auspices of the Institute of Forensic Medicine of the University of Essen in order to classify cases according to the recommendations of the Brighton Collaboration Work Group on SIDS.
RKI will verify all case reports from the pathological and the epidemiological approach in order to avoid double-counting and in order to avoid parents to be surveyed twice. RKI will transmit personal data and case numbers to the project team at MD from where questionnaires to parents and physicians will be sent.
Completed questionnaires will be returned to MD. In addition plausibility and completeness of data will be checked. Data entry takes place at the RKI. Anonymised data will be made available to the LMU.
If informed consent could not be obtained, an anonymous report form will be used. LMU will label every spontaneous report form and the requested short report forms according to the ‚institutsinterne Sektionsnummer' and an identifier of the reporting institute. Additional medical data will be conjoined by the LMU by using this number.

Scientific data analyses will be facilitated by the study case number. LMU will perform capture-recapture analyses on the basis of sufficient identifiers. Data analyses will be performed on an in-depth descriptive manner. Descriptive analyses of the pathological data will be performed in collaboration with the Institute of Forensic Medicine of the University of Essen.

9.3 Study base

The population of the Federal Republic of Germany, aged within the second to 24th months of life.
(Study base of the pathological approach is limited to the German population aged within the tenth and 24th months of life.)

9.4 Study population

9.4.1 Self-Controlled Case Series design (SCCS)

Cases:
Every death of a vaccinated infants in the second to 24th months of life, reported by a LHA, for whom informed consent of a parent or guardian has been obtained.

Inclusion criteria:

- age at death in the second to the 24th month of life (after the first month of life has been completed and before the 24th month of life has been completed).
- at least one vaccination within the last six months prior to death.

Exclusion criteria:

- inclusion criteria not met
- informed consent of parent or guardian not obtained.

9.4.2 Case-control study

Cases:
Every death in an infant in the second to 24th months of life, reported by LHA, for whom informed consent of a parent or guardian has been obtained.

Inclusion criteria:

- age at death in the second to the 24th month of life (after the first month of life has been completed and before the 24th month of life has been completed

Exclusion criteria:

- age at death does not meet inclusion criteria
- informed consent of parent or guardian not obtained.

Controls:
Controls will be participants of the German Child and Youth Health Examination Survey (KIGGS), matched to cases on age and time of examination. Matching will be performed following these rules:

1. the date of survey examination in a control is not earlier than the date of death in a case minus 1 month and not later than the date of death in a case plus 1 month

and

2. age at survey examination in a control is not lower than the age a case has died plus 5 weeks and not higher than the age a case has died plus (5 weeks + 2 months =) 13 weeks

The reason for this is the mode of invitation and examination established in the KIGGS survey. Participants are invited two to five weeks prior to their scheduled date of examination. An effect on vaccination and doctor's appointments in this period is to be expected, not only by participants avoiding additional appointments, but also possibly in their catching up on missed vaccinations. This may bias any results: the former by increasing, the latter by decreasing the OR for vaccination because of an artificially lower (higher) probability of the KIGGS children to be immunised.

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

> 35 days will be subtracted from the date of examination, specifying a point in time that lies safely before the invitation to the KIGGS examination.

For each case, as many KiGGS study subjects as fulfil the above criteria will be selected as controls. If a KiGGS study subject is a suitable control for more than one case, it will only be selected once into the control group. Data of cases and controls will make a frequency-matched case-control study and will be analysed as such. In a simulation study with real cases notified to the PEI and KiGGS data of May 2003 to December 2004, 85 controls could be frequency-matched to 20 cases, yielding an average of 4.3 controls per case. The number of controls suitable for each case varied between 0 and 13. 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 in older cases.

The KiGGS survey and this study will run parallel in time for about half of the study period, so the above method to select controls is applicable only for that time. In order to include all cases identified during this study, another analysis needs to be performed: Only step 2 of the above rules will be applied and all age-matched controls selected, irrespective of the time of their examination. The difference in time periods between cases and controls will then be adjusted for in the logistic model. Sales figures of hexavalent products by time periods will be used to estimate whether the likelihood of being exposed varies over time and to adjust for this potential confounder.

9.4.3 Pathological approach

Cases:
Every infant deceased within the tenth to 24th months of life, for whom standardised post mortem examination has been performed and informed consent of a parent or guardian has been obtained.

9.5 Sample Size

9.5.1Estimated number of cases

First year of life:

According to official mortality data published by the Federal Office of Statistics for 2002, mortality rate in live births is 4,2/1000 in the first year of life; and mortality is 1,5/1000 in infants between two and 12 months of age. On the basis of data received from the Federal Office of Statistics in March 2004, von Kries calculates an incidence of SUD (ICD 10 coding R95-99) for the first year of life of 0.663/1000 (von Kries 2004).

The absolute number of children who died in 2002 at the age of over 28 days and under one completed year, was 1058. Following ICD-10, 420 of these cases were attributed to the categories R95-99. About 10% of SIDS cases occur during the 10. to 12. month of life.

Second year of life:
According to the Federal Office of Statistics, there were 377 deaths in the second year of life in 2001 (of which 33 deaths were SUD). Von Kries calculates an incidence of SUD in the second year of 0.04/1000 (von Kries 2004). In 2002, 24 cases of SUD were recorded for the second year of life.

For the number of expected cases in this study see section 9.10.1.

9.5.2 Exposure

Vaccination coverage
Information on the proportion of vaccinated children has been supplied from the school entry check-ups of the federal states.

In 2002, the proportion of vaccinated children was over 90% for Diphtheria (96.6%), Tetanus (96.9%) and Polio (94.7%), more than 80% for Pertussis (87.1%) and Hib (87.6%), and 70.9% for Hepatitis B (Reiter 2004).

These data were derived from vaccination cards presented during school entry check-ups. The proportion of children for whom a vaccination card was not presented was as high as 20% in some federal states.

Further information on the proportion of vaccinated children for the age group of 2- to 6-year-olds derives from the pilot study of the KiGGS survey. Using theses non-representative data, the proportion of vaccinated children is 96% for Diphtheria and Tetanus, 92-93% for Polio, over 90% for Hib, 83-89% for Pertussis (87%) and approximately 70% for Hepatitis B. These data were obtained by computer-assisted interview by a physician and were based on the vaccination card data. Less than 5% of children could not provide a vaccination card (Dippelhofer et al 2002)
However, from the data acquired at school entry examinations, no conclusion can be drawn about the proportion of vaccinated children for the first two years of life. A representative investigation of this age group in Germany was undertaken by Laubereau, et al. in 1999, involving 837 children. Response proportion of the 1345 representative households interviewed by telephone was 58%. Only 59% (95%Cl: 54-65%) of children had completed the basic vaccination schedule on reaching 19 months. At seven months, only 50% of the children had all the immunisations recommended for this age. Similar delays could be observed with booster vaccinations administered in the second year of life; only 50% of children aged 19 months had had it (Laubereau, et al. 2001).

Von Kries, et al., estimated exposure to hexavalent vaccines in the second year of life from data of a birth cohort study born in 1997/98: 69.7% of cohort subjects had received a Diphtheria/Tetanus/Pertussis/Hib vaccination. Unpublished data by Helen Kalies from a birth cohort

for the year 2000/01 show that 93.4% (95% CI:: 91,9-94,8) of 24-months-old children were vaccinated with vaccines including Hib. At the age of 24 months 77.4% (95%Cl: 74.8-79.9) of children had received at least one vaccine containing Hib since their 11th month of life. A further increase in this proportion was noted in the birth cohort of 2002/03.

On the basis of these data, it seems realistic to assume renewed vaccination exposure for at least 70-80% of children in their second year. In the first year of life, vaccination prevalence increases with every completed month of life. It is realistic to expect 90% of the KIGGS subjects to have received at least one vaccination in their first year of life.

9.6 Parameter and Instruments

An international workgroup of experts is currently finalising a consensus paper with recommendations for studies into sudden death following vaccination. The paper includes recommendations for case definition, data collection, analysis and presentation. This study has been designed in a way that most of the recommendations of the Brighton Collaboration Workgroup on SIDS are met.
Data will be gained by postal questionnaires for parents (Annex 1) and physicians (Annex 2). The questionnaires gather information and data on immunization, on the infant 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 will be made available in order to facilitate adequate data analyses.

All information available from death certificates, from parents and physicians questionnaires, from potential clinical reports and any available autopsy reports will be used to perform a best possible classification of the cause of death by a paediatrician expert at the RKI who will be blinded against history of exposure and specially trained on ICD-10 classification. An indepedet second classification will be performed by another trained physician at the RKI. If one or both of these experts classifiy the cause of death to ICD-10 R95-99, the death certificate will be send to the DIMDI (Deutsches Institut für Medizinische Dokumentation und Information). At the DIMDI the national expert for ICD-10 classification will also perform ICD-10 classification. Complete data and assessment of all three coding experts will be provided to a multi-disciplinary case conference. Decision on classification to ICD-10 R95-R99 will be performed by this case conference. Every death classified to R95-R99 will be defined as case (this procedure meets requirements for classification category 4 according to the recommendations of the Working Group on Sudden infant death syndrome (SIDS) of the Brighton Collaboration). A 10% sample of all death certificates will also be re-assessed by DIMDI experts.

Implementation of the ‘Standardized Autopsy Protocol’ - SAP (Annex 3) together with the Additional Investigations (Annex 4) and the detailed standard operating procedure ‘Manual related to the Standard Autopsy Protocol’ (Annex 5) will provide data for classification according to agreed international criteria (‚San-Diego‘ Case Definition of SIDS) and thereby facilitating compliance with the guideline of the Working Group on Sudden infant death syndrome (SIDS) of the Brighton Collaboration allowing for case classification with the best level of diagnostic certainty. Cases who have been classified according to this high level of certainty will be labelled and made available for subgroup analyses.

9.7 Risk factors and exposure

9.7.1 Risk factors for sudden deaths and SIDS

So far, no common causes have been identified in SIDS deaths. From analyses of such cases, however, some characteristics could be consistently found in various studies. Male gender, smoking during pregnancy, household smoking , no breastfeeding or short duration of breastfeeding, young age of the mother and prone sleeping position (Westphalian study on child death 1990-1992) are some of them. From the CESDI SUDI study, further risk factors have been identified, such as multiple pregnancies, premature birth or admission to a neonatal intensive care unit (NICU) at any point, multiparity, a household with several children and also socio-economic factors such as unemployed parents, low professional status or a low level of education in the parents (Leach 1999).

An analysis of the CESDI SUDI study by Fleming, et al. in 2003, indicate that some of the well-established risk factors (e. g. mothers' young age, single parenthood, premature birth, previous miscarriages, a previous case of infant death in the family and the refusal to breastfeed, or short duration of breastfeeding) may no longer be statistically significant when controls are matched to cases very closely on socio-economic status (Fleming 2003).

Studies by Leach (1999) and Platt (2000) show that some of the risk factors for SIDS may be also associated with risk of sudden death in infancy with explained causes (SUDI). Such risk factors are: premature birth, problems in the newborn phase, multiple pregnancy, young age of the mother, single parenthood, multiparity, smoking during pregnancy and unemployment, low professional status, income support, low educational status and crowded parental accommodation. As was shown for SIDS deaths, cases are more likely to be male even across deaths from verifiable causes (Leach, et al. 1999; Platt, et al. 2000).

9.7.2 Exposure

Hexavalent vaccinations in the first two years of life

According to official German recommendations issued by the STIKO, vaccinations against Diphtheria, Haemophilus Influenza type B (Hib), Hepatitis B, Pertussis, Poliomyelitis and Tetanus should be started as early as possible and should be completed no later than 14 months of age (STIKO 2003). Combined vaccines containing Pertussisantigen should be administrated at of 2, 3, 4 and 11-14 months of age. The gap between the third and fourth (booster vaccination) should be at least 6 months. In principle, administration of combined vaccines is recommended to keep the number of injections as low as possible.

Since 23 October 2000, two hexavalent vaccines, Infanrix Hexa® and Hexavac® have been authorised in Germany via the central European authorisation procedure. Belgium and Germany are reporter and co-reporter for Infanrix Hexa® while, for Hexavac®, Germany and Italy took these roles. In April 2003 and again in November 2003, the scientific committee of EMEA, the Committee for Proprietary Medicinal Products (CPMP), conducted a re-assessment of the benefit-risk profile of these hexavalent vaccines. These new evaluations were initiated by sudden cases of death that occurred in close temporal association with the administration of hexavalent vaccines. The new evaluations led to an unchanged positive judgement on the benefit-risk profile of the hexavalent vaccines. The conclusions of these discussions are publicly vailable http://www.emea.eu.int/pdfs/human/press/pus/851903en.pdf.

Available data on the prevalence of children immunised according to German recommendations are presented and discussed in section 9.4.2. As a basis for power analyses of this prospective study, prescription data of the Institute for Medical Statistics (IMS) and sales figures

of the pharmacological industry shall be obtained and data from the ongoing KIGGS survey used.

9.8 Potential confounders

Studies on adverse events of vaccination can be biased by various sources. Completeness of case ascertainment, or at least non-selective sampling of cases, is a vital prerequisite of any study, since selective enrolment of vaccinated cases would over-estimate any risk associated with vaccines.

The way in which this study will enrol all relevant deaths via the LHA, link them with autopsied cases from the pathological approach and check them against the number of cases reported by the Federal Office of Statistics, and the fact that all persons involved in case ascertainment, reporting, and coding of diagnoses or causes of death will be blinded to any exposure history represents the best possible way to avoid any possible selection bias.

Studies on risk of vaccinations may be subject to so-called 'confounding by indication' (Greenland 1980) or by 'confounding by contraindication'. Confounding by contraindication would arise from selective avoidance of (hexavalent) vaccination in children at risk for SUD. Fine and Chen (1992) described a variety of ways 'confounding by indication' can operate, indicating that factors associated with no vaccination or belated vaccination may also be associated with the endpoint of interest itself. Some of the factors being associated with both non-immunisation and 'sudden infant death syndrome' are: poorly educated parents, multiparity, young age of the mother, the mother smoking and low birth weight.

According to the investigations by Leach (1999) and Platt (2000), it can be assumed that many of the risk factors of SIDS are also associated with sudden deaths with verified causes (SUDI). This is especially the case with factors such as premature birth, problems in the newborn phase, multiple pregnancy, young age of the mother, single parenthood, multiparity, smoking during pregnancy and unemployment, low professional status, income support, low educational status and crowded parental accommodation (Leach, et al. 1999; Platt, et al. 2000).

Factors associated with SIDS may also be associated with risk of sudden death with verifiable causes and must therefore to be thoroughly obtained in this study to control for confounding.

The direction in which any such confounding may bias results is difficult to anticipate. Luman, et al., showed in 2003 that black, young, unmarried mothers with a low level of education who live close to the poverty line are less likely to have their children completely vaccinated. On the other hand, however, Smith, et al., from 2004 showed that white, married, well-educated mothers with a high household income and who described themselves as against vaccination were more likely to have their children not immunised.

There is little data on this issue for Germany. Analyses of data from the pilot study of the KiGGS survey revealed that in the 2- to6-year-old group a high level of maternal education was associated with a low completion for the vaccination schedule (exception Hepatitis B). Therefore marked education-related differences concerning the probability of exposure to vaccines must be expected in Germany as well (Dippelhofer, et al. 2002).

The direction and extent to which any such bias may operate in the German population cannot be reliably concluded from existing data. If a critical attitude towards vaccination were more

likely in people with a high level of education or social standing, the study would overestimate any association between vaccination and risk of death. Deaths are more likely to occur in low SES groups, for other medical reasons, but would then coincide with a higher occurrence of vaccination.

If, according to Fine and Chen (1992), lower SES groups were less likely to have their children immunised in Germany, this study would have a tendency to underestimate any risk of sudden death after vaccination.

Furthermore, study participants of the KiGGS survey may be more health conscious than non-participants, which could introduce another bias into this study's control group. A high health consciousness in general can be associated with a greater willingness to take preventative measures like vaccinations.

Ongoing comparisons of responders and non-responders reveal, however, that differences in SES are low and thet there is virtually no difference in parent-reported health of children.On the basis of the extensive data currently being gathered the KIGGS survey, however, any such confounding by "proneness to immunisation" can be described and adjusted for in this prospective study at the time of data analysis.

Since over 90% of KiGGS participants present vaccination documents during examination, any recall bias can be ruled out in the control group of this prospective study.

A mis-classification of non-cases as cases may bias any true association towards the null. This may be also true when irrelevant cases are included in this study. In order to avoid misclassification, it was decided to include all cases of death, even if as the cause of death stated on the death certificate is unlikely to be associated with vaccinations. It cannot be excluded that even in cases with a clear diagnosis written on their death certificates (malignancy, severe metabolic disorder, severe infection etc.), vaccinations may be the trigger of a premature death.

9.9 Data collection and archiving approaches

9.9.1 Recording deaths and post mortems

In the field phase (months 4-39 of the project), the occurrence of relevant deaths or post mortem examinations will be enrolled over three years via local health authorities (LHA = GA) or institutes of forensic medicine (IFM = RM).

9.9.2 Requesting death and post mortem information

In a monthly interval, LHAs and IFMs will be queried to provide information on relevant cases of death in the previous month (months 5-40 of the project). Copies of the death certificates will be processed by the RKI after informed consent of a parent or guardian will be obtained by the LHA concerned.

Post mortem examinations will be conducted according to an internationally compiled, standard autopsy protocol (SAP) and documented; informed consent of a parent or guardian for the use of autopsy data will be obtained by the IFMs.

9.9.3 Gathering data on cases and controls

Collection of medical data on both cases (MD) and controls (RKI) will happen in months 6-41 of the project. All data will be made anonymous, entered into databases and checked for plausibility.

9.9.4 Activity flow chart

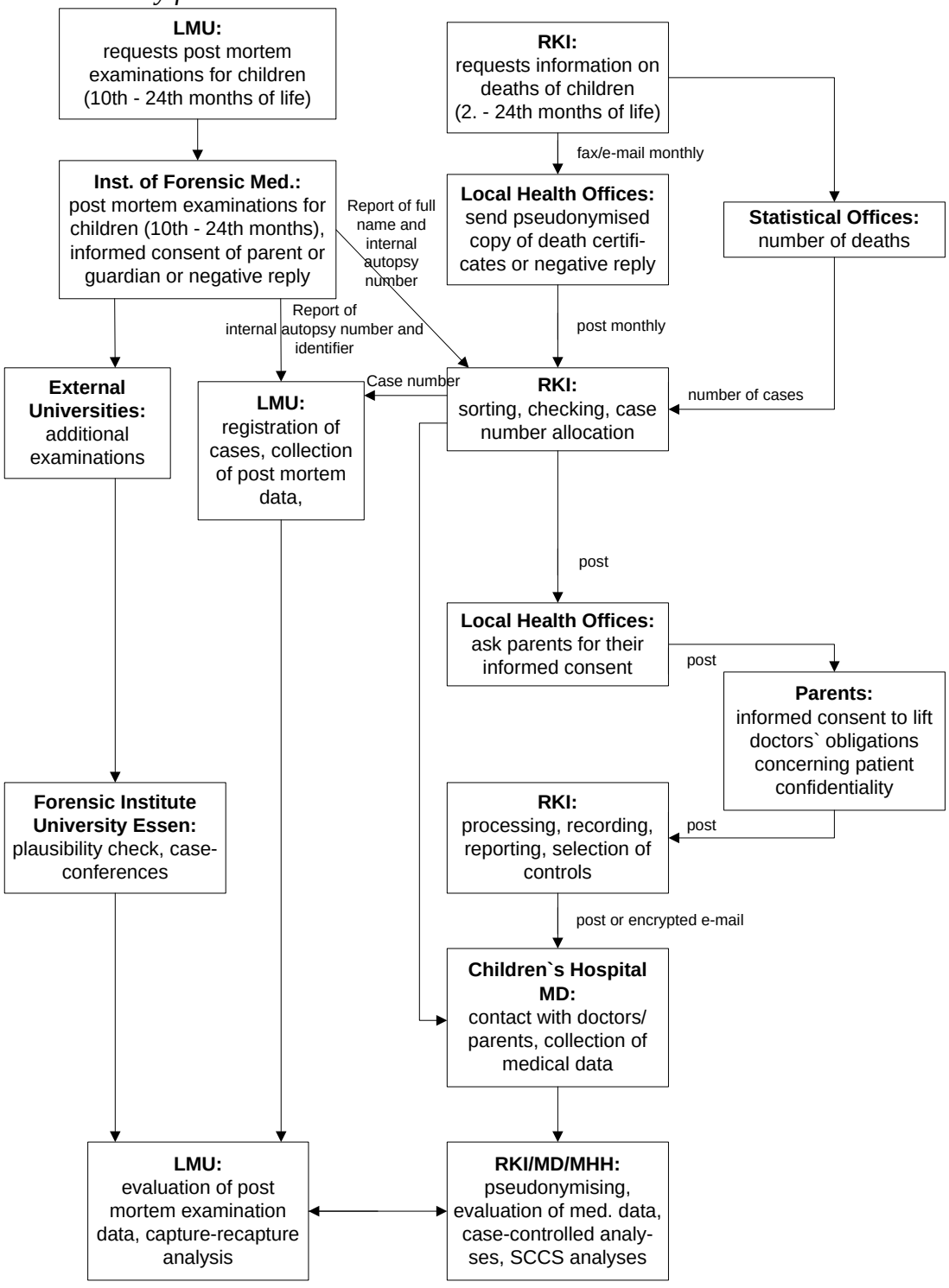


Figure 1: Chart of activities and data flow

9.10 Evaluation strategies and statistical models

Statistical analyses of epidemiological data will be done at the RKI whilst data obtained in the pathological approach will be analysed at the LMU.

After descriptive evaluation, data from the epidemiological approach will be statistically analysed by following methods.

9.10.1 Self-Controlled Case Series design

With this method, shifts in time of death in pre-specified periods of risk are examined (Farrington 1995, 1996, 2004; Andrews 2002). Age dependence of risk of dying from SIDS/SUD will be accounted for by adjusting for age categories. In the case of seasonal variations in the rates of both vaccination frequency and the incidents themselves, season will be included as a second confounder (in addition to age). As mentioned earlier, the principle advantage of the self-controlled case series design is the complete control of temporally stable, individual confounders (e.g. SES, age of mother, gestational age, complications at birth, weight and smoking during pregnancy or in the household). The following study questions (see 6) will be investigated by using the SCCS method:

1. Is there a temporal association between vaccination and risk of sudden death in the first two years of life?
2. For what length of time after vaccination is the risk of death potentially increased?
3. Is this potential association quantitatively the same at different stages of life?
4. Has this potential association the same magnitude across different – hexavalent – vaccines?

By these primary study analyses the following hypotheses will be examined:

1. After vaccination with hexavalent vaccine, the number of deaths in the first interval of 72 hours is higher than expected.
2. This is only true in the second year of life (booster vaccination).
3. This is only true for one hexavalent vaccine.

Null hypothesis formulated for the SCCS approach:

H_0 Risk of sudden death after vaccination is the same in all classes (up to 6 months). So the conditional probability of occurrence in the first three days, given an event is 0.0164.

H_1 The risk following vaccination in the first period (0-3 days) is increased by $\rho = e^{\beta} = 16$ (and 20 respectively for separate analyses of the two different hexavalent products) compared to the risk afterwards (4 days to 6 months). So the probability of occurrence in the first three days = 0.2105 (and 0.25 respectively for separate analyses of the two different hexavalent products).

This Null hypothesis will be tested seperately

1. for cases deceased in their second to 24th month of life following any hexavalent vaccination during the previous six month

2. for cases deceased in their second to 12th month of life following any hexavalent vaccination during the previous six month
3. for cases deceased in their 13th to 24th month of life following any hexavalent vaccination during the previous six month
4. for cases deceased in their second to 24th month of life following vaccination with Hexavac® during the previous six month
5. for cases deceased in their second to 24th month of life following vaccination with Infanrix Hexa® during the previous six month
6. for cases deceased in their second to 12th month of life following vaccination with Hexavac® during the previous six month
7. for cases deceased in their second to 12th month of life following vaccination with Infanrix Hexa® during the previous six month
8. for cases deceased in their 13th to 24th month of life following vaccination with Hexavac® during the previous six month
9. for cases deceased in their 13th to 24th month of life following vaccination with Infanrix Hexa® during the previous six month

The following definitions were made for implementing the SCCS method:

Cases:
Every sudden death of a vaccinated infant in the second to 24th months of life, reported by a LHA, for whom informed consent of a parent or guardian has been obtained.

Inclusion criteria:

- ICD-10 classification of cause of death is R 95 – 99 (classification based on information from death certificate and parents and physicians questionnaire, from potential clinical reports and any available autopsy reports see 9.6)
- Age at death in the second to the 24th month of life (after the first month of life has been completed and before the 24th month of life has been completed).
- At least one vaccination under study within the last six months prior to death.

Exclusion criteria:

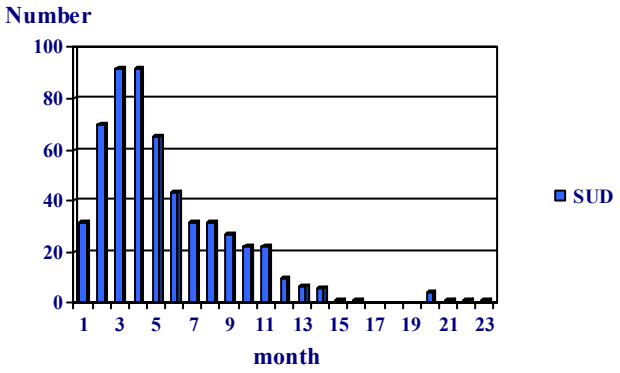
- Inclusion criteria not met or
- Informed consent of parent or guardian not obtained.

1. The age range is divided into age categories of:

1	month
2	months
3 - 4	months
5	months
6 – 8	months
9 – 11	months

12 – 14 months
15 – 23 months

These catagories discriminate age groups of high, medium or low risk of SUD, derived from the age distribution of SUD deaths in Germany in 2001 (von Kries 2004).



(BMBF Study and Bavarian Bureau of Statistics, von Kries 2004)

2. Elapsed time after vaccination is divided into risk periods of:

   Primary analysis

   a.)
   Risk period (risk class 1): 0 – 3 days
   Control period: 4 – 183 days

   The hazard rate in the risk period will be estimated in relation to the control period with a one-sided test of significance at the level $\alpha = 0.05$. Analogously, a one-sided 95%confidence interval will be calculated.

   The 'high risk' interval of 0-3 days has been defined according to the recommendations of the Brighton Collaboration Working Group on SIDS.

   b.)
   (risk class 2): 4 –7 days
   Control period: 8 – 183 days

   The hazard rate in the risk period will be estimated in relation to the control period with a one-sided test of significance at the level $\alpha = 0.05$. Analogously, a one-sided 95%-confidence interval will be calculated.

   The additional 'high risk' interval of 4 – 7 days has been defined in the light of the results of the Italian Hera Study report. These results suggest that the risk period of a potential temporal association between vaccination and sudden death may extend up to 7 days or – more particular – in the time slot of the 4^{th} to 7^{th} day after vaccination.

3. Seasonal classes *k*.
4. For every case, from the combination of age category, seasonal category and risk period, there is a particular constant 'hazard'.

5. 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 .

Exploratory analyses

In addition, exploratory analyses with additional risk periods will be performed for comparison to the risk periods set out *a priori* under hypotheses 1.

For these secondary (explorative) analyses the elapsed time after vaccination is divided into risk periods of:

(risk class 3): 8-14 days
(risk class 4): 15-28 days
(risk class 5): 29-183 days.

The risk periods represent categories with markedly different levels of incidence, according to cases of death after hexavalent vaccination observed so far. The borderline of 28 days has been set as a plausible, but arbitrary boundary for a possibly causal association.

In these secondary analyses, the risk class 5 (29-183 days) was chosen as the reference class. Hazard rates of classes 1-4 will be estimated in relation to class 5, with a one-sided test of significance at the level $\alpha = 0.05$. Analogously, one-sided 95% confidence intervals will be calculated. The tests will be performed sequentially, beginning with class 1. If a significant result is seen in one class, then the next class will be tested. Thus, the multiple level of $\alpha = 0.05$ will be kept.

In addition to these specific hypotheses, potential temporal associations of any vaccination – not only hexavalent products – and sudden deaths will be investigated by exploratory analyses. Explorative analyses will also investigate whether there are differences between the first, second, third and the booster dose.

Subgroup analyses will be performed for which case definition must meet category 1 or 2 of the recommendations by the Working Group on Sudden infant death syndrome (SIDS).

Power calculation (SCCS)

The necessary number of cases will be estimated in accordance with Farrington, et al. (1995, 1996). It relies on the following, simplified assumptions:

1. No age effects.
2. Identical risk period R_1 and control period R_0 for all N individuals; time of observation: R_1 followed by R_0.
3. Vaccination as the start of the observation time.

The following parameters enter into the formula:

$\rho = e^{\beta}$ the relative incidence in the risk group compared to the control group

v number of cases vaccinated at the beginning of the period (starting with 1, since only vaccinated cases of SUD can enter the analyses)

r = (length of risk period) / (length of observation period)

α = error-I probability for the two-sided test

(1 -β) = power of the test (β = error-II probability)

$Z_{\alpha/2}$ and Z_{β} the corresponding upper quartiles of the standard normal distribution.

The formula used can be found in appendix 1.

The (revised) formula for calculating the number of cases in the SCCS analysis (translated into the syntax of the S-Plus program) is:

events<- function (nu, r, ro, zahalbe, zbeta)

{ (1/(nu*r*(1r)*(ro-1)^2))* (zahalbe + zbeta*sqrt((1 + nu*r*(ro-1)) *(1 + r*(ro-1))*ro))^2 }
The following parameter values are assumed: α = 0.05; one-sided test; (1 -β) = 0.2 (power = 80%); risk period: 3 days; observation phase: 6 months; $\rho = e^{\beta}$ (relative incidence): 8, 10, 16, 20. The latter values (16 and 20) are considered for performing a separate test for each hexavalent product. So the resulting numbers will have to be multiplied by 2, assuming equal proportion of both types of vaccine.

Given the assumptions made above, the relative risk of a case occurring in the risk period compared to occurrence in the control period, provided there is a case and the vaccination took place within the observation period, is:

RR = e^{β} x (length of risk period) / (length of control period)
= e^{β} x (3 days) / (duration of observation in days - 3)

The (relative) probability of occurrence within the risk period is:

p_1 = RR / (1+RR)

This probability can be calculated under the Null-hypothesis H_0: $\rho = e^{\beta} = 1$ ($\beta = 0$) on the assumption that ρ = 10 and for different alternatives.

For the power analysis, it is assumed that the Null-hypothesis will 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 α = 0.05, was calculated as 35, 29, 13 and 11 for $\rho = e^{\beta}$ = 8, 10, 16 and 20, respectively (StatXact version 6.0) using the parameter mentioned above; the formula quoted from Farrington gives the results 24, 17, 10 and 8. Thus, to detect an relative incidence of 16 or 20 for each hexavalent product separately, a total number of 26 resp. 22 cases will be necessary (20 resp. 16 following the formula of Farrington).

The total number of deaths in children aged 28 days to one year was 1058 in 2002. Of these cases, 420 were attributed to ICD-10 categories R95-99. For the age group containing babies, the suggested selection strategy should provide a sufficient number of cases.

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, 22 to 26 (or 16 to 20) children vaccinated within 6 months of death, is realistic considering that it will have three years for the sub-evaluation of sudden and unexpected death in the second year of life under these conditions, and there is a completion rate for the vaccination schedule of over 85% in the second year (data from an, as yet unpublished, representative survey by H. Kalies and von Kries). After a model calculation, 25 cases are expected if it is assumed that there are 24 SUD cases per year and there is a temporal shift in the SUD cases after vaccination. With 33 cases of SUD per year, and a general increase in intensity by a factor of 2, this number increases to 43. The separate SCCS analysis of the two hexavalent vaccines, however, in light of the number of cases expected for the group of subcases in the second year of life, detection of a relative incidence of 20 for each hexavalent product separately can be achieved.

9.10.2 Case-control design

The following study questions (see 6) will be investigated by using case-control analyses:

3. Is this potential association qualitatively and quantitatively the same at different stages of life?
4. Has this potential association the same magnitude across different – hexavalent – vaccines?
6. Is the risk of sudden death in vaccinated children different from unvaccinated children?

During this secondary study analyses the following hypotheses will be 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 one hexavalent vaccine.

Null hypotheses formulated for the case-control approach:

The 'vaccination history' will be separated into classes (vaccination status). Lowest class: no vaccination. Condition after vaccination (up to 6 months) will either be assessed as a whole (study question 6) or differentiated according to the classification of time periods. In this differentiated version '0-3 days' is the highest class, and so on (study question 3). Let p_{1i} and p_{2i} denote the probability for a case and for a control, respectively, to be in class c_i .The hypotheses to be tested are:

H_0 $p_{1i} = p_{2i}$ for all classes c_i , against the alternative

H_1 $p_{1i} \neq p_{2i}$ for at least one class c_i

For the test of a distinct vaccine, the hypotheses to be tested are of the same form, however p_{1i} and p_{2i} are to be interpreted as conditional probabilities:

For the test of an association of vaccine *type 1* with mortality, p_{1i} and p_{2i} are the probabilities for a case and a control, respectively, to be in class c_i, *given there was no vaccination with vaccine type 2*. Accordingly, for the test of an association of vaccine *type 2* with mortality, p_{1i}

and p_{2i} are the probabilities for a case and a control, respectively, to be in class c_i , *given there was no vaccination with vaccine type 1*

The following definitions were made for implementing the case-control design:

Cases:
Every sudden death of an infant in the second to 24th months of life, reported by a LHA, for whom informed consent of a parent or guardian has been obtained.

Inclusion criteria:

- ICD-10 classification of cause of death is R 95 – 99 (according classification based on information from death certificate and parents and physicians questionnaire, from potential clinical reports and any available autopsy reports see 9.6)
- Age at death in the second to the 24th month of life (after the first month of life has been completed and before the 24th month of life has been completed).

Exclusion criteria:

- Age at death does not meet inclusion criteria
- Informed consent of a parent or guardian not obtained.

Controls:
Controls will be participants of the German Child and Youth Health Examination Survey (KIGGS), matched to cases on age and time of examination. Matching will be performed following these rules:

- The date of survey examination in a control is not earlier than the date of death in a case minus 1 month and not later than the date of death in a case plus 1 month

and

- Age at survey examination in a control is not lower than the age a case has died plus 5 weeks and not higher than the age a case has died plus (5 weeks + 2 months =) 13 weeks

Differences of vaccination history in cases and controls will be analysed by unconditional logistic regression, adjusting for matching criteria of this frequency-matched study. Relative risks of vaccination will be estimated by adjusted odds ratios and their 95% confidence intervals.

The following parameter are known factors associated with sudden unexpected death (see 9.8) and will be included in the model of the logistic regression models: age, socio-economic status (SES), age of mother, smoking during pregnancy, premature birth, problems in the newborn phase, multiple pregnancy, crowded parental accommodation, mother smoking. Some of these variables are also associated with vaccination coverage.

Power calculation (case-control study)

Power analyses of the case-control study was calculated using the programme nQuery Advisor 5.0 with given error probabilities of $\alpha = 0.05$ (two-sided) and ß=0.2. From German vacci-

nation data cited above and the simulation study of matching KiGGS controls to real cases, the following assumptions were made:

- probability of being vaccinated by hexalavent product A = 40%,
- probability of being vaccinated by hexavalent product B = 40%,
- probability of not being vaccinated = 20%.,
- average number of controls per case = 4.

As this analysis focus on differences of vaccination history within the three-day period prior to the cases deaths the following power analysis has been performed. For analysis of a potential risk of any hexavalent vaccine, calculation of power and sample size assumed the probability of being exposed in controls to be 0.0066 (0.8* (3/365) / [0.8 * (3/365) + (1 – 0.8*(3/365)] = 0.0066). In order to detect a smallest relative risk (OR) of 20 the required sample size is 33 cases and 139 controls.

For analysing a potential risk of a certain hexavalent product, the probability of being exposed was calculated to be 0.0033 (0.4 * (3/365) / [0.4 * (3/365) + (1 – 0.8*(3/365)] = 0.0033). Detection of a smallest relative risk (OR) of 20 requires a sample size of 69 cases and 293 controls. Thus, in light of the number of cases expected in the first year of life, detection of a relative risk of 20 for each hexavalent product separately can be achieved in the case-control analysis as well. Assuming that vaccination as well as occurrence of cases will mainly arise during the first half of second year the probability of exposition in the control group in the second year of life was calculated to be 0.0066 (0.4* (3/183) / [0.4 * (3/183) + (1 – 0.8*(3/183)] = 0.0066). In order to detect a smallest relative risk (OR) of 20, the required sample size is 33 cases and 139 controls. Thus, in light of the number of cases expected in the second year of life, detection of a relative risk of 20 for each hexavalent product separately can be achieved.

The additional analyses focus on estimation the overall potential effect of a vaccination on risk of death. A general, but delayed effect of a vaccination may qualitatively and quantitatively differ from the immediate effects shortly after vaccination. For analysing a potential risk of a certain hexavalent vaccine, the probability of being exposed is 40% among controls, and a smallest relative risko (OR) of 16 is to be detected. The required sample size to achieve this is 8 cases and 31 controls

Exploratory analyses

In addition to these main analyses of a potential effects of hexavalent vaccines, any vaccination –not only hexavalent products – and sudden deaths will be investigated by exploratory analyses. These exploratory analyses are not related to the study questions that have been defined.

For the case-control study and the SCCS design, main analyses focus on unexplained sudden deaths. Level of diagnostic certainty is expected to be different between the pathological and the epidemiological study approach. Autopsies may not be performed in cases who are reported by the LHA's resulting in levels of diagnostic certainty of not more than 3 according the recommendation of the Brighton Collaboration Workgroup on SIDS. Subgroup analyses of cases with higher level of diagnostic certainty (pathological approach) will be performed. In addition exploratory analyses applying a widened case definition will evaluate those cases in which a link with vaccination may be plausible. For these additional analyses cases are defined as any death of an infant in the second to 24th month of life (not only ICD 10 R 95-

99), reported by a LHA, for whom informed consent of a parent or guardian has been obtained.
For these analyses the following exclusion criteria apply:

Cause of death according to the information on the death certificate is one of the following ICD classifications:

- V01-W74: accidents with means of transport (V01-V99), falls (W00-W19), accidental drowning (W65-W74)
- new malignant growth (C00-C97)
- severe endocrinal, nutritional or metabolism disorders (from E00-E90)
- malformations, deformities and chromosomal anomalies (Q00-Q99)
- injuries, poisonings and certain other outcomes with external causes (S00-T98)

9.10.3 *Sequential analysis*
The sequential analysis is intended as a monitoring instrument. Since important new insights relevant to public health could be gained while the study is underway, data analyses will not be left to the end of the field phase. An independent biometrical institute will undertake ongoing monitoring using the one-sided open Sequential Probability Ratio Tests (SPRT) of Wald. For this, a warning line will be defined in the field between the x-axis (number of cases) and the y-axis (cumulated test results). Should the path of test points cross the warning line, a full interim analysis will be performed.

Sequential data analyses will be performed for both the SCCS and the case-control study. In both versions, they can only give rough hints on potential associations, as the existing models do not permit consideration of any confounder (age + season, and the confounding variables of the case-control study).

Hypotheses formulated for the SCCS approach:

H_0 The risk after vaccination is the same in all classes (up to 6 months). So the conditional probability of occurrence in the first three days, given an event is 0.0164.

H_1 The risk following vaccination in the first period (0-3 days) is increased by $\rho = e^{\beta} = 16$ (and 20 respectively for separate analyses of the two different hexavalent products) compared to the risk afterwards (4 days to 6 months). So the probability of occurrence in the first three days = 0.2105 (and 0.25 respectively for separate analyses of the two different hexavalent products).

A one-sided (open) sequential test will be used in accordance to Wald. This test only identifies a stop if there is an increase of the risk in the first period. The type I error will be set at α = 0.05; the power 1-β will be 80 percent.

For the SCCS approach, the parameter π of the binomial distribution is $\pi = \pi_0 = 0.0164$ under H_0, and $\pi = \pi_1 = 0.2105$ under the alternative H_1. Let $\alpha = 0.05$ and $\beta = 0.2$ be the probabilities of error type I and II respectively. Furthermore, let *m* denote the actual number cases in the sequential trial (cases with vaccination), and $r \leq m$ the number of events (cases with vaccination in the first risk period). Then the warning limit to indicate an increased number of events, is reached if

$$r \geq \frac{\log(\frac{1-\beta}{\alpha})}{\log\left(\frac{\pi_1(1-\pi_0)}{\pi_0(1-\pi_1)}\right)} + \frac{\log\left(\frac{1-\pi_0}{1-\pi_1}\right)}{\log\left(\frac{\pi_1(1-\pi_0)}{\pi_0(1-\pi_1)}\right)} m$$

Thus, for the given parameter values the warning limit *w* as a function of cases *m* is

$$w(m) = 1.0002 + 0.0793\, m$$

This sequential plan is an open plan in the following sense: The probability that the warning limit will be reached at any time of the process is restricted to $\alpha = 0.05$ under H_0, irrespective of the duration of the trial. Vice versa, under H_1 the warning limit will be reached with probability 1- $\beta = 0.8$ if the duration is unlimited.

Hypotheses formulated for the case-control approach:

The 'vaccination history' will be separated into two classes c_i (vaccination status positive or negative).. Let p_1 and p_2 denote the probability for a case and for a control, respectively, to be in class 1 (positive vaccination status). The hypothesis to be tested is:

H_0 $p_1 = p_2$, against the alternative

H_1 $p_1 \neq p_2$

A two-sided (open) sequential test will be used in accordance to Wald. This test identifies a stop if there is an increase or decrease of the odds for positive vaccine status. The type I error will be set at $\alpha = 0.05$; the power 1-β will be 80 percent.

For the case-control approach the parameter $\theta = \log\left(\frac{\pi_2(1-\pi_1)}{(1-\pi_2)\pi_1}\right) =$ log odds ratio is $\theta = \theta_0 = 0$ under H_0, and $\theta = \theta_1 = \log(20) = 3.00$ under the alternative. Let $\alpha = 0.05$ and $\beta = 0.2$ be the probabilities of error type I and II respectively. Furthermore, let $m_i \quad (i = 1,2)$ denote the actual number of children in the case and control group , and $r_i \leq m_i$ the number of children in class 1 (vaccination) within each group.
With $h_i = \frac{r_i}{m_i}$ (the relative frequency of class 1 in group i), $h = \frac{r_1 + r_2}{m_1 + m_2}$ (the pooled relative frequency of class 1), the warning limit for an increased odd in group 1 is reached if

$$\frac{m_1\, m_2}{m_1 + m_2}\left(h_1 - h_2\right) \geq \frac{1}{\theta_1}\log\left(\frac{1-\beta}{\alpha/2}\right) + \frac{1}{\theta_1}\frac{m_1\, m_2}{m_1 + m_2}\, h(1-h)$$

For the given parameter values this reads as

$$\frac{m_1\, m_2}{m_1 + m_2}\left(h_1 - h_2\right) \geq 1.157 + 0.334\frac{m_1\, m_2}{m_1 + m_2}\, h(1-h)$$

Accordingly, the warning limit for an increased odd in group 2 is reached if

$$\frac{m_1\, m_2}{m_1 + m_2}\left(h_2 - h_1\right) \geq 1.157 + 0.334\frac{m_1\, m_2}{m_1 + m_2}\, h(1-h)$$

9.10.4 Pathological approach

In the pathological party of the study, the following study question will be investigated:

5. Is there a common pathological mechanism for cases of sudden death following vaccination (autopsied cases only)?

Descriptive statistics will be applied to the data obtained from the 'Standardized Autopsy Protocol' and the 'Additional Investigation'.

10 Quality assurance measures

In order to check the cases reported by health offices for completeness, the RKI will request the number of deaths at 2 to 24 months of life from the statistical offices at regular intervals. Cross checks of cases reported by the forensic and pathologic institutes and the local health authorities will be performed in order to assess completeness.

ICD-10 coding of the cause of death as stated on the death certificate will be performed by a specially trained expert who is 'blinded' against any information on vaccination status. For reasons of quality assurance a random 10% sample will be coded again by a second expert. Consistence will be evaluated.
All persons involved in case ascertainment, reporting, and coding of diagnoses or causes of death will be blinded to any exposure history in the epidemiological part of the study. Implementation of the Standard Autopsy Protocol will be supervised by a colleague of the project team at the Institute of Forensic Medicine of the University of Essen.

If there are inconsistencies in medical data between parents and physicians questionnaires the physician's statement will be used because of assumed higher validity.

11 Maintaining data protection and ethical principles

Study protocol and additional documents (forms and questionnaires) had been provided to the federal data protection officer and the sixteen data protection officers of the states. Their advice has been taken into account.

Approval of the ethics committee of the Hannover Medical School was obtained.

Personal data will only be used for the scientific purposes of the study, and will not be passed on to other parties. Organisational measures – e.g. the design of the Institute's internal post distribution system – will ensure that only staff involved in the study has access to the data. As medical personnel, they are also bound by strict rules on confidentiality.

After linking all data to a certain case (death certificate, doctor's and parents' questionnaires and the post mortem examination results, if any), data on individual name and address are no longer necessary. They will be separated from the epidemiological and medical data, and substituted with a case number. A list holding case numbers and names/addresses will be stored in a secure place, just in case any implausibilities, questions or checks require later reference. This list will be abolished two years after finalisation of the study at the latest.

All data will only be stored and evaluated in a pseudonymised form, and all results of the study will be published in such a way that it is impossible to identify individuals.

12 Time-frame and responsibilities

The steps necessary to achieve efficient data collection, with evaluation soon after, are set out in Figure 2.

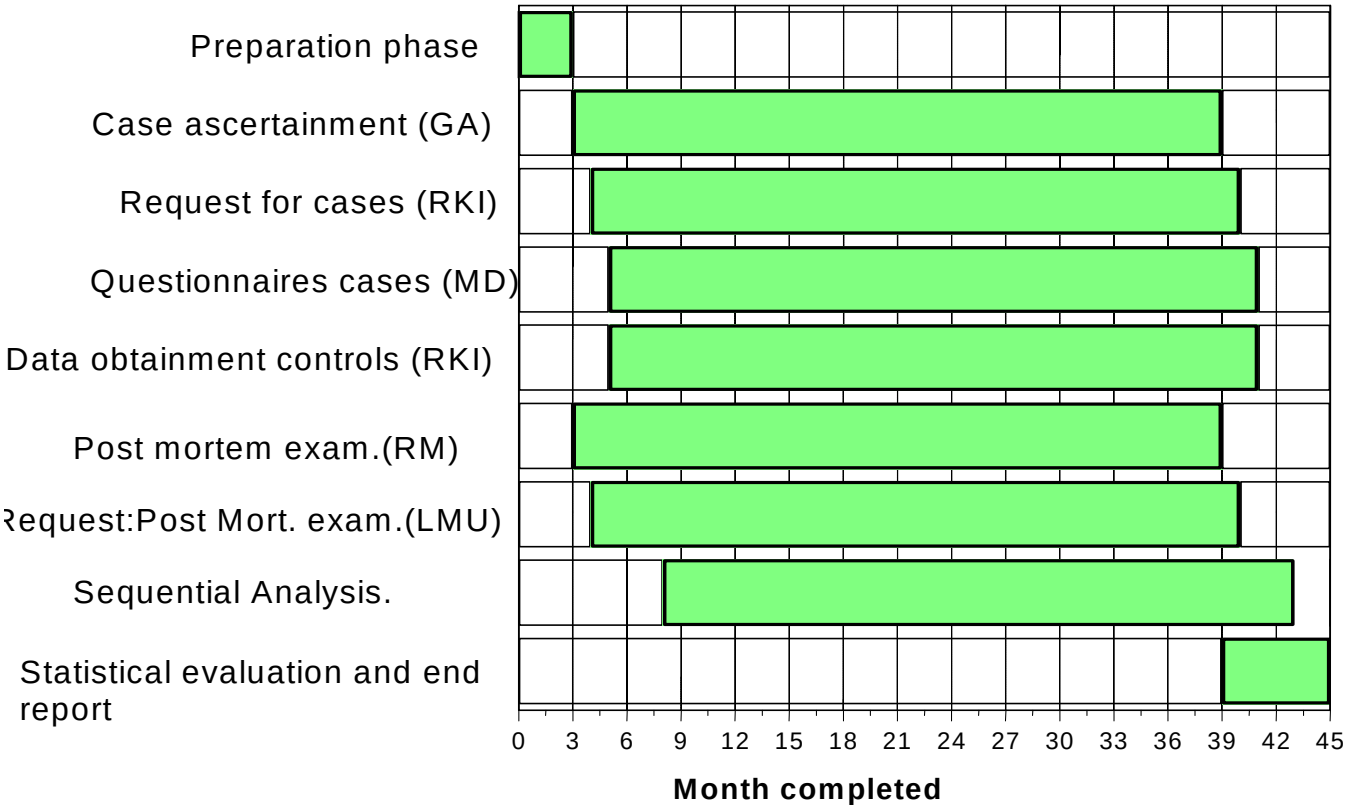


Figure 2: Project activity plan

12.1 Prep aration phase

In the preparation phase (months 1-3 of the project), the following tasks should be completed:

- Process of informing federal health ministries and motivating all administrative levels, LHAs, as well as professional associations.
- Preparation for active surveillance in LHAs (establishing addresses, fax numbers, e-mail addresses; constructing distribution systems; creating study-related registration forms; and agreement and testing of the procedure).
- Preparation of information material, informed consent forms for parents that include an explanation of data protection, and suggested cover letters for LHAs to send to parents.
- Finalisation and testing of standardised questionnaires for doctors and parents, as well as documentation for post mortem examination data.
- Construction of databases and user interfaces with plausibility check on data entry.
- Process of informing and motivating all institutes of forensic medicine and pathology, and specialist and professional associations.
- Preparation for active surveillance in ILMs (establishing addresses, fax numbers, e-mail addresses; constructing distribution systems; creating registration forms; and agreement and testing of the procedure).

12.2 Data evaluation and report compilation

Sequential-analytical analyses will be run with every new case. If the results transgress defined limits, a full interim evaluation will be conducted and, if necessary, regulative measures initiated.

The final data analyses of the self-controlled case series study and the case-control study will take place after the end of the field phase; the report will be drawn up in months 40-45 of the project.
Conspicuous results arising from the in-depths investigation of the pathological approach which are likely to change to overall benefit –risk assessment will be contemporarily reported by the Institute of Forensic Medicine of the University of Essen to the RKI and the PEI.

12.3 Publication of results

The study co-ordinators are entitled to publish the study results. Recommendation of the Scientific Advisory Board will be taken into account. Study results will be published by the study co-ordinators irrespective of the meaning or consequences of these findings. Undesirable results must not delay or inhibit publication.

13 Budget

The resources (both human and financial) needed to achieve the objective of the project are listed in the tables below *[not included in this version]*. Besides the combined list, there are also individual tables arranged after the institutions.

14 List of abbreviations

BMGS	Bundesministerium für Gesundheit und soziale Sicherung
CPMP	Committee for Proprietary Medicinal Products
EMEA	European Agency for the Evaluation of Medicinal Products
GA	Gesundheitsämter
KIGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland
LfD	Landesbeauftragte für Datenschutz
LMU	Institut für Soziale Pädiatrie der Ludwigs-Maximilians-Universität München
MD	Kinderklinik der Otto-von-Guericke-Universität Magdeburg
MHH	Institut für Biometrie Medizinische Hochschule Hannover
PEI	Paul-Ehrlich-Institut
RKI	Robert-Koch-Institut,
RM	Rechtsmedizinische Institute
SCCS	Self controlled case series
SIDS	Sudden Infant Death Syndrom
SUD	Sudden unexpected Death
SUDI	Sudden unexpected death in infancy

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First Amendment

Darstellung der mit dem 10.3.2006 veränderten Abschnitte des Studienprotokolls ‚Study on deaths in young children (2. – 24th mont h of life) im Vergleich z ur Vorversion vom 14.6.2005

1. Verändert:
   In Abschnitt 6 Study questions

   Studienfrage 4:

   Has this potential association the same magnitude across ~~different~~ hexavalent and non-hexavalent– vaccines?

2. Ergänzt:
   In Abschnitt 9.2 Pathological Approach

   Complete ascertainment of sudden and unexpected deaths occurring during the tenth to 24th month of life for which post mortem examinations have been carried out is aspired. If post-mortems are performed in children who died in their 2nd to 9th month of life and it comes to the attention of the pathologist that theses children had been immunised within 7 days prior to death, these cases are also to be included in this study.

3. Gestrichen:
   In Abschnitt 9.3 Study base
   The population of the Federal Republic of Germany, aged within the second to 24th months of life.
   ~~(Study base of the pathological approach is limited to the German population aged within the tenth and 24th months of life.)~~

4. Ergänzt:
   In Abschnitt 9.4.3 Pathological approach

   Cases:
   Every infant deceased within the tenth to 24th months of life, for whom standardised post mortem examination has been performed and informed consent of a parent or guardian has been obtained.
   If post-mortems are performed in children who died in their 2nd to 9th month of life and it comes to the attention of the pathologist that theses children had been immunised within 7 days prior to death, these cases are also to be included in this study.

5. Ergänzt:
   In Abschnitt 9.7.2 Exposure

   However, in September 2005 the Committee for Medicinal Products for Human Use (CHMP) of 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 (see also:www.emea.eu.int/pdfs/human/press/pr/29736905en.pdf).

6. Verändert:
   In Abschnitt 9.10 Evaluation strategies and statistical models

Statistical analyses of epidemiological data will be done at the RKI whilst data obtained in the pathological approach will be analysed at the LMU.

After descriptive evaluation, data from the epidemiological approach will be statistically analysed by following methods.

9.10.1 Self-Controlled Case Series design

With this method, shifts in time of death in pre-specified periods of risk are examined (Farrington 1995, 1996, 2004; Andrews 2002). Age dependence of risk of dying from SIDS/SUD will be accounted for by adjusting for age categories. In the case of seasonal variations in the rates of both vaccination frequency and the incidents themselves, season will be included as a second confounder (in addition to age). As mentioned earlier, the principle advantage of the self-controlled case series design is the complete control of temporally stable, individual confounders (e.g. SES, age of mother, gestational age, complications at birth, weight and smoking during pregnancy or in the household). The following study questions (see 6) will be investigated by using the SCCS method:

1. Is there a temporal association between vaccination and risk of sudden death in the first two years of life?
2. For what length of time after vaccination is the risk of death potentially increased?
3. Is this potential association quantitatively the same at different stages of life?
4. Has this potential association the same magnitude across ~~different~~ hexavalent and non-hexavalent – vaccines?

By these primary study analyses the following hypotheses will be examined:

1. After vaccination with hexavalent vaccine, the number of deaths in the first interval of 72 hours is higher than expected.
2. This is only true in the second year of life (booster vaccination).
3. ~~This is only true for one hexavalent vaccine~~.

Null hypothesis formulated for the SCCS approach:

H_0 Risk of sudden death after vaccination is the same in all classes (up to 6 months). So the conditional probability of occurrence in the first three days, given an event is 0.0164.

H_1 The risk following vaccination in the first period (0-3 days) is increased by $\rho = e^{\beta} =$ ~~16~~ 10 (~~and 20 respectively for separate analyses of the two different hexavalent products~~) compared to the risk afterwards (4 days to 6 months). So the probability of occurrence in the first three days is 0.1429 (~~and 0.25 respectively for separate analyses of the two different hexavalent products~~).

This Null hypothesis will be tested seperately

1. for cases deceased in their second to 24th month of life following any hexavalent vaccination during the previous six month
2. for cases deceased in their second to 12th month of life following any hexavalent vaccination during the previous six month

3. for cases deceased in their 13th to 24th month of life following any hexavalent vaccination during the previous six month

~~4. for cases deceased in their second to 24th month of life following vaccination with Hexavac® during the previous six month~~

~~5. for cases deceased in their second to 24th month of life following vaccination with Infanrix Hexa® during the previous six month~~

~~6. for cases deceased in their second to 12th month of life following vaccination with Hexavac® during the previous six month~~

~~7. for cases deceased in their second to 12th month of life following vaccination with Infanrix Hexa® during the previous six month~~

~~8. for cases deceased in their 13th to 24th month of life following vaccination with Hexavac® during the previous six month~~

~~9. for cases deceased in their 13th to 24th month of life following vaccination with Infanrix Hexa® during the previous six month~~

The following definitions were made for implementing the SCCS method:

Cases:
Every sudden death of a vaccinated infant in the second to 24th months of life, reported by a LHA, for whom informed consent of a parent or guardian has been obtained.

Inclusion criteria:

- ICD-10 classification of cause of death is R 95 – 99 (classification based on information from death certificate and parents and physicians questionnaire, from potential clinical reports and any available autopsy reports see 9.6)
- Age at death in the second to the 24th month of life (after the first month of life has been completed and before the 24th month of life has been completed).
- At least one vaccination under study within the last six months prior to death.

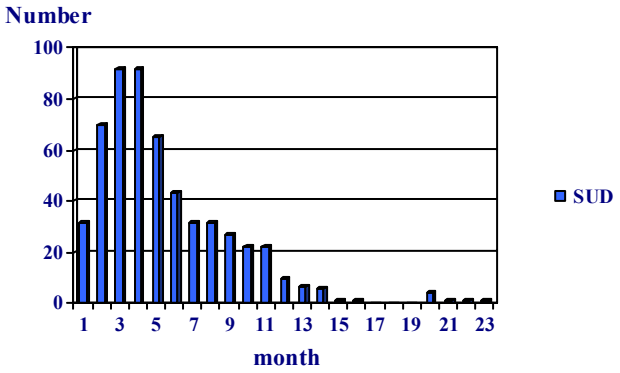
Exclusion criteria:

- Inclusion criteria not met or
- Informed consent of parent or guardian not obtained.

1. The age range is divided into age categories of:

1	month
2	months
3 - 4	months
5	months
6 – 8	months
9 – 11	months
12 – 14	months
15 – 23	months

These catagories discriminate age groups of high, medium or low risk of SUD, derived from the age distribution of SUD deaths in Germany in 2001 (von Kries 2004).



(BMBF Study and Bavarian Bureau of Statistics, von Kries 2004)

2. Elapsed time after vaccination is divided into risk periods of:

   Primary analysis

   a.)
   Risk period (risk class 1): 0 – 3 days
   Control period: 4 – 183 days

   The hazard rate in the risk period will be estimated in relation to the control period with a one-sided test of significance at the level $\alpha = 0.05$. Analogously, a one-sided 95%confidence interval will be calculated.

   The 'high risk' interval of 0-3 days has been defined according to the recommendations of the Brighton Collaboration Working Group on SIDS.

   b.)
   (risk class 2): 4 –7 days
   Control period: 8 – 183 days

   The hazard rate in the risk period will be estimated in relation to the control period with a one-sided test of significance at the level $\alpha = 0.05$. Analogously, a one-sided 95%-confidence interval will be calculated.

   The additional 'high risk' interval of 4 – 7 days has been defined in the light of the results of the Italian Hera Study report. These results suggest that the risk period of a potential temporal association between vaccination and sudden death may extend up to 7 days or – more particular – in the time slot of the 4^{th} to 7^{th} day after vaccination.

3. Seasonal classes *k*.
4. For every case, from the combination of age category, seasonal category and risk period, there is a particular constant 'hazard'.
5. 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 .

Exploratory analyses

In addition, exploratory analyses with additional risk periods will be performed for comparison to the risk periods set out *a priori* under hypotheses 1.

For these secondary (explorative) analyses the elapsed time after vaccination is divided into risk periods of:

(risk class 3): 8-14 days
(risk class 4): 15-28 days
(risk class 5): 29-183 days.

The risk periods represent categories with markedly different levels of incidence, according to cases of death after hexavalent vaccination observed so far. The borderline of 28 days has been set as a plausible, but arbitrary boundary for a possibly causal association.

In these secondary analyses, the risk class 5 (29-183 days) was chosen as the reference class. Hazard rates of classes 1-4 will be estimated in relation to class 5, with a one-sided test of significance at the level $\alpha = 0.05$. Analogously, one-sided 95% confidence intervals will be calculated. The tests will be performed sequentially, beginning with class 1. If a significant result is seen in one class, then the next class will be tested. Thus, the multiple level of $\alpha = 0.05$ will be kept.

In addition to these specific hypotheses, potential temporal associations of any vaccination – not only hexavalent products – and sudden deaths will be investigated by exploratory analyses. Explorative analyses will also investigate whether there are differences between the first, second, third and the booster dose.

Subgroup analyses will be performed for which case definition must meet category 1 or 2 of the recommendations by the Working Group on Sudden infant death syndrome (SIDS).

Power calculation (SCCS)

The necessary number of cases will be estimated in accordance with Farrington, et al. (1995, 1996). It relies on the following, simplified assumptions:

1. No age effects.
2. Identical risk period R_1 and control period R_0 for all N individuals; time of observation: R_1 followed by R_0.
3. Vaccination as the start of the observation time.

The following parameters enter into the formula:

$\rho = e^{\beta}$	the relative incidence in the risk group compared to the control group
v	number of cases vaccinated at the beginning of the period (starting with 1, since only vaccinated cases of SUD can enter the analyses)

r = (length of risk period) / (length of observation period)

α = error-I probability for the two-sided test

(1 -β) = power of the test (β = error-II probability)

$Z_{\alpha/2}$ and Z_{β} the corresponding upper quartiles of the standard normal distribution.

The formula used can be found in appendix 1.

The (revised) formula for calculating the number of cases in the SCCS analysis (translated into the syntax of the S-Plus program) is:

events<- function (nu, r, ro, zahalbe, zbeta)

{ (1/(nu*r*(1- r)*(ro-1)^2))* (zahalbe + zbeta*sqrt((1 + nu*r*(ro-1)) *(1 + r*(ro-1))*ro))^2 }
The following parameter values are assumed: α = 0.05; one-sided test; (1 -β) = 0.8 (power = 80%); risk period: 3 days; observation phase: 6 months; $\rho = e^{\beta}$ (relative incidence): 2, 4, 8, 10, ~~16, 20. The latter values (16 and 20) are considered for performing a separate test for each hexavalent product. So the resulting numbers will have to be multiplied by 2, assuming equal proportion of both types of vaccine~~.

Given the assumptions made above, the relative risk of a case occurring in the risk period compared to occurrence in the control period, provided there is a case and the vaccination took place within the observation period, is:

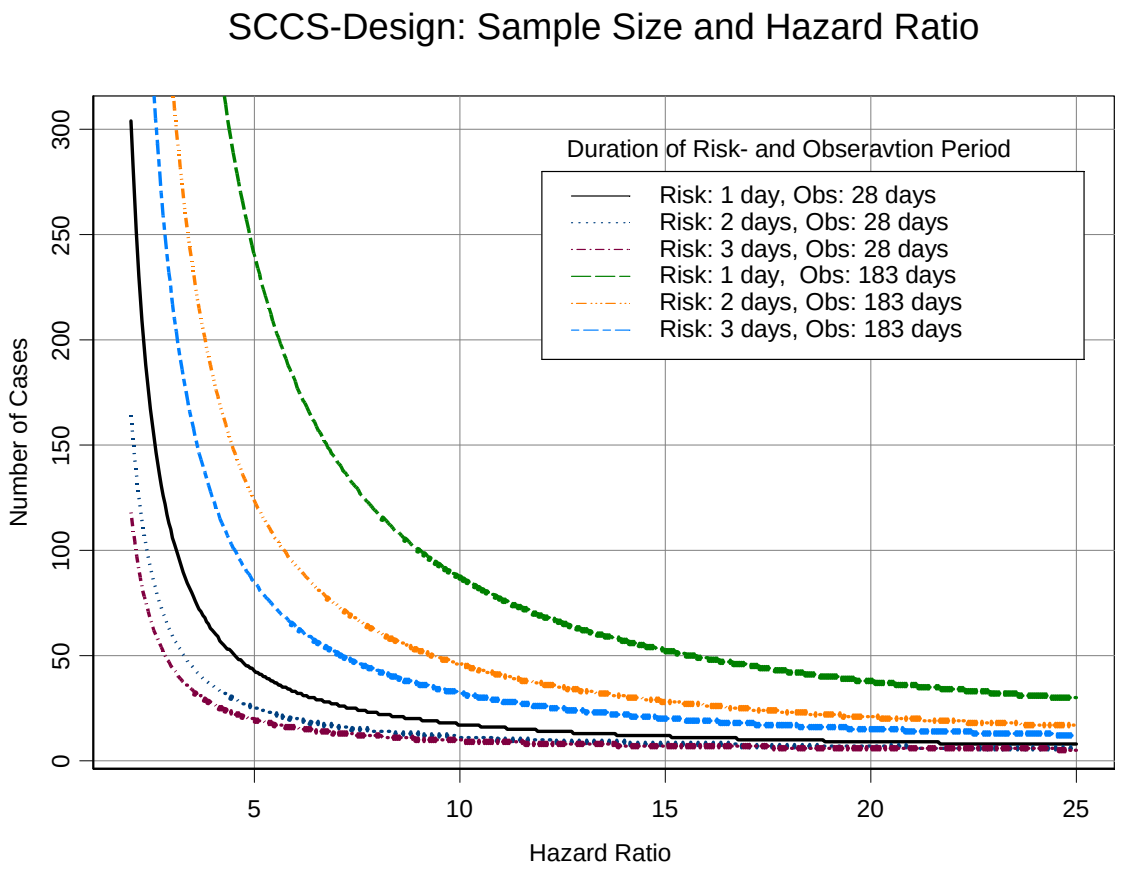
RR = e^{β} x (length of risk period) / (length of control period)
= e^{β} x (3 days) / (duration of observation in days - 3)

The (relative) probability of occurrence within the risk period is:

p_1 = RR / (1+RR)

This probability can be calculated under the Null-hypothesis H_0: $\rho = e^{\beta} = 1$ ($\beta = 0$) on the assumption that ρ = 10 and for different alternatives.

For the power analysis, it is assumed that the Null-hypothesis will 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 α = 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. ~~Thus, to detect a relative incidence of 16 or 20 for each hexavalent product separately, a total number of 26 resp. 22 cases will be necessary (20 resp. 16 following the formula of Farrington)~~.
To give a complete overview on the sample size in dependence of both the relative incidence ρ and the length of different risk and observation periods, sample sizes were calculated for risk periods of 1, 2 or 3 days, observation periods of 28 or 183 days, and ρ varying from 2 to 25. Calculations were performed by using the program "binomial.sample.size" of S-PLUS 6.2 with the option of Yates correction to allow for small sample sizes. The results are presented graphically in the following figure:



Generally, it can be seen that longer risk periods affords less cases given the same hazard ratio. However, this would assume a constant high hazard ratio over the whole period. Roughly, a 3-day hazard ratio of 5 corresponds to a hazard ratio of 15 if the total effect is concentrated on the first day. Also, a long observation period appears inferior to a short period. However, with a short observation period the number of cases to meet the inclusion criterion (vaccination within the observation period) would be reduced.

The total number of deaths in children aged 28 days to one year was 1058 in 2002. Of these cases, 420 were attributed to ICD-10 categories R95-99. For the age group containing babies, the suggested selection strategy should provide a sufficient number of cases.

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) (ρ = 10) children vaccinated within 6 months of death, is realistic considering that it will have three years for the sub-evaluation of sudden and unexpected death in the second year of life under these conditions, and there is a completion rate for the vaccination schedule of over 85% in the second year (data from an, as yet unpublished, representative survey by H. Kalies and von Kries). ~~After a model calculation, 25 cases are expected if it is assumed that there are 24 SUD cases per year and there is a temporal shift in the SUD cases after vaccination. With 33 cases of SUD per year, and a general increase in intensity by a factor of 2, this number increases to 43. The separate SCCS analysis of the two hexavalent vaccines, however, in light of the number of cases expected for the group of subcases in the second year of life, detection of a relative incidence of 20 for each hexavalent product separately can be achieved.~~

9.10.2 Case-control design

The following study questions (see 6) will be investigated by using case-control analyses:

3. Is this potential association qualitatively and quantitatively the same at different stages of life?
4. Has this potential association the same magnitude across ~~different~~ hexavalent and non-hexavalent~~–~~ vaccines?
6. Is the risk of sudden death in vaccinated children different from unvaccinated children?

During this secondary study analyses the following hypotheses will be 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 ~~one~~ hexavalent vaccination.

Null hypotheses formulated for the case-control approach:

The 'vaccination history' will be separated into classes (vaccination status). Lowest class: no vaccination. Condition after vaccination (up to 6 months) will either be assessed as a whole (study question 6) or differentiated according to the classification of time periods. In this differentiated version '0-3 days' is the highest class, and so on (study question 3). Let p_{1i} and p_{2i} denote the probability for a case and for a control, respectively, to be in class c_i .The hypotheses to be tested are:

H_0 $p_{1i} = p_{2i}$ for all classes c_i , against the alternative

H_1 $p_{1i} \neq p_{2i}$ for at least one class c_i

For the test of a distinct vaccine, the hypotheses to be tested are of the same form, however p_{1i} and p_{2i} are to be interpreted as conditional probabilities:

For the test of an association of vaccine *type 1* with mortality, p_{1i} and p_{2i} are the probabilities for a case and a control, respectively, to be in class c_i, *given there was no vaccination with vaccine type 2*. Accordingly, for the test of an association of vaccine *type 2* with mortality, p_{1i} and p_{2i} are the probabilities for a case and a control, respectively, to be in class c_i , *given there was no vaccination with vaccine type 1*

The following definitions were made for implementing the case-control design:

Cases:

Every sudden death of an infant in the second to 24th months of life, reported by a LHA, for whom informed consent of a parent or guardian has been obtained.

Inclusion criteria:

- ICD-10 classification of cause of death is R 95 – 99 (according classification based on information from death certificate and parents and physicians questionnaire, from potential clinical reports and any available autopsy reports see 9.6)

- Age at death in the second to the 24th month of life (after the first month of life has been completed and before the 24th month of life has been completed).

Exclusion criteria:

- Age at death does not meet inclusion criteria
- Informed consent of a parent or guardian not obtained.

Controls:
Controls will be participants of the German Child and Youth Health Examination Survey (KIGGS), matched to cases on age and time of examination. Matching will be performed following these rules:

- The date of survey examination in a control is not earlier than the date of death in a case minus 1 month and not later than the date of death in a case plus 1 month

and

- Age at survey examination in a control is not lower than the age a case has died plus 5 weeks and not higher than the age a case has died plus (5 weeks + 2 months =) 13 weeks

Differences of vaccination history in cases and controls will be analysed by unconditional logistic regression, adjusting for matching criteria of this frequency-matched study. Relative risks of vaccination will be estimated by adjusted odds ratios and their 95% confidence intervals.

The following parameter are known factors associated with sudden unexpected death (see 9.8) and will be included in the model of the logistic regression models: age, socio-economic status (SES), age of mother, smoking during pregnancy, premature birth, problems in the newborn phase, multiple pregnancy, crowded parental accommodation, mother smoking. Some of these variables are also associated with vaccination coverage.

Power calculation (case-control study)

~~Power analyses of the case-control study was calculated using the programme nQuery Advisor 5.0 with given error probabilities of α = 0.05 (two-sided) and ß=0.2.~~
The calculations were performed by using the program "binomial.sample.size" of S-PLUS 6.2 with the option of Yates correction to allow small sample sizes with given error probabilities of α = 0.05 (two-sided) and ß=0.2.

~~From German vaccination data cited above and the simulation study of matching KiGGS controls to real cases, the following assumptions were made:~~

- ~~probability of being exposed to a hexalavent vaccine = 40% 60%,~~
- ~~probability of being exposed to a non-hexavalent vaccine = 40% 20%,~~
- ~~probability of not being vaccinated = 20%.,~~
- ~~average number of controls per case = 4.~~

~~As this analysis focus on differences of vaccination history within the three-day period prior to the cases deaths the following power analysis has been performed. For analysis of a potential risk of any hexavalent vaccine, calculation of power and sample size assumed the~~

~~probability of being exposed in controls to be 0.0066 (0.8* (3/365) / [0.8 * (3/365) + (1 – 0.8*(3/365)] = 0.0066). In order to detect a smallest relative risk (OR) of 20 the required sample size is 33 cases and 139 controls.~~

~~For analysing a potential risk of a certain hexavalent product, the probability of being exposed was calculated to be 0.0033 (0.4 * (3/365) / [0.4 * (3/365) + (1 – 0.8*(3/365)] = 0.0033). Detection of a smallest relative risk (OR) of 20 requires a sample size of 69 cases and 293 controls. Thus, in light of the number of cases expected in the first year of life, detection of a relative risk of 20 for each hexavalent product separately can be achieved in the case-control analysis as well. Assuming that vaccination as well as occurrence of cases will mainly arise during the first half of second year the probability of exposition in the control group in the second year of life was calculated to be 0.0066 (0.4* (3/183) / [0.4 * (3/183) + (1 – 0.8*(3/183)] = 0.0066). In order to detect a smallest relative risk (OR) of 20, the required sample size is 33 cases and 139 controls. Thus, in light of the number of cases expected in the second year of life, detection of a relative risk of 20 for each hexavalent product separately can be achieved.~~

~~The additional analyses focus on estimation the overall potential effect of a vaccination on risk of death. A general, but delayed effect of a vaccination may qualitatively and quantitatively differ from the immediate effects shortly after vaccination. For analysing a potential risk of a certain hexavalent vaccine, the probability of being exposed is 40% among controls, and a smallest relative risko (OR) of 16 is to be detected. The required sample size to achieve this is 8 cases and 31 controls~~

Definition
Cases:
Any SUD after month 1 of age until end of month 24. For subanalyses this age interval will be split by end of month 12
Controls:
Any selected control child of the study (matched by calender time and age as defined in the study protocol).
Exposure:
Description of vaccination history before timepoint of event (death in cases) or matched time point (controls) in classes X .

The exposure classes X are defined as:

X class 0: No vaccination within the risk class of interest

X class 1: Hexavalent vaccination within the risk class of interest

X class 2: Vaccination of other type within the risk class of interest

The risk classes of interest, R_i, will be specified as periods of different length (1, 2, 3, 7, 28 or 183 days)

Parameter of interest

The primary aim of the case-control study is to estimate the odds of occurrence of the event (SUD) in dependence of the vaccination status. Let Y denote the outcome, that is the occurrence of the event:

$Y = 0$: no event

$Y = 1$: event

Thus, the parameters of interests are

$$\begin{aligned} p_{i1} &= P(Y = 1 \mid X = i) \\ &= \text{Probability of event, given exposure class } i \quad (i = 0,1) \end{aligned}$$

and

$$\begin{aligned} p_{i0} &= P(Y = 0 \mid X = i) \\ &= 1 - p_{i1} \\ &= \text{Probability of no event, given exposure class } i \quad (i = 0,1) \end{aligned}$$

These parameters are listet in the following table:

	Event Y			
Exposure	X	0 (Controls)	1 (Cases)	Sum
	0 (No vaccination)	p_{00}	p_{01}	1
	1 (Hexavalent vaccination)	p_{10}	p_{11}	1
	2 (Other vaccination)	p_{20}	p_{21}	1

The "effect" of the exposure is measured as the odds ratio:

$$\begin{aligned} OR &= \frac{\text{Odds for event under exposure 1}}{\text{Odds for event under exposure 0}} \\ &= \frac{p_{11} / p_{10}}{p_{01} / p_{00}} \end{aligned}$$

In the case-control study the paramters p_{ij} are not estimable. Instead, in the retrospective view, the probabilites of the risk classes are estimated separately for cases and controls:

$$\begin{aligned} q_{i0} &= P(X = i \mid Y = 0) \\ &= \text{Probability of risk class } i \text{ for cases} \quad (i = 0,1,2) \end{aligned}$$

and

$$\begin{aligned} q_{i1} &= P(X = i \mid Y = 1) \\ &= \text{Probability of risk class } i \text{ for controls} \quad (i = 0,1,2) \end{aligned}$$

These parameters are listed in the following table:

	Event	Y	
Exposure	X	0 (Controls)	1 (Cases)
	0 (No vaccination)	q_{00}	q_{01}
	1 (Hexavalent vaccination)	q_{10}	q_{11}
	2 (Other vaccination)	q_{20}	q_{21}
	Sum	1	1

The following relations hold:
Cases:

$$\begin{aligned} q_{i0} &= P(X = i \mid Y = 0) \\ &= P(Y = 0 \mid X = i)\frac{P(X = i)}{P(Y = 0)} \\ &= p_{io}Q_{i0} \quad \text{where} \\ Q_{i0} &= \frac{P(X = i)}{P(Y = 0)} \end{aligned}$$

Controls:

$$\begin{aligned} q_{i1} &= P(X = i \mid Y = 1) \\ &= P(Y = 1 \mid X = i)\frac{P(X = i)}{P(Y = 1)} \\ &= p_{i1}Q_{i1} \quad \text{where} \\ Q_{i1} &= \frac{P(X = i)}{P(Y = 1)} \end{aligned}$$

In this design, we may by ignoring risk class 2 (other type of vaccination) and calculate the odds for class 1 versus class 0 and compare these odds between cases and controls:

$$
\begin{aligned}
OR_{cc} &= \frac{q_{11}/q_{01}}{q_{10}/q_{00}} \\
&= \frac{P(X=1\,|\,Y=1)/P(X=0\,|\,Y=1)}{P(X=1\,|\,Y=0)/P(X=0\,|\,Y=0)} \\
&= \frac{p_{11}Q_{11}/(p_{01}Q_{01})}{p_{10}Q_{10}/(p_{00}Q_{00})} \\
&= \frac{p_{11}/p_{01}}{p_{10}/p_{00}}\,\frac{Q_{11}/Q_{01}}{Q_{10}/Q_{010}} \\
&= \frac{p_{11}/p_{01}}{p_{10}/p_{00}}\,\frac{\frac{P(X=1)}{P(Y=1)}/\frac{P(X=0)}{P(Y=1)}}{\frac{P(X=1)}{P(Y=0)}/\frac{P(X=0)}{P(Y=0)}} \\
&= \frac{p_{11}/p_{01}}{p_{10}/p_{00}} \\
&= OR
\end{aligned}
$$

Conclusion:

The odds ratio for the occurrence of an event comparing exposure class 1 with exposure class 0 can be estimated and tested in the case-control design by ignoring exposure class 2 (other type of vaccination) and calculating and testing the odds ratio for exposure class 1 versus class 0 with respect to cases and controls.

Estimation of the probability of exposure to risk for controls: q_{10}

Let T denote the reference time (age in days) of a control child. The distribution of T will be similar to the age distribution of the SUD -cases, since they will be matched by age.
Similar, let V_H denote the age of hexavalent vaccination, and V_O denote the age of vaccination with other vaccines.
If we regard the whole study period for age, the following relations hold:

$$\sum_{t\geq 32}^{730} P(T=t) = 1$$

$$P_{VH} := \sum_{t\geq 1}^{730} P(V_H = t) = \text{Probabilty of hexavalent vaccination within the first 24 months}$$

$$P_{VO} := \sum_{t\geq 1}^{730} P(V_O = t) = \text{Probabilty of other vaccination within the first 24 months}$$

(Two ore more vaccinations per child would raise the value for exposure probability; they are ignored in these considerations)
Let Δ denote the length of the risk class in days.
Then, the probability, that the reference date T of a control falls into the risk class of hexavalent vaccination, is

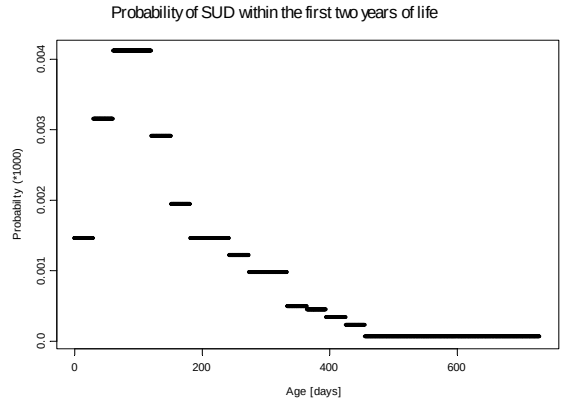
$$
\begin{aligned}
q_{10} &= P(T \in \text{Hexavalent Risk Class}) \\
&= \sum_{t \geq 31}^{730} P(T = t, V_H \in (t-\Delta, t]) \\
&= \sum_{t \geq 31}^{730} P(T = t)\, P(V_H \in (t-\Delta, t]) \text{ (independence of } T \text{ and } V \text{ under } H_0) \\
&= \sum_{t \geq 31}^{730} P(T = t) \left[\sum_{\tau \in (t-\Delta, t]} P(V_H = \tau) \right]
\end{aligned}
$$

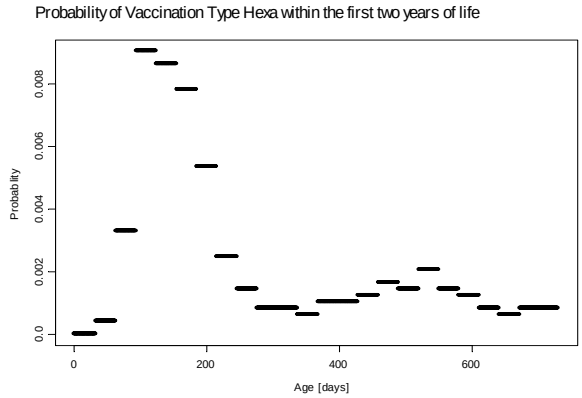
Similar;

$$
\begin{aligned}
q_{20} &= P(T \in \text{Other Vaccination Risk Class}) \\
&= \sum_{t \geq 31}^{730} P(T = t) \left[\sum_{\tau \in (t-\Delta, t]} P(V_O = \tau) \right]
\end{aligned}
$$

Thus, given the distributions $\{P(T=t)\}_t$, $\{P(V_H = t)\}_t$ and $\{P(V_o = t)\}_t$, the parameters q_{10}, q_{20} and $q_{00} = 1-(q_{10}+q_{20})$ can be computed.

Computations are performed on the basis of the data of the BMBF Study and Bavarian Bureau of Statistics, von Kries, 2004:





In the latter figure, the relation of hexavalent type to other vaccinations is assumed to be 5 : 3.

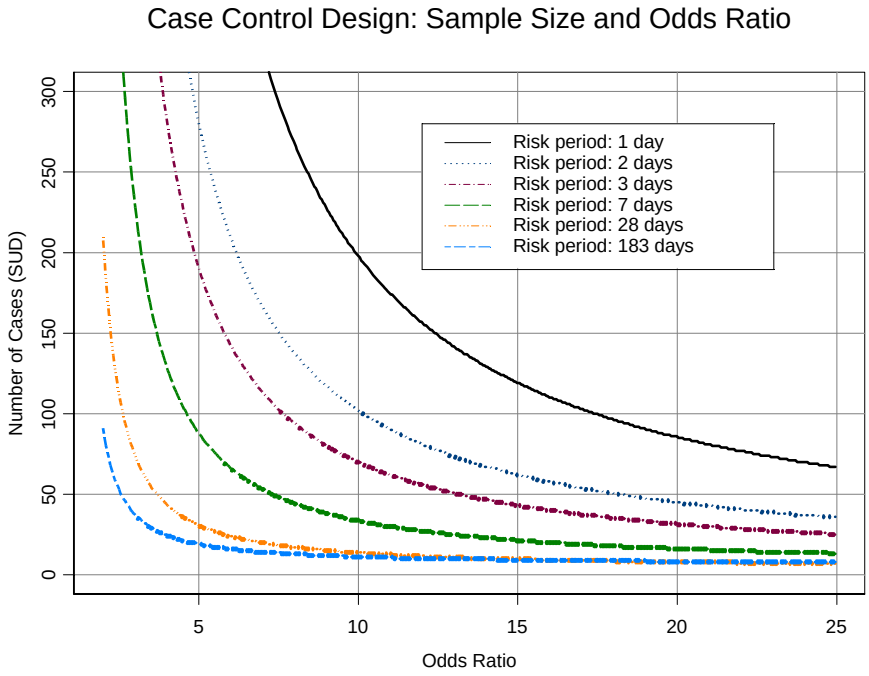
In the following computations the length Δ of the risk class is varied as : 1, 2, 3, 7, 28, 183. This will allow calcula ting the sam ple sizes for comparing cases with co ntrols for different lengths of risk periods. The base probabilities q_{10} for controls to fall into th e risk class

(Hexavalent vaccinations within the last ✌ days) are estimated by this computation as: [Δ = 1:] 0.0032, [Δ = 2:] 0.0064, [Δ = 3:] 0.0096 ,
[Δ = 7:] 0.0221, [Δ = 28:] 0.0812 , and [Δ = 183:] 0.320
For these values, the sample size calculation is performed under following assumptions:

- The chisquare test is performed two sided on the level $\alpha = 0.05$
- The power of the test is 80 %
- The relation of number of cases to number of controls is 4.3.
- The odds ratios are varied from 2 to 25

The calculations were performed by using the program "binomial.sample.size" of S-PLUS 6.2 with the option of Yates correction to allow small sample sizes.

Results
The results are presented graphically in the following figure:



Interpretation
Example:

1) To compare a risk period of 3 days between cases and controls under the assumption that an odds ratio of 20 is to be detected with a power of 80 %, $n_1 = 32$ cases and $n_2 = 4.3 * 30 \rightarrow 138$ controls are needed. A "case" is here defined as an SUD with Hexavalent vaccination within the last 3 days or without any vaccination in this period. It is assumed that the odds for SUD are raised in this period after Hexavalent vaccination by the factor 20 compared to no vaccination within this period.
2) Comparibly, if an odds ratio of 20 holds even for a 7-day period, the corresponding numbers are $n_1 = 16$ cases and $n_2 = 4.3 * 16 \rightarrow 69$
3) If the number of cases of the first example, $n_1 = 32$, is given, this will be sufficient to detect an odds ratio of 10 , if this is valid for a 7-day period after vaccination.

4) If the odds ratio is 16 for a half year period, corresponding to a general (positive or negative) vaccination effect, the necessary sample sizes are $n_1 = 9$ cases and $n_2 = 4.3 * 9 \rightarrow 39$ controls. The same holds for a risk period of 28 days.
5) For the focus of a 3-day period it is seen, that odds ratios of 5 , 10 and 15 need sample sizes of $n_1 = 190,\ 70$ and 43 cases, respectively.

Exploratory analyses

In addition to these main analyses of a potential effects of hexavalent vaccines, any vaccination –not only hexavalent products – and sudden deaths will be investigated by exploratory analyses. These exploratory analyses are not related to the study questions that have been defined.

For the case-control study and the SCCS design, main analyses focus on unexplained sudden deaths. Level of diagnostic certainty is expected to be different between the pathological and the epidemiological study approach. Autopsies may not be performed in cases who are reported by the LHA's resulting in levels of diagnostic certainty of not more than 3 according the recommendation of the Brighton Collaboration Workgroup on SIDS. Subgroup analyses of cases with higher level of diagnostic certainty (pathological approach) will be performed. In addition exploratory analyses applying a widened case definition will evaluate those cases in which a link with vaccination may be plausible. For these additional analyses cases are defined as any death of an infant in the second to 24th month of life (not only ICD 10 R 95-99), reported by a LHA, for whom informed consent of a parent or guardian has been obtained.
For these analyses the following exclusion criteria apply:

Cause of death according to the information on the death certificate is one of the following ICD classifications:

- V01-W74: accidents with means of transport (V01-V99), falls (W00-W19), accidental drowning (W65-W74)
- new malignant growth (C00-C97)
- severe endocrinal, nutritional or metabolism disorders (from E00-E90)
- malformations, deformities and chromosomal anomalies (Q00-Q99)
- injuries, poisonings and certain other outcomes with external causes (S00-T98)

9.10.3 *Sequential analysis*
The sequential analysis is intended as a monitoring instrument. Since important new insights relevant to public health could be gained while the study is underway, data analyses will not be left to the end of the field phase. An independent biometrical institute will undertake ongoing monitoring using the one-sided open Sequential Probability Ratio Tests (SPRT) of Wald. For this, a warning line will be defined in the field between the x-axis (number of cases) and the y-axis (cumulated test results). Should the path of test points cross the warning line, a full interim analysis will be performed.

Sequential data analyses will be performed for both the SCCS and the case-control study. In both versions, they can only give rough hints on potential associations, as the existing models do not permit consideration of any confounder (age + season, and the confounding variables of the case-control study).

Hypotheses formulated for the SCCS approach:

H_0 The risk after vaccination is the same in all classes (up to 6 months). So the conditional probability of occurrence in the first three days, given an event is 0.0164.

H_1 The risk following vaccination in the first period (0-3 days) is increased by $\rho = e^{\beta} = 16$ (~~and 20 respectively for separate analyses of the two different hexavalent products~~) compared to the risk afterwards (4 days to 6 months). So the probability of occurrence in the first three days = 0.2105 (~~and 0.25 respectively for separate analyses of the two different hexavalent products~~).

A one-sided (open) sequential test will be used in accordance to Wald. This test only identifies a stop if there is an increase of the risk in the first period. The type I error will be set at $\alpha = 0.05$; the power 1-β will be 80 percent.

For the SCCS approach, the parameter π of the binomial distribution is $\pi = \pi_0 = 0.0164$ under H_0, and $\pi = \pi_1 = 0.2105$ under the alternative H_1. Let $\alpha = 0.05$ and $\beta = 0.2$ be the probabilities of error type I and II respectively. Furthermore, let m denote the actual number cases in the sequential trial (cases with vaccination), and $r \leq m$ the number of events (cases with vaccination in the first risk period). Then the warning limit to indicate an increased number of events, is reached if

$$r \geq \frac{\log(\frac{1-\beta}{\alpha})}{\log\left(\frac{\pi_1(1-\pi_0)}{\pi_0(1-\pi_1)}\right)} + \frac{\log\left(\frac{1-\pi_0}{1-\pi_1}\right)}{\log\left(\frac{\pi_1(1-\pi_0)}{\pi_0(1-\pi_1)}\right)} m$$

Thus, for the given parameter values the warning limit w as a function of cases m is

$$w(m) = 1.0002 + 0.0793\, m$$

This sequential plan is an open plan in the following sense: The probability that the warning limit will be reached at any time of the process is restricted to $\alpha = 0.05$ under H_0, irrespective of the duration of the trial. Vice versa, under H_1 the warning limit will be reached with probability 1- $\beta = 0.8$ if the duration is unlimited.

Hypotheses formulated for the case-control approach:

The 'vaccination history' will be separated into two classes c_i (vaccination status positive or negative).. Let p_1 and p_2 denote the probability for a case and for a control, respectively, to be in class 1 (positive vaccination status). The hypothesis to be tested is:

H_0 $p_1 = p_2$, against the alternative

H_1 $p_1 \neq p_2$

A two-sided (open) sequential test will be used in accordance to Wald. This test identifies a stop if there is an increase or decrease of the odds for positive vaccine status. The type I error will be set at $\alpha = 0.05$; the power 1-β will be 80 percent.

For the case-control approach the parameter $\theta = \log\left(\frac{\pi_2(1-\pi_1)}{(1-\pi_2)\pi_1}\right) =$ log odds ratio is $\theta = \theta_0 = 0$ under H_0, and $\theta = \theta_1 = \log(20) = 3.00$ under the alternative. Let $\alpha = 0.05$ and $\beta = 0.2$ be the probabilities of error type I and II respectively. Furthermore, let $m_i \quad (i = 1,2)$ denote the actual number of children in the case and control group , and $r_i \leq m_i$ the number of children in class 1 (vaccination) within each group.

With $h_i = \frac{r_i}{m_i}$ (the relative frequency of class 1 in group i), $h = \frac{r_1 + r_2}{m_1 + m_2}$ (the pooled relative frequency of class 1), the warning limit for an increased odd in group 1 is reached if

$$\frac{m_1\, m_2}{m_1 + m_2}\left(h_1 - h_2\right) \geq \frac{1}{\theta_1}\log\left(\frac{1-\beta}{\alpha/2}\right) + \frac{1}{\theta_1}\frac{m_1\, m_2}{m_1 + m_2}\, h(1-h)$$

For the given parameter values this reads as

$$\frac{m_1\, m_2}{m_1 + m_2}\left(h_1 - h_2\right) \geq 1.157 + 0.334\frac{m_1\, m_2}{m_1 + m_2}\, h(1-h)$$

Accordingly, the warning limit for an increased odd in group 2 is reached if

$$\frac{m_1\, m_2}{m_1 + m_2}\left(h_2 - h_1\right) \geq 1.157 + 0.334\frac{m_1\, m_2}{m_1 + m_2}\, h(1-h)$$

Second Amendment

Darstellung der mit dem 15.02.2007 veränderten Abschnitte des Studienprotokolls ‚Study on deaths in young children (2. – 24th month of life) im Vergleich zur Vorversion vom 10.3.2006

Die Veränderungen betreffen die Kontrollgruppe des Fall-Kontroll-Studienteils der TOKEN-Studie. Im Rahmen der TOKEN-Studie werden alle Todesfälle von Kindern im 2.-24. Lebensmonat erfasst und die Daten der in die Studie aufgenommenen Fälle überprüft auf

1. einen zeitlichem Zusammenhang zwischen unerwarteten Todesfällen und (hexavalenten) Impfungen (Self Controlled Cases Series Design - SCCS)
2. einen generellen Zusammenhang zwischen dem Risiko, unerwartet zu versterben, und vorangegangenen Impfungen (Fall-Kontroll-Design).

Bisher wurden die Kontrollen für den Fall-Kontroll-Studienteil aus dem Pool der anonymen Daten des vom Robert Koch-Institut (RKI) durchgeführten Kinder- und Jugendgesundheitssurveys (KiGGS) gezogen. Im Studienplan war ursprünglich vorgesehen, die Kontrollen auch nach Beendigung der KiGGS-Feldphase als historische Kontrollen aus den KiGGS-Probanden zu ziehen. Die Marktrücknahme eines der beiden hexavalenten Impfpräparate führte jedoch zu einer grundsätzlichen Änderung der Exposition von Säuglingen in Deutschland und lässt aus methodischen Gründen das geplante Vorgehen nicht mehr zu.

Es wurde deshalb eine Änderung zum Studienplan erarbeitet, die die zukünftige Ziehung der Kontrollprobanden - vergleichbar zur Ziehungsmethode bei KiGGS - bevölkerungsbasiert, prospektiv beinhaltet.

1. Verändert in Kapitel 9 ‘Study population’ Abschnitt 9.4.2 ‘Case-Control study’

Veränderungen zur Vorversion sind in roter Schriftfarbe markiert.

9.4.2 Case-control study

Cases:
Every death in an infant in the second to 24th months of life, reported by LHA, for whom informed consent of a parent or guardian has been obtained.

Inclusion criteria:

- age at death in the second to the 24th month of life (after the first month of life has been completed and before the 24th month of life has been completed

Exclusion criteria:

- age at death does not meet inclusion criteria
- informed consent of parent or guardian not obtained.

Controls:
Controls will be participants of the German Child and Youth Health Examination Survey (KIGGS) or prospective controls after the KiGGS survey has ended. KiGGS controls will be matched to cases on age and time of examination. Matching will be performed following these rules:

1. the date of survey examination in a control is not earlier than the date of death in a case minus 1 month and not later than the date of death in a case plus 1 month

and

2. age at survey examination in a control is not lower than the age a case has died plus 5 weeks and not higher than the age a case has died plus (5 weeks + 2 months =) 13 weeks

The reason for this is the mode of invitation and examination established in the KIGGS survey. Participants are invited two to five weeks prior to their scheduled date of examination. An effect on vaccination and doctor's appointments in this period is to be expected, not only by participants avoiding additional appointments, but also possibly in their catching up on missed vaccinations. This may bias any results: the former by increasing, the latter by decreasing the OR for vaccination because of an artificially lower (higher) probability of the KIGGS children to be immunised.

The reference point to assess any exposure in controls is 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.
>
> ~~35 days will be subtracted from the date of examination, specifying a point in time that lies safely before the invitation to the KIGGS examination.~~

For each case, as many KiGGS study subjects as fulfil the above criteria will be selected as controls. If a KiGGS study subject is a suitable control for more than one case, it will only be selected once into the control group. Data of cases and controls will make a ~~frequency~~ matched case-control study and will be analysed as such. In a simulation study with real cases notified to the PEI and KiGGS data of May 2003 to December 2004, 85 controls could be ~~frequency~~ matched to 20 cases, yielding an average of 4.3 controls per case. The number of controls suitable for each case varied between 0 and 13. 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 in older cases.

The KiGGS survey and this study will run parallel in time for about half of the study period, so the above method to select controls is applicable only for that time. In order to include all cases identified during this study, ~~another analysis needs to be performed: Only step 2 of the above rules will be applied and all age matched controls selected, irrespective of the time of their examination. The difference in time periods between cases and controls will then be adjusted for in the logistic model. Sales figures of hexavalent products by time periods will be used to estimate whether the likelihood of being exposed varies over time and to adjust for this potential confounder.~~ selection of suitable controls will be continued by the same multi stage sample procedure after the end of the KiGGS survey. The initially planned procedure of selecting KiGGS controls irrespective of time of their investigation needs to be modified due to substantial changes of the marketing authorisations of hexavalent vaccines (see 9.7.2). As a result of the suspension of the marketing authorisation of Hexavac, the exposure to hexavalent vaccines in the study population changed substantially and historic controls would introduce serious bias.

Participants of the KiGGS survey were enrolled according to a two-step sampling frame: First a random sample of 167 communities (clusters) was identified in strata of states and BIK[1] classes of communities. Individuals were then randomly sampled from the registration office in each selected community. The strategy to match KiGGS participants as controls to TOKEN cases has been described above.

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

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

1. After the photocopies of the death certificates have been received from the LHAs, the date of birth of each reported case is ascertained.
2. Controls for that case must be born on the same day as the case, plus/minus one month.
3. Two communities are randomly selected from the 167 KiGGS sample points.
4. A letter is 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. A letter is sent to the parents with information about the study, asking them for consent to participate.
6. If parents do not respond within 14 days, a second letter is sent out as a reminder.
7. If parents still do not respond after another 14 days, tries will be made to contact them by phone at different times of day.
8. If parents declare to be not willing to participate, they are asked to complete the non-responder questionnaire.
9. If parents consent, they are sent a questionnaire which is most similar to the questionnaire for cases. However, questions about the circumstances of death are not asked and the reference date for answers is the age at death in the corresponding case.

Parental questionnaire

ROBERT KOCH INSTITUT

Elternfragebogen

Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat

U2

Elternfragebogen

Studie über Todesfälle
bei Kindern im
2. bis 24. Lebensmonat

Liebe Eltern,

Sie haben sich trotz des tragischen Verlusts Ihres Kindes bereit erklärt, an unserer Untersuchung über Todesfälle bei Säuglingen und Kleinkindern teilzunehmen.

Dafür danken wir Ihnen sehr. Wir wissen wohl, dass die Beantwortung unserer Fragen für Sie nicht einfach ist. Doch soll diese Untersuchung Erkenntnisse über Ursachen gewinnen und dadurch helfen, zukünftig solche Fälle zu verhindern.

Wir befragen Sie zunächst kurz zu Ihren Lebensumständen und möchten auch wissen, wer diesen Bogen ausfüllt. Es werden dann Fragen zu Schwangerschaft, Geburt, medizinischen Behandlungen und Impfungen Ihres Kindes gestellt. Wir erfragen auch Namen und Adressen von weiteren behandelnden Ärzten und Krankenhäusern. Wenn Sie uns diese Namen mitteilen, werden wir einen Fragebogen an diese Ärzte versenden und um die medizinischen Befunde bitten. Es folgen dann die Fragen, die sich auf den Zeitpunkt des Todes Ihres Kindes beziehen. Abschließend bitten wir Sie um einige Angaben zu Ihren Lebensgewohnheiten und -bedingungen.

- Bitte beantworten Sie möglichst alle Fragen vollständig! Sie können zwar Fragen auslassen, die Ihnen unangenehm sind, allerdings würde das die wissenschaftlichen Ergebnisse dieser Untersuchung sehr beeinträchtigen.
- Kreuzen Sie bitte bei jeder Frage an, was auf Sie oder Ihr verstorbenes Kind am besten zutrifft.
- Bitte senden Sie uns dann den Fragebogen zusammen mit dem Impfbuch Ihres verstorbenen Kindes (oder einer Kopie davon) und dem Kinderuntersuchungsheft (oder einer Kopie davon) zu.

Bei Fragen und Unklarheiten können Sie sich an uns wenden.

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Angaben zu den Eltern

Patientencode: ☐☐☐☐☐☐

1 Wer beantwortet diesen Fragebogen?

- Leibliche Mutter ○
- Leiblicher Vater ○
- Mutter und Vater ○
- Großeltern, andere Verwandte ○
- Pflegeeltern/Adoptiveltern ○
- Betreuer ○

2 **Wie alt sind Sie?** Bitte für beide Elternteile angeben!

Leibliche Mutter
☐☐ Jahre

Leiblicher Vater
☐☐ Jahre

3 **In welchem Land sind Sie geboren?** Bitte für beide Elternteile angeben!

Leibliche Mutter

In Deutschland ○

In einem anderen Land: ○
In welchem anderen Land?
.....

Weiß nicht ○

Leiblicher Vater

In Deutschland ○

In einem anderen Land: ○
In welchem anderen Land?
.....

Weiß nicht ○

4 **Welchen Familienstand haben Sie?** Bitte für beide Elternteile angeben!

	Leibliche Mutter	Leiblicher Vater
Alleinlebend	○	○
Zusammenlebend in häuslicher Partnerschaft oder Ehe	○	○
Weiß nicht	○	○

Angaben zu den Lebensumständen des Kindes

5 **Bei wem lebte Ihr Kind hauptsächlich?** (Hier bitte nur **ein** Kreuz machen!)

Das Kind lebte hauptsächlich bei

- Leiblichen Eltern ○
- Mutter und ihrem Partner ○
- Vater und seiner Partnerin ○
- Alleinlebender Mutter ○
- Alleinlebendem Vater ○
- Großeltern oder anderen Verwandten ○
- Pflegeeltern/Adoptiveltern ○
- In einem Heim ○
- Weiß nicht ○

6 **Mit wie vielen älteren und jüngeren Geschwistern lebte Ihr Kind zusammen?**
Gemeint sind in diesem Fall auch Halbgeschwister und angeheiratete Geschwister.

- Mein Kind lebte mit **keinen** Geschwistern zusammen ○
- Mein Kind lebte mit einem (1) Geschwisterkind zusammen ○
- Mein Kind lebte mit zwei (2) Geschwisterkindern zusammen ○
- Mein Kind lebte mit drei (3) Geschwisterkindern zusammen ○
- Mein Kind lebte mit mehr als drei Geschwisterkindern zusammen ○
- Weiß nicht ○

7 Wie groß ist die Wohnung, in der Ihr Kind hauptsächlich gelebt hat?

☐☐☐ m²

Weiß nicht ..... ○

8 Wie viele Personen haben außer Ihrem Kind in dieser Wohnung gelebt?

☐☐ Personen

Weiß nicht ..... ○

9 Wurde Ihr Kind gestillt?

Nein ..... ○ → **weiter mit Frage 11!**

Ja, es wurde

bis zum ☐☐. Lebensmonat gestillt ..... ○

bis zu seinem Tod gestillt ..... ○

Weiß nicht ..... ○

10 Wie lange wurde Ihr Kind ausschließlich gestillt?

Es wurde nie ausschließlich gestillt ..... ○

Es wurde bis zu seinem Tod ausschließlich gestillt ..... ○

Es wurde bis zum ☐☐. Lebensmonat ausschließlich gestillt ..... ○

Weiß nicht ..... ○

11 Wurde in der Gegenwart Ihres Kindes in der Wohnung geraucht?

Täglich ..... ○

Mehrmals pro Woche ..... ○

Einmal pro Woche ..... ○

Seltener ..... ○

Nie ..... ○

Weiß nicht ..... ○

Schwangerschaften

Die folgenden Fragen zur Schwangerschaft richten sich an die Mutter des verstorbenen Kindes. Kann die Mutter den Fragebogen nicht ausfüllen, so bitten wir die oder den Ausfüllende/n die Fragen so genau wie möglich zu beantworten.

12 War die Geburt Ihres verstorbenen Kindes eine Mehrlingsgeburt?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

13 Wie viele (Lebend-)Geburten hatten Sie vor der Geburt des verstorbenen Kindes?

☐☐ Geburten Weiß nicht ..... ○

14 Wenn Sie mehrere Kinder geboren haben, ist eines Ihrer anderen Kinder im Alter unter 24 Monaten verstorben?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

↓

Wenn ja, in welchem Lebensmonat ist das andere Kind verstorben?

Im ☐☐. Lebensmonat

↓

Wenn ja, welches war die Todesursache?

.....

.....

15 Haben Sie während der Schwangerschaft Ihres jetzt verstorbenen Kindes geraucht?

Ja, täglich über 10 Zigaretten ..... ○

Ja, täglich bis zu 10 Zigaretten ..... ○

Ja, gelegentlich ..... ○

Nein, nie ..... ○

Weiß nicht ..... ○

Geburt und Neugeborenenzeit

16 In welcher Schwangerschaftswoche wurde Ihr jetzt verstorbenes Kind geboren?

☐☐. Schwangerschaftswoche Weiß nicht ..... ○

Falls Sie sich daran nicht mehr erinnern können:

Mein Kind wurde

zu früh geboren ..... ○
(mehr als 3 Wochen **vor** dem errechneten Geburtstermin)

termingerecht geboren ..... ○
(bis zu 3 Wochen **vor** und bis zu 2 Wochen **nach** dem errechneten Geburtstermin)

zu spät geboren ..... ○
(mehr als 2 Wochen **nach** dem errechneten Geburtstermin)

17 Wie schwer und wie groß war Ihr Kind bei der Geburt?

Ca. ☐☐☐☐ Gramm schwer Weiß nicht ..... ○

Ca. ☐☐ Zentimeter lang Weiß nicht ..... ○

18 Sind bei Ihrem Kind in den ersten 4 Lebenswochen nach der Geburt Probleme aufgetreten?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche? (Hier sind **mehrere** Antworten möglich.)

Schwierigkeiten bei der Atmung, Anpassungsstörungen ..... ○
Infektion ..... ○
Neugeborenengelbsucht ..... ○
Untergewicht, Frühgeburt ..... ○
Sonstige ..... ○
Verlegung in eine Kinderklinik ..... ○
Wie lange lag es dort? ..... ☐☐☐ Nächte

Krankheiten

19 Hatte Ihr verstorbenes Kind jemals folgende Krankheit?

Angeborene Fehlbildungen

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

.....

.....

Andere angeborene Erkrankungen

z. B. Stoffwechsel-Störungen, hormonelle Störungen wie z. B. Schilddrüsenunterfunktion, Blutkrankheiten

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

.....

.....

Körperliche oder geistige Entwicklungsstörungen

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

.....

.....

Herzerkrankungen

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

.....

.....

Fortsetzung von Frage 19

Atemwegserkrankungen

z. B. Asthma, obstruktive Bronchitis

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

.....

.....

Erkrankungen des Nervensystems

z. B. Bewegungsstörungen, Lähmungen

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

.....

.....

Anfallsleiden (Fallsucht, Epilepsie)

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

.....

.....

Bösartige Tumorerkrankung

z. B. Hirntumor, Leukämie, Knochenkrebs, Neuroblastom

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

.....

.....

20 **War Ihr Kind ein so genanntes „Schreibaby“, das vermehrt** (d. h. über mehrere Wochen täglich oder fast täglich mehrere Stunden ohne erkenntlichen Grund) **geschrien hat und nicht oder kaum zu trösten war?**

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

21 **Haben Sie Ihr Kind vor seinem Tod schon einmal scheinbar leblos aufgefunden** (mit Atemstillstand, schlaffer Muskulatur, blasser oder bläulicher Hautfarbe und stark verlangsamtem Herzschlag „ALTE“, von dem es sich erst nach heftigem Schütteln (Stimulation) oder Wiederbelebung erholte)**?**

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, wann?

		.			.				
T	T		M	M		J	J	J	J

(Datum) ..... (z. B.: 2 8 . 0 3 . 2 0 0 5)

Wenn ja, ist Ihr Kind damals in einem Krankenhaus nachuntersucht worden?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, in welchem Krankenhaus?

.....

.....

.....

.....

.....

Wenn Sie uns Namen und Adressen der behandelnden Krankenhäuser mitteilen, senden wir diesen ebenfalls einen Fragebogen zu und erfragen deren medizinische Befunde zu Ihrem verstorbenen Kind.

Medizinische Behandlungen und Impfungen

22 **Wurde Ihr Kind vor seinem Tod jemals wegen einer Verletzung in der Notaufnahme eines Krankenhauses behandelt?**

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, in welchem Krankenhaus?

.....

.....

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.....

Wenn Sie uns Namen und Adressen der behandelnden Krankenhäuser mitteilen, senden wir diesen ebenfalls einen Fragebogen zu und erfragen deren medizinische Befunde zu Ihrem verstorbenen Kind.

23 **Wurde Ihr Kind in den letzten vier Wochen vor seinem Tod regelmäßig mit Medikamenten behandelt?**

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, mit welchen? (Bitte geben Sie möglichst auch die Dosierung an.)

.....

.....

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.....

24 Wurde Ihr Kind in den letzten zwei Tagen vor seinem Tod mit Medikamenten behandelt?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, mit welchen? (Bitte geben Sie möglichst auch die Dosierung an.)

.....

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Bitte beantworten Sie die folgenden Fragen unbedingt so gut es geht.
Bitte fügen Sie **zusätzlich** entweder eine **Kopie des Impfausweises** bei **oder** senden uns den **Impfausweis zur Ansicht**. Sie erhalten den Impfausweis schnellstmöglich zurück.

25 Wurde Ihr Kind jemals geimpft?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

26 Hatten Sie Gründe, Ihrem Kind Impfungen nicht oder noch nicht geben zu lassen?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche Gründe hatten Sie?

Mein Kind war noch zu jung ..... ○

Mein Kind hatte Erkrankungen, wegen derer die Impfung aufgeschoben/verhindert wurde ..... ○

Angst vor Nebenwirkungen ..... ○

Ich hielt für mein Kind das Durchmachen der Krankheiten für besser als die entsprechende Impfung ..... ○

Ich war über die Notwendigkeit der Impfung nicht informiert ..... ○

Der Arzt hat von der Impfung abgeraten ..... ○

Die Impfung wurde vergessen ..... ○

Fortsetzung von Frage 26

Sonstiges:

.....

.....

.....

.....

.....

Wenn Ihr Kind **nie** geimpft wurde, **weiter mit Frage 32!**

Bitte nehmen Sie jetzt den **Impfausweis** Ihres verstorbenen Kindes zur Hand und übertragen Sie die Angaben zu den **letzten beiden Impfungen** vor seinem Tod aus dem Impfausweis in die Tabelle.

27 Wenn Ihr Kind je geimpft wurde, welches waren die letzte und vorletzte Impfung vor seinem Tod?

Bitte übertragen Sie Handelsnamen und Chargennummern möglichst genau!

Datum	Handelsname und Chargennummer (Ch.-B.:) des Impfstoffes	Tetanus	Diphtherie	Pertussis	Haemophilus influenzae b (Hib)	Hepatitis B	Poliomyelitis		Masern	Mumps	Röteln

28 **Bitte geben Sie möglichst genau das Datum und die Uhrzeit der letzten Impfung des Kindes an:**

Die **letzte** Impfung des Kindes fand statt am

☐☐ . ☐☐ . ☐☐☐☐ (Datum) (z. B.: 28 . 03 . 2005)
T T M M J J J J

um ☐☐ . ☐☐ Uhr (z. B.: 09 . 15 Uhr)

Weiß nicht ..... ○

29 **Wie lange lag diese letzte Impfung vor dem Tode des Kindes zurück?**

Weniger als 24 Stunden ..... ○
24 bis unter 48 Stunden ..... ○
48 bis unter 72 Stunden (3 Tage) ..... ○
72 Stunden bis unter 7 Tage ..... ○
7 bis unter 14 Tage ..... ○
14 Tage bis unter vier Wochen ..... ○
Mehr als vier Wochen ..... ○
Weiß nicht ..... ○

30 **Hat Ihr Kind diese letzte Impfung gut vertragen?**

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn nein, welche Schwierigkeiten gab es?

.....

.....

Wurde im Zusammenhang mit der letzten Impfung ein Medikament verabreicht (z. B. ein fiebersenkendes Arzneimittel), wenn ja, welches?

.....

.....

Angaben zu Ärzten und Kliniken

Patientencode: | | | | | | |

31 Wer hat die letzte Impfung bei dem Kind durchgeführt?

Bitte geben Sie Name und Adresse des **impfenden Arztes** an.

.....

.....

.....

32 Wenn Ihr Kind nie geimpft wurde, geben Sie bitte Name und Adresse des behandelnden Arztes an:

.....

.....

.....

33 War das Kind seit seiner Geburt in einer Klinik?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, in welcher Klinik war es zuletzt?

Bitte geben Sie Name und Adresse der Klinik an:

.....

.....

.....

Zu Fragen 21, 22 und 31 bis 33 sowie 35:

Wenn Sie uns Namen und Adressen der behandelnden Ärzte oder Krankenhäuser mitteilen, senden wir diesen ebenfalls einen Fragebogen zu und erfragen deren medizinische Befunde zu Ihrem verstorbenen Kind. **Bitte erteilen Sie hierzu auf der Rückseite Ihr Einverständnis.**

Entbindung von der ärztlichen Schweigepflicht

zu den Fragen 21, 22 und 31 bis 33 sowie 35

Mit meiner Unterschrift entbinde ich als Sorgeberechtigter von

.....
Vor- und Familienname des Kindes

.....
Geburtsdatum des Kindes

die von mir in den Fragen 21, 22 und 31 bis 33 sowie 35 genannten Ärzte, Krankenhäuser und Institute von ihrer ärztlichen Schweigepflicht und gestatte die Anforderung von Unterlagen zur medizinischen Vorgeschichte meines Kindes.

....
Ort Datum

.....
Unterschrift/en Sorgeberechtigte/r

Todesumstände

34 Ist Ihr Kind in einem Krankenhaus verstorben?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

35 Ist Ihr Kind obduziert worden?

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welches Krankenhaus oder Institut hat die Obduktion durchgeführt?

.....

.....

.....

.....

36 Bitte teilen Sie uns Datum und Uhrzeit vom Tod Ihres Kindes mit:

Das Kind ist am

□□ . □□ . □□□□ (Datum) (z. B.: 28 . 03 . 2005)

T T M M J J J J

verstorben.

○ Die Uhrzeit des Todes ist bekannt: □□ . □□ Uhr → **weiter mit Frage 38!**

(z. B.: 09 . 15 Uhr)

○ Die Uhrzeit des Todes ist **nicht** bekannt.

37 **Wenn die genaue Uhrzeit des Todes nicht bekannt ist, wann wurde das Kind zuletzt lebend gesehen und wann wurde es tot aufgefunden?**

Das Kind wurde **zuletzt lebend gesehen** am:

☐☐ . ☐☐ . ☐☐☐☐ (Datum) (z. B.: 28 . 03 . 2005)

T T M M J J J J

um ☐☐ . ☐☐ Uhr (z. B.: 20 . 15 Uhr)

Das Kind wurde **tot aufgefunden** am:

☐☐ . ☐☐ . ☐☐☐☐ (Datum) (z. B.: 29 . 03 . 2005)

T T M M J J J J

um ☐☐ . ☐☐ Uhr (z. B.: 07 . 15 Uhr)

38 **Zeigte Ihr Kind in den letzten 2 Tagen vor seinem Tod neu aufgetretene Krankheitszeichen oder andere Auffälligkeiten?**

Ja ..... ○ Nein ..... ○ Weiß nicht ..... ○

Wenn ja, welche?

Fieber ..... ○

Erbrechen ..... ○

Schrilles Schreien ..... ○

Atemnot ..... ○

Schmerzen ..... ○

Andere Symptome ..... ○

Wenn ja, welche?

.....

.....

.....

.....

39 **Ist Ihr Kind während des Schlafens verstorben?**

Ja ○ Nein ○ Weiß nicht ○

Wenn nein, **weiter mit Frage 47!**

40 **Wenn Ihr Kind während des Schlafens verstorben ist, in welche Liegeposition wurde es vor seinem Tod zum Schlafen hingelegt?**

Auf den Rücken ○
Auf den Bauch, Gesicht nach unten ○
Auf den Bauch, Gesicht zur Seite ○
Auf die Seite ○
Weiß nicht ○

41 **Wenn Ihr Kind während des Schlafens verstorben ist, in welcher Liegeposition wurde es nach seinem Tod aufgefunden?**

Auf dem Rücken ○
Auf dem Bauch, Gesicht nach unten ○
Auf dem Bauch, Gesicht zur Seite ○
Auf der Seite ○
In einer anderen Position ○
Weiß nicht ○

42 **In welche Liegeposition wurde Ihr Kind in den letzten 4 Wochen vor seinem Tod überwiegend zum Schlafen hingelegt?**

Rücken ○ Seite ○ Bauch ○
Weiß nicht ○

43 **Veränderte Ihr Kind in den letzten 4 Wochen selbstständig seine Schlafposition?**

Ja ○ Nein ○ Weiß nicht ○

44 **Welche Schlafposition nahm es dann überwiegend selbstständig ein?**

Rückenlage ○
Bauchlage, Gesicht nach unten ○
Bauchlage, Gesicht zur Seite ○
Seitenlage ○
Wechselnd ○
Weiß nicht ○

45 **Wenn Ihr Kind während des Schlafens verstorben ist, wurde es zur Zeit des Todes von außen gewärmt?** (z. B. Heizdecke, Wärmestrahler, Wärmflasche)

Ja ○ Nein ○ Weiß nicht ○

Wenn ja, wodurch wurde Ihr Kind gewärmt?

Wärmflasche ○
Elektrisches Heizkissen ○
Das Bett befand sich in unmittelbarer Nähe einer eingeschalteten Heizung ○
Wärmestrahler ○
Andere Formen direkter Wärme ○

Wenn ja, welche?

.....

.....

46 **Wenn Ihr Kind während des Schlafens verstorben ist, wie weit war es da mit dem Bettzeug zugedeckt, als Sie es tot auffanden?**

Der Kopf war total überdeckt ○
Der Körper war bedeckt, der Kopf aber frei ○
Es war gar nicht bedeckt ○
Weiß nicht ○

Angaben zu den Eltern

Die folgenden Fragen betreffen die Beschreibung der Lebenssituation des Kindes.

Mit der Rubrik „Mutter“ und „Vater“ sind jetzt auch diejenigen Personen gemeint, die möglicherweise für das Kind diese Funktion übernommen haben, wie z. B. der Lebenspartner der Mutter (für „Vater“) oder die Lebenspartnerin des Vaters (für „Mutter“) oder sonstige Personen, falls das Kind nicht bei den leiblichen Eltern gelebt hat.

47 **Rauchen Sie zurzeit?** Bitte für beide Elternteile angeben!

	Mutter	Vater
Ja, täglich über 20 Zigaretten	○	○
Ja, täglich bis zu 20 Zigaretten	○	○
Ja, aber nicht täglich	○	○
Nein	○	○
Weiß nicht	○	○

48 **Welchen Schulabschluss haben Sie?** Nennen Sie bitte nur den höchsten Abschluss. Bitte für beide Elternteile angeben!

	Mutter	Vater
Hauptschulabschluss/Volksschulabschluss	○	○
Realschulabschluss (Mittlere Reife)	○	○
Abschluss Polytechnische Oberschule (POS, 10. Klasse)	○	○
Fachhochschulreife (Abschluss einer Fachoberschule)	○	○
Abitur (Gymnasium bzw. EOS)	○	○
Anderer Schulabschluss	○	○
Schule beendet ohne Schulabschluss	○	○
(Noch) keinen Schulabschluss	○	○
Weiß nicht	○	○

49 **Haben Sie eine abgeschlossene Berufsausbildung? Wenn ja, welche?**
Nennen Sie bitte nur den höchsten Abschluss. Bitte für beide Elternteile angeben!

	Mutter	Vater
Lehre (beruflich-betriebliche Ausbildung)	○	○
Berufsschule, Handelsschule (beruflich-schulische Ausbildung)	○	○
Fachschule (z. B. Meister-Technikerschule, Berufs- oder Fachakademie)	○	○
Fachhochschule, Ingenieurschule	○	○
Universität, Hochschule	○	○
Anderer Ausbildungsabschluss	○	○
Kein beruflicher Abschluss (und auch nicht in der Ausbildung)	○	○
In beruflicher Ausbildung (Auszubildender, Student)	○	○
Weiß nicht	○	○

50 **Welche der folgenden Angaben trifft auf Sie zu?**

	Mutter	Vater
Zurzeit ...		
... nicht berufstätig (Rentner, Student usw.)	○	○
... arbeitslos	○	○
... vorübergehende Freistellung (z. B. Erziehungsurlaub)	○	○
... Teilzeit oder stundenweise berufstätig	○	○
... voll berufstätig	○	○
... Auszubildender (z. B. Lehrling)	○	○
Weiß nicht	○	○

51 **Wie hoch ist Ihr durchschnittliches monatliches Haushaltseinkommen, d. h. das Nettoeinkommen, das alle Haushaltsmitglieder zusammen nach Abzug von Steuern und Sozialabgaben haben?** (Einschließlich Erziehungs- und Kindergeld)

- Unter 500 € ○
- 500 bis unter 1.000 € ○
- 1.000 bis unter 2.000 € ○
- 2.000 bis unter 4.000 € ○
- 4.000 € und mehr ○
- Weiß nicht ○

Vielen Dank, Sie haben unsere Fragen jetzt beantwortet.

Gibt es vielleicht noch etwas, das Sie uns gerne mitteilen möchten?

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Vielen Dank für die Beantwortung der Fragen!

Bitte prüfen Sie Ihre Angaben noch einmal auf Vollständigkeit.

Bitte senden Sie dann den Fragebogen zusammen mit dem

- Impfbuch (oder einer Kopie davon) und dem
- Kinderuntersuchungsheft/Vorsorgeheft (oder einer Kopie davon)

im beiliegenden Freiumschlag portofrei an:
Klinik für Allgemeine Pädiatrie und Neonatologie
PD Dr. Klaus Mohnike
Emanuel-Larisch-Weg 17–19
39112 Magdeburg

Wir übersenden Ihnen Ihre Originale umgehend zurück!

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Physicians’ questionnaire

Patientencode: |___|___| - |___|___|___|___|
Ländercode Patientennummer

Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat

Arztfragebogen

Bitte dieses Deckblatt vor Rücksendung abtrennen und zu Ihren Akten nehmen!

Geplant ist jeweils ein individueller Ausdruck des Fragebogens mit der Angabe von

Fallnummer |__|__|__|__|__|__|

Name, _____ _____-
Vorname **Nachname**

Geburtsdatum, |__|__|.|__|__|.|__|__|__|__|
T T M M J J J J

Geschlecht |__|

Todesdatum |__|__|.|__|__|.|__|__|__|__|
T T M M J J J J

Zusätzlich wird das Todesdatum an den erforderlichen Stellen im Text eingefügt.

Sehr geehrte Frau Kollegin,
sehr geehrter Herr Kollege,

wir bitten Sie, an einer Studie zur Klärung medizinischer Hintergründe von plötzlichen Todesfällen bei Säuglingen und Kleinkindern im Alter bis zu 2 Jahren teilzunehmen.

Diese Studie ist dringend notwendig um zu untersuchen, ob ein Zusammenhang zwischen bestimmten Impfungen und plötzlichen Todesfällen besteht.
Der Wert und die Aussagekraft dieser Studie hängen wesentlich von der vollständigen Erfassung der Fälle und der zugehörigen Informationen ab. Die Angaben werden den datenschutzrechtlichen Bestimmungen entsprechend pseudonymisiert ausgewertet.
Wir danken Ihnen sehr für Ihre Bereitschaft, mit Ihrer Zeit und Arbeitskraft zur Klärung der Fragen beizutragen! Als Aufwandsentschädigung können wir Ihnen einen Betrag von 30 Euro anbieten. Bitte geben Sie dafür auf der letzten Seite des Fragebogens Ihre Kontoverbindung an.

Bei Rückfragen können Sie sich an die folgende Kontaktadresse wenden:

Klinik für Allgemeine Pädiatrie und
Neonatologie
PD Dr. Klaus Mohnike
Emanuel-Larisch-Weg 17 - 19
39112 Magdeburg

Tel.: 03 91/67-1 71 01
Fax: 03 91/67-1 71 05

1. Wie oft war das Kind in Ihrer Sprechstunde? (von Geburt bis zum Zeitpunkt des Todes, am |__|__|.|__|__|.|__|__|.)

Anzahl |___|___|___| davon Vorsorgeuntersuchungen |___|___|

2. Hatte das Kind jemals folgende Krankheit?

	Ja	**Nein**	**unbekannt**
Störungen in der Neugeborenenperiode?			
Früh- oder Mangelgeburt	☐	☐	☐
Asphyxie	☐	☐	☐
Behandlungspflichtige Hyperbilirubinämie	☐	☐	☐
Andere schwerwiegende Störungen (z.B. Krämpfe, Sepsis, intrauterin/perinatal erworbene Infektionen...)	☐	☐	☐
Sonstige wenn ja, welche?	☐	☐	☐
	.....		
	.....		
Angeborenen Stoffwechsel-Störungen? wenn ja, welche?	☐	☐	☐
	.....		
	.....		
Endokrine Störungen, Vitaminosen? wenn ja, welche?	☐	☐	☐
	.....		
	.....		

Fortsetzung Frage 2: Hatte das Kind jemals folgende Krankheit?

	Ja	**Nein**	**unbekannt**
Blutkrankheiten?	☐	☐	☐
wenn ja, welche?	.....		
	.....		
Entwicklungs- und Verhaltensstörungen?			
Somatische Entwicklungsstörungen	☐	☐	☐
Kognitiver Entwicklungsrückstand	☐	☐	☐
Störungen der motorischen Entwicklung	☐	☐	☐
Sonstige	☐	☐	☐
wenn ja, welche?	.....		
	.....		
Erkrankungen oder Fehlbildungen des Nervensystems?			
cerebrale Bewegungsstörungen	☐	☐	☐
Fehlbildungen des ZNS (z.B. Spina bifida)	☐	☐	☐
Anfallsleiden	☐	☐	☐
Sonstige	☐	☐	☐
wenn ja, welche?	.....		
	.....		

Fortsetzung Frage 2: Hatte das Kind jemals folgende Krankheit?

	Ja	**Nein**	**unbekannt**
Erkrankungen oder Fehlbildungen der Sinnesorgane?	☐	☐	☐
wenn ja, welche?	.....		
	.....		
Erkrankungen oder Fehlbildungen von Kiefer und Mundhöhle?	☐	☐	☐
wenn ja, welche?	.....		
	.....		
Erkrankungen oder Fehlbildungen des Herzens oder der herznahen Gefäße?	☐	☐	☐
wenn ja, welche?	.....		
	.....		
Erkrankungen oder Fehlbildungen der Atmungsorgane?	☐	☐	☐
wenn ja, welche?	.....		
	.....		
Erkrankungen oder Fehlbildungen der Verdauungsorgane?	☐	☐	☐
wenn ja, welche?	.....		
	.....		
Erkrankungen oder Fehlbildungen der Nieren und Harnwege?	☐	☐	☐
wenn ja, welche?	.....		
	.....		

Fortsetzung Frage 2: Hatte das Kind jemals folgende Krankheit?

	Ja	**Nein**	**unbekannt**
Erkrankungen oder Fehlbildungen von Skelett oder Muskulatur?	☐	☐	☐
wenn ja, welche?			
.....			
.....			
Erkrankungen oder Fehlbildungen der Haut?	☐	☐	☐
wenn ja, welche?			
.....			
.....			
Multiple Fehlbildungen, einschließlich **chromosomaler Aberrationen (z.B. Trisomie 21)?**	☐	☐	☐
wenn ja, welche?			
.....			
.....			
Malignom?	☐	☐	☐
wenn ja, welches?			
.....			
.....			
Sonstige schwere Erkrankungen?	☐	☐	☐
wenn ja, welche?			
.....			
.....			

3. Erhielt das Kind wegen dieser oder anderer schweren Erkrankungen Arzneimittel?

	Ja	**Nein**	**unbekannt**
	☐	☐	☐

Wenn ja, welche?

Chemotherapeutika	☐	☐	☐
Kortisonhaltige Arzneimittel	☐	☐	☐
Blut- oder Blutbestandteile	☐	☐	☐
Sonstige	☐	☐	☐

Wenn ja, welche? (Bitte geben Sie auch die Dosierung an)

.....

.....

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4. Hatte das Kind Ihrer Kenntnis nach vor seinem Tod jemals ein ‚ALTE' (Apparent Life-Threatening Event), ‚ALE' (Anscheinend Lebensbedrohliches Ereignis) oder auch ‚Near SIDS'?

Ja ☐ **Nein** ☐ **unbekannt** ☐

Wenn ja, wann?

|__|__|.|__|__|.|__|__|
T T M M J J

|__|__|.|__|__|.|__|__|
T T M M J J

5. A) Bitte geben Sie alle Konsultationen an, die Sie bei dem Kind in den <u>dem Todeszeitpunkt vorangehenden vier Wochen</u> (in der Zeit vom |__|__|.|__|__|.|__|__| bis zum |__|__|.|__|__|.|__|__|) durchgeführt haben. Berücksichtigen Sie hierbei bitte auch Hausbesuche oder Telefonkontakte mit den Eltern.

Welche Diagnose oder Verdachtsdiagnose wurde gestellt? (Bitte geben Sie Ihre – auch vorläufige – Diagnose in Blockschrift an.)

Datum **T T M M J J**	(Verdachts-)Diagnose	Kind untersucht	Telefon. Beratung	Impfung	Vorsorge
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐
|__|__|.|__|__|.|__|__|	____________	☐	☐	☐	☐

B) Welche Diagnostik wurde in diesen letzten vier Wochen durchgeführt?

☐ **laborchemisch** ☐ **apparativ** ☐ **keine**

Wenn apparative Diagnostik durchgeführt wurde, welche?

☐ **Ultraschall:** ☐ Kopf ☐ Hüfte ☐ Herz ☐ Niere ☐ Oberbauch
☐ **Röntgen:** ☐ Kopf ☐ Hüfte ☐ Skelett ☐ Lunge ☐ Oberbauch
☐ **MRT:** ☐ Kopf ☐ Hüfte ☐ Skelett ☐ Niere ☐ Oberbauch
☐ **CT:** ☐ Kopf ☐ Hüfte ☐ Skelett ☐ Lunge ☐ Oberbauch
☐ **EKG**
☐ **EEG**
☐ **Sonstige, bitte spezifizieren**

Bitte fügen Sie Kopien der Befunde bei.
Falls keine Kopien verfügbar sind, geben Sie bitte wichtige Befunde mit Datum der Erhebung und Ergebnis an. Sollte der Platz nicht ausreichend sein, führen Sie bitte die Erläuterungen auf einem separaten Blatt fort.

.....

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C) Welche Therapien wurden in diesen letzten vier Wochen durchgeführt?

☐ **Medikamente** (Bitte füllen Sie das Formular „Medikation des Kindes S.18“ aus!)

☐ **Ernährungsumstellung**

☐ **Physiotherapie**

☐ **Keine**

☐ **Sonstige, bitte spezifizieren**

.....

.....

.....

.....

6. Wurde das Kind jemals von Ihnen geimpft? **Ja** ☐ **Nein** ☐

↓

weiter mit Frage 13

7. Wann haben Sie die letzte Impfung bei dem Kind durchgeführt?

Datum |__|__|.|__|__|.|__|__|

8. Wurde das Kind vor dieser letzten Impfung körperlich untersucht?

Ja ☐ **Nein** ☐

9. War das Kind zu diesem Zeitpunkt der letzten Impfung völlig frei von Zeichen einer Infektion oder Erkrankung?

Ja ☐ **Nein** ☐ **Unsicher** ☐

Wenn nein, welche Symptome haben Sie festgestellt?

.....

.....

10. Wurde im Zusammenhang mit dieser letzten Impfung ein Arzneimittel (z.B. Paracetamol) verordnet? (Wenn ja, bitte füllen Sie das Formular „Medikation des Kindes im Zusammenhang mit der letzten Impfung S.19“ aus

Ja ☐ **Nein** ☐ **Unbekannt** ☐

Patientencode: |___|___| - |___|___|___|___| **Patienteninitialen:** |___|___|
Ländercode Patientennummer V N

11. Bitte dokumentieren Sie jetzt (so genau und vollständig wie möglich) die bei dem Kind jemals durchgeführten Impfungen!

	T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
1.	__.__.__			☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

	T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
2.	__.__.__			☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

	T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
3.	__.__.__			☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

***** Wenn nein, bitte spezifizieren Sie die Nebenwirkungen unter Nr.12.

Patientencode: |___|___| - |___|___|___|___| **Patienteninitialen:** |___|___|
Ländercode Patientennummer V N

Fortsetzung Frage 11: Bitte dokumentieren Sie jetzt (so genau und vollständig wie möglich) die bei dem Kind jemals durchgeführten Impfungen!

	Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
4.	__|__|.|__|__|.|__|__|	_____	_____	☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

	Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
5.	__|__|.|__|__|.|__|__|	_____	_____	☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

	Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
6.	__|__|.|__|__|.|__|__|	_____	_____	☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

***** Wenn nein, bitte spezifizieren Sie die Nebenwirkungen unter Nr.12.

Patientencode: |___|___| - |___|___|___|___| **Patienteninitialen:** |___|___|
Ländercode Patientennummer V N

Fortsetzung Frage 11: Bitte dokumentieren Sie jetzt (so genau und vollständig wie möglich) die bei dem Kind jemals durchgeführten Impfungen!

7. Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
7. |__|__|.|__|__|.|__|__|	_____	_____	☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

8. Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
8. |__|__|.|__|__|.|__|__|	_____	_____	☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

9. Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1.	2.	3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
9. |__|__|.|__|__|.|__|__|	_____	_____	☐	☐	☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

***** Wenn nein, bitte spezifizieren Sie die Nebenwirkungen unter Nr.12.

Patientencode: |___|___| - |___|___|___|___| **Patienteninitialen:** |___|___|
Ländercode Patientennummer V N

Fortsetzung Frage 11: Bitte dokumentieren Sie jetzt (so genau und vollständig wie möglich) die bei dem Kind jemals durchgeführten Impfungen!

	Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1. 2. 3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
10.	__.__.__			☐ ☐ ☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

	Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1. 2. 3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
11.	__.__.__			☐ ☐ ☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

	Impfdatum: T T M M J J	Impfpräparat (Handelsname)	Chargennummer	Grundimmunisierung 1. 2. 3.	Wiederholungsimpfung	Impfung gut vertragen? Ja	Nein*
12.	__.__.__			☐ ☐ ☐	☐	☐	☐

Applikationsart: intramuskulär ☐ subkutan ☐ **Applikationsort**: Oberschenkel ☐ Oberarm ☐ glutäal ☐

***** Wenn nein, bitte spezifizieren Sie die Nebenwirkungen unter Nr.12.

12. Bitte beschreiben Sie hier Nebenwirkungen, die nach den unter 10. dokumentierten Impfungen aufgetreten sind:

Bei Impfung Nr. |__|__| **sind aufgetreten**:..

Beginn der Symptome |__|__|.|__|__|.|__|__|

War die Impfreaktion lebensbedrohlich? Ja ☐ Nein ☐

War eine ambulante Behandlung notwendig? Ja *☐ Nein ☐

War eine stationäre Behandlung notwendig? Ja* ☐ Nein ☐

Bei Impfung Nr. |__|__| **sind aufgetreten**:..

Beginn der Symptome |__|__|.|__|__|.|__|__|

War die Impfreaktion lebensbedrohlich? Ja ☐ Nein ☐

War eine ambulante Behandlung notwendig? Ja *☐ Nein ☐

War eine stationäre Behandlung notwendig? Ja* ☐ Nein ☐

Bei Impfung Nr. |__|__| **sind aufgetreten**:..

Beginn der Symptome |__|__|.|__|__|.|__|__|

War die Impfreaktion lebensbedrohlich? Ja ☐ Nein ☐

War eine ambulante Behandlung notwendig? Ja *☐ Nein ☐

War eine stationäre Behandlung notwendig? Ja* ☐ Nein ☐

* Wenn ja, fügen Sie bitte ggf. Kopien der Befunde von abklärenden Untersuchungen bei.

Fortsetzung Frage 12: Beschreibung von Nebenwirkungen, die nach den unter 10. dokumentierten Impfungen aufgetreten sind:

Bei Impfung Nr. |__|__| **sind aufgetreten**:..

Beginn der Symptome |__|__|.|__|__|.|__|__| **War die Impfreaktion lebensbedrohlich?** Ja ☐ Nein ☐

War eine ambulante Behandlung notwendig? Ja *☐ Nein ☐

War eine stationäre Behandlung notwendig? Ja* ☐ Nein ☐

Bei Impfung Nr. |__|__| **sind aufgetreten**:..

Beginn der Symptome |__|__|.|__|__|.|__|__| **War die Impfreaktion lebensbedrohlich?** Ja ☐ Nein ☐

War eine ambulante Behandlung notwendig? Ja *☐ Nein ☐

War eine stationäre Behandlung notwendig? Ja* ☐ Nein ☐

Bei Impfung Nr. |__|__| **sind aufgetreten**:..

Beginn der Symptome |__|__|.|__|__|.|__|__| **War die Impfreaktion lebensbedrohlich?** Ja ☐ Nein ☐

War eine ambulante Behandlung notwendig? Ja *☐ Nein ☐

War eine stationäre Behandlung notwendig? Ja* ☐ Nein ☐

* Wenn ja, fügen Sie bitte ggf. Kopien der Befunde von abklärenden Untersuchungen bei.
Sollten bei mehr als sechs Impfungen Nebenwirkungen aufgetreten sein, vermerken Sie diese bitte auf einem zusätzlichen Blatt

Zusatzfragebogen zu Frage 5 c)

„Medikation des Kindes in den letzten vier Wochen vor seinem Tod“

Handelsname/Name der Generika	**Dosierung**	**Start** Tag/Monat/Jahr	**Ende** Tag/Monat/Jahr
Beispiel AMOXICILLIN	4 x 100 mg/Tag p.o	30.03.04	10.04.04
1.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
2.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
3.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
4.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
5.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
6.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
7.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
8.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
9.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
10.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
11.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
12.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
13.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
14.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
15.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
16.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
17.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
18.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
19.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|

Zusatzfragebogen zu Frage 10)

„Medikation des Kindes im Zusammenhang mit der letzten Impfung“

Handelsname/Name der Generika	**Dosierung**	**Start** Tag/Monat/Jahr	**Ende** Tag/Monat/Jahr
Beispiel Paracetamol	250 mg Supp.am Abend des Impftages	30.03.04	30.03.04
1.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
2.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
3.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
4.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|
5.		|__|__|.|__|__|.|__|__|	|__|__|.|__|__|.|__|__|

Patientencode: |___|___| - |___|___|___|___| **Patienteninitialen:** |___|___|
Ländercode Patientennummer V N

Vielen Dank für Ihre Mitarbeit, Sie haben unsere Fragen jetzt beantwortet. Gibt es vielleicht noch etwas, das Sie uns gerne mitteilen möchten?

.....

.....

.....

.....

Bitte überprüfen Sie den Fragebogen nochmals auf Vollständigkeit und senden ihn dann im beiliegenden Freiumschlag an:

Klinik für Allgemeine Pädiatrie und Neonatologie
PD Dr. Klaus Mohnike
Emanuel-Larisch-Weg 17 - 19
39112 Magdeburg

Für die Überweisung der Aufwandsentschädigung bitten wir um die Angabe Ihrer Bankverbindung. Dieser Abschnitt wird von uns vom Fragebogen abgetrennt und vom Robert Koch-Institut nach der Überweisung vernichtet:

∀ ∀ ∀ ∀ ∀ ∀ ∀ ∀

Name Kontoinhaber/in:

Geldinstitut:

Bankleitzahl:

|__|__|__|__|__|__|__|__|

Kontonummer:

|__|__|__|__|__|__|__|__|__|__|

Non-responder questionnaire
- cases -

ROBERT KOCH INSTITUT

Robert Koch-Institut | Seestraße 10 | 13353 Berlin

Kurzfragebogen-Studie über Todesfälle bei Kindern im 2. – 24. Lebensmonat

Laufende Nummer des Falls im Gesundheitsamt ☐☐☐☐

Gesundheitsamt (Stempel):

1. **Aus welchen Gründen möchten bzw. können Sie an der Studie nicht teilnehmen?** (Mehrfachantworten möglich)

   Nehme grundsätzlich nicht an Studien teil ..... ☐
   Sehe für mich keinen Nutzen ..... ☐
   Thema belastet mich seelisch zu sehr..... ☐
   Aus zeitlichen Gründen ..... ☐

   Sonstige Gründe, ... ☐

   und zwar (*bitte eintragen!*): _____

2. **Welches Geschlecht hatte Ihr verstorbenes Kind?** Junge ... ☐ Mädchen ... ☐

3. **Bei wem lebte Ihr verstorbenes Kind hauptsächlich?** (Hier bitte nur ein Kreuz machen!)

   Leibliche Eltern ..... ☐
   Mutter und ihrem Partner ..... ☐
   Vater und seiner Partnerin ..... ☐
   Mutter ..... ☐
   Vater ..... ☐
   Großeltern oder anderen Verwandten . ☐
   Pflegeeltern/Adoptiveltern ..... ☐
   In einem Heim ..... ☐

4. **Wer beantwortet diesen Kurzfragebogen?**

   Mutter ..... ☐
   Vater ..... ☐
   Sonstige Person ... ☐
   Lebenspartner der Mutter .... ☐
   Lebenspartnerin des Vaters . ☐

5. **Wie alt sind Sie?** (Bitte für beide angeben)

   Mutter... ☐☐ (Jahre) **Vater**... ☐☐ (Jahre)

6. **Rauchen Sie zurzeit?** (Bitte für beide angeben)

   Mutter: Ja ... ☐ Nein ... ☐ **Vater:** Ja ... ☐ Nein ... ☐

7. **Wieviel Stunden (oder Tage) vor seinem Tod wurde Ihr Kind das letzte Mal geimpft?**

☐☐ Stunden wenn nicht bekannt oder länger her als 3 Tage: ☐☐ Tage

8. Wogegen wurde Ihr Kind vor seinem Tod das letzte Mal geimpft?

Mein Kind war noch nie geimpft worden	☐	
5-fach Impfung	☐	welches Impfpräparat?_____
6-fach Impfung	☐	welches Impfpräparat?_____
Masern, Mumps, Röteln	☐	welches Impfpräparat?_____
Windpocken	☐	welches Impfpräparat?_____
Sonstige Impfung	☐	

und zwar (*bitte eintragen!*):

_____

9. **Welche Staatsangehörigkeit haben Sie?**

Mutter: deutsch .... ☐ andere ... ☐ welche? _____

Vater: deutsch .... ☐ andere ... ☐ welche? _____

10. **Welchen Schulabschluss haben Sie?**
(Wenn Sie mehrere Abschlüsse haben, nennen Sie bitte nur den höchsten!)

	Mutter	**Vater**
Hauptschulabschluss / Volksschulabschluss	☐	☐
Realschulabschluss (Mittlere Reife)	☐	☐
Abschluss Polytechnische Oberschule (POS) 10.Klasse	☐	☐
Fachhochschulreife (Abschluss Fachoberschule)	☐	☐
Abitur (Gymnasium bzw. EOS)	☐	☐
Anderer Schulabschluss	☐	☐
Schule beendet ohne Schulabschluss	☐	☐
(Noch) keinen Schulabschluss	☐	☐

11. Welche der folgenden Angaben zur Berufstätigkeit trifft auf Sie zu?

	Mutter	**Vater**
Zurzeit nicht berufstätig (Rentner, Student usw.)	☐	☐
Arbeitslos	☐	☐
Vorübergehende Freistellung (z.B. Erziehungsurlaub)	☐	☐
Teilzeit oder stundenweise berufstätig	☐	☐
Voll berufstätig	☐	☐
Auszubildender (z.B. Lehrling)	☐	☐

Vielen Dank für Ihre Mitarbeit!

Standardized autopsy protocol (SAP)

Anlage 3 –Standardautopsieprotokoll

I. Standardautopsieprotokoll

bitte diese Seite vor Obduktion als Fallmeldebogen per Fax oder e-mailan Studienzentrale versenden:

Fax-Nr.: e-mail:

Name des Säuglings:	Rechtsmedizinisches Institut Leichenöffnungsprotokoll-Nummer
Geburtsdatum:	Totenscheindiagnose
Geschlecht: Nationalität:	Name des Rechtsmediziners
Wohnort und Adresse Telefon-Nr. der Eltern	durch Staatsanwaltschaft angeordnet Ja / Nein hat der StA Bedenken gegen weitere Studienteilnahme? Ja / Nein
Sterbedatum und Uhrzeit Datum: __.__.__ Uhrzeit: __.__ Uhr	Einverständnis der Eltern zur Sektion Ja / Nein Einverständnis zur weiteren Studienteilnahme liegt bereits vor Ja / Nein
Autopsiedatum und Uhrzeit Datum: __.__.__ Uhrzeit: __.__ Uhr	**Fallnummer der Studie** (wird durch Studienzentrale vergeben!)

Mikrobiologie Ja / Nein Stoffwechselscreening Ja / Nein

Virologie Ja / Nein

Toxikologie Ja / Nein Neuropathologie Ja / Nein

Institut _____Sektionsnummer:_____

	JA	NEIN	Keine Unters.
Mikrobiologie	Datum/Uhrzeit		
Leptomeninx			
Mittelohr re./li.			
Pharynx			
Trachea			
Dünndarm			
Milz			
Pilze, wenn erforderlich			
Fotografien			
Röntgen			
gesamtes Skelett			
spezifische Veränderungen	Frakturen Pneumothorax Hämatome Hyperostosen Epiphysiolysen sonstiges		
äußere Besichtigung			
Geschlecht	männlich weiblich		
Totenstarre	fehlend beginnend komplett gelöst		
Totenflecke	fehlend beginnend konfluierend komplett wegdrückbar		
Rektaltemperatur	°C		
Maße und Gewichte			
Körpergewicht	g		
Körperlänge	cm		
Kopfumfang	cm		
Brustumfang (in Mamillenhöhe)	cm		
Ernährungszustand	reduziert normal adipös		

	JA	NEIN	Keine Unters
Reanimationszeichen	Injektionen HDM Intubation Elektrodenmarken		
Haut			
Ikterus			
Punktblutungen			
Effloreszenzen			
Muttermale			
Impfstelle erkennbar			
Falls Impfstelle erkennbar, wo und welcher Befund?			
Turgor: Verstreichen der angehobenen Hautfalte	sec.		
Augen			
Lidhämatome			
Irisfarbe	braun blau grün grau mehrfarbig		
Pupillendurchmesser	rechts mm links mm		
Katarakt			
Stellung der Bulbi abnorm			
Sklerenikterus			
Konjuktiven Punktblutugen Gefäßzeichnung Verletzungen			
sonstige Auffälligkeiten:			

		JA	NEIN	Keine Unters.
Ohren				
tiefer Ohransatz				
Fremdinhalt im Gehörgang				
sonstige Auffälligkleiten				
Nase				
Sekretspuren				
Septumdeviation				
Atresie der Choanen	rechts links			
sonstige Auffälligkeiten:				
Mund				
Sekretspuren				
Lippenbändchen abnorm				
Zahnstatus (vorhandene Zähne bitte markieren)	rechts / links Oberkiefer: 55□ 54□ 53□ 52□ 51□ / 61□ 62□ 63□ 64□ 65□ Unterkiefer: 85□ 84□ 83□ 82□ 81□ / 71□ 72□ 73□ 74□ 75□			
Zunge				
Position	zwischen Kiefern hinter Kiefern gegen Gaumen gedrückt			
Makroglossie				
Frenulum abnorm				
sonstige Auffälligkeiten				

	JA	NEIN	Keine Unters.
Gaumen			
hoher Bogen			
Gaumenspalte			
sonstige Auffälligkeiten			
Unterkiefer			
Mikrognathie			
sonstige Auffälligkeiten			
Hals			
Hämatome			
Hautabschürfungen			
sonstige Auffälligkeiten			
Brust			
Narben			
Hämatome			
Brustkorb symmetrisch			

	JA	NEIN	Keine Unters.
sonstige Auffälligkeiten			
Bauch			
gebläht			
Hämatome			
Narben			
Nabel abnorm			
Hernien			
sonstige Auffälligkeiten			
äußeres Genitale			
Knaben:			
Descensus abgeschlossen rechts links			
Zirkumzision			
Phimose			
Mädchen:			
Verletzungen der Labien			
Hymen intakt			
Ostium vaginae			
After			
Verletzungen			
Gesäßfaltenasymmetrie			

		JA	NEIN	Keine Unters.
Extremitäten				
Hämatome				
Hautabschürfungen				
Vierfingerfurche				
sonstige Auffälligkeiten				
innere Besichtigung				
Dicke der Subcutis 1 cm unterhalb des Nabels				cm
Hautemphysem				
Situs inversus				
Zwerchfellstand	rechts links			
Brusthöhlen				
Pneumothorax	rechts links			
Flüssigkeit	rechts			ml
	links			ml
Pleuraadhäsionen				
Herzbeutel				
Flüssigkeit				ml
sonstige Auffälligkeiten:				

	JA	NEIN	Keine Unters.
Bauchhöhle			
Flüssigkeit			ml
Dünndarminvagination			
Verwachsungen			
Peritonitis			
Retroperitonealraum			
Hämatome			
sonstige Auffälligkeiten			

Petechien	keine	wenige	mittel	massenhaft
parietale Pleura rechts				
links				
viscerale Pleura rechts				
links				
perikardial				
epikardial				
Thymus				
parietales Peritoneum				
viscerales Peritoneum				

Obstruktion der Luftwege	JA	NEIN	Keine Unters.
Fremdkörper			
Schleim			
anderes			
Pharynx			
Fremdkörper			
Entzündung			
Tonsillen			
Hyperplasie			
Entzündung			
Blutung in den Halsweichteilen			
Platysma			
Gefäß-Nervenstrang re./li.			
untere Zungenbeinmuskeln			
Skalenusgruppe			
Zungenbeinfrakturen			
Kehlkopf			
Frakturen			
Blutungen			
Lumeneinengung			
Fremdkörper			
Rinnenstellung der Epiglottis			
Glottisödem			
Epiglottitis			
Laryngitis			

	JA	NEIN	Keine Unters.
Thymus			
Gewicht			g
Atrophie			
sonstige Auffälligkeiten:			
Trachea			
Stenose			
Obstruktion durch Schleim			
Mageninhaltsaspiration			
Entzündung			
Hauptbronchien			
Ödem			
Schleim			
Mageninhalt			
Entzündung			
Lunge			
Gewicht rechts links			 g g
Lappung normal			
Blutstauung			
Blutungen			
Ödem	gering	mittel	stark
Lungenembolie			
Bronchitis			
Pneumonie			

	JA	NEIN	Keine Unters.
Pleura			
zart			
Adhäsionen			
sonstige Auffälligkeiten			
Rippen			
unterblutete Frakturen			
Kallus			
normale Konfiguration			
Diaphragma abnorm			
Herz-Kreislauf-System			
Herzmasse (mit großen Gefäßen)			g
Dicke des linken Ventrikels maximal			cm
Dicke des rechten Ventrikels maximal			cm
Dicke des Septums maximal			cm
Mitralklappenumfang			cm
Aortenklappenumfang			cm
Trikuspidalklappenumfang			cm
Pulmonalklappenumfang			cm
Endokardfibrose			
Endokardblutungen			

	JA	NEIN	Keine Unters.
Myokard			
Myokardblutungen			
Fibrosen			
sonstige Auffälligkeiten			
Einengung der Einfluß-/Ausflußbahn			
Klappenveränderungen			
Koronararterien			
regelrecht angelegt			
zart			
Auffälligkeiten			
Aortenbogen regelrecht			
Isthmusstenose			
Ductus arteriosus geschlossen			
Leichenblut	flüssig	geronnen	
Vitien			
VHSD			
VSD			
Gefäßanomalien			
andere			
normale Lage ZVK			
Gefäßthrombosen			
sonstige Auffälligkeiten			

	JA	NEIN	Keine Unters.
Ösophagus			
regelrecht			
Ösophagitis			
sonstige Auffälligkeiten			
Magen			
Schleinhaut regelrecht			
Mageninhalt Qualität Menge			ml
Pylorusstenose			
Dünndarm			
Duodenum			
Schleimhaut regelrecht			
Schleinhautblutungen			
sonstige Auffälligkeiten			
Ileum, Jejunum			
Invagination			
Volvolus			
Blutungen			
Entzündung			
sonstiges			

	JA	NEIN	Keine Unters.
Colon			
Schleimhaut regelrecht			
Blutungen			
Entzündung			
Beschaffenheit des Inhalts			
Appendizitis			
Mesenterium regelrecht			
Leber			
Gewicht			g
regelrecht gelappt			
Blutstauung			
Verfettung			
sonstige Auffälligkeiten			
Gallenbalse abnorm			
äußere Gallengänge	regelrecht	Ektasie	Stenose
Pankreas regelrecht			
Milz regelrecht			
Gewicht			g
Nieren regelrecht			
Gewicht (mit Faserkapsel, ohne Ureter)			
rechts			g
links			g

	JA	NEIN	Keine Unters.
foetale Lappung			
Hydronephrose			
Punktblutungen			
Entzündung			
sonstige Auffälligkeiten			
Ureter regelrecht			
Stenose			
Hydroureter			
sonstige Auffälligkeiten			
Harnblase			
Schleimhaut regelrecht			
Entzündung			
Inhalt (Volumen)			ml
Glukose in Urin positiv (Teststreifen)			
Azeton im Urin positiv (Teststreifen)			
Prostata regelrecht			
Uterus, Tuben, Ovarien regelrecht			
After regelrecht			
Kotabgang			
Schleimhautverletzungen/ - blutungen			
klaffend			cm
Schilddrüse regelrecht			

	JA	NEIN	Keine Unters.
Nebennieren regelrecht			
Blutungen			
Knoten			
Gewicht zusammen		g	
Hypophyse regelrecht			
innere Mißbildungen:			
ZNS			
Haarlänge			cm
Galea - Kopfschwartenhämatome:			
Suturen	geschlossen überlappend erweitert		
große Fontanelle	gespannt eingesunken		
Durchmesser der Fontanelle - längs - quer - schräg			cm
Blutungen in der Schläfenmuskulatur			
Frakturen des Schädeldaches			
Durasepten Falx cerebri intakt Tentorium cerebellum intakt			
Schädelbasis regelrecht konfiguriert			
Frakturen Schädelbasis			
Foramen magnum regelrecht			

	JA	NEIN	Keine Unters.
Paukenhöhlen/Siebbeinzellen			
Schleimhaut regelrecht			
Schleim			
Eiter			
Blutungen			
epidural			
subdural			
subarachnoidal			
intracerebral			
Hirn (vor dem Schneiden fixieren) Hirngewicht nativ	g		
normale Konfiguration und Konsistenz			
Hirndruckzeichen			
Meningitis			
Enzephalitis			
Fäulnis			
sonstige Auffälligkeiten welche?			
Hirnnerven regelrecht			
Hirnbasisarterien zart			

	JA	NEIN	Keine Unters.
Rückenmark			
Rückenmark regelrechte Konfiguration			
….Myelitis			
….Blutungen			
…sonstige Auffälligkeiten, wenn ja welche?			

II. Histologiebefund

L-Nummer	Histologiebefund

		o.p.B.	
1	Tons.,	☐	
	Gaumen,	☐	
	Uvula,	☐	
	Zunge	☐	
2	Trachea	☐	
	Gl. Thyr.,	☐	
	Gl. Parath.,	☐	
	Öso.,	☐	
3	Bifurcatio	☐	
4	Larynx	☐	
5	LK, cervical	☐	
6a	Lunge, ROL	☐	
6b	Lunge, RML	☐	
6c	Lunge, RUL	☐	
6d	Lunge, LOL	☐	
6e	Lunge, LUL	☐	
7	Lunge, zentral	☐	
8	Herz, quer	☐	
9	Herz, längs, re.	☐	
10	Herz, längs, li.	☐	
11	Thymus	☐	
12	Milz	☐	
13	Diaphragma	☐	
14	Speicheldrüsen, Parotis	☐	
	Submandib.	☐	
15	Haut	☐	
16	Pylorus	☐	
	Duodenum	☐	

17	Pancreas Kopf Corpus	☐ ☐	
18	Ileum / Cäcum	☐	
19	Colon	☐	
20a,b	Leber	☐	
21a,b	Nieren re/li	☐	
22a,b	Nebennieren re/li	☐	
23	Hypophyse	☐	
24	M. iliopsoas	☐	
25	Rippe	☐	
26	Chonchae nasales	☐	
27	Felsenbein	☐	
28	Impfstelle	☐	

Diagnosen:

Additional investigations

Anlage 4 -Standardautopsieprotokoll- Zusatzuntersuchungen

I Neuropathologie

a) Makromorphologische Beurteilung

Die makroskopische Untersuchung erfolgt im Rahmen der Obduktion sowie ergänzend durch den Neuropathologen. Ziel ist es, Erkrankungen des ZNS nachzuweisen oder auszuschließen (Todesursachendiagnostik) und eventuell Festellungen zur Bedeutung und Pathogenese des Hirnödems zu treffen.

b) Asservate

Teile des Gehirns (Cerebrum, Cerebellum, Pons, Medulla oblongata und Teile des Rückenmarks)

c) Zuschneideschema Neurohistologie

27 Cortex (different parts: Margo superior cerebralis, Insula, temporal lob, frontal lob, Area striata, Gyrus cinguli, Corpus callosum) - HE, van Gieson

28 periventricular part of the cerebrum, left - HE, van Gieson

29 Ammon's horn right (Corpus gen. lat.) - HE, van Gieson

30 Thalamus left - HE, van Gieson

31 Ncl. caudatus und Striatum, right (Comm. ant.) - HE, van Gieson

32 Pineal gland - HE, van Gieson

33 Hypothalamus left - HE, van Gieson

34 Midbrain, cross, van Gieson

35 Bridge - HE, van Gieson

36 Medulla including olives and pyramid - HE, van Gieson

37 Cerebellum right including dentate nucleus - HE, van Gieson

38 Medulla (C2/C3) - HE, van Gieson

39 Halsmark - HE, wenn möglich auch Thorakal- und Lendenmark, van Gieson

Zusätzliche Färbungen:
- Nissl
- PAS
- Heidenhain-Wölcke (Melinisierungsgrad)
- Sudan (Nachweis der interstitiellen Encephalitis, Gliazellmetamorphose - Block 34)

d) Immunhistochemie

Antikörper gegen:

- GFAP (glial fibrillary acidic protein)
- MBP (myelin basic protein)
- LCA (leucocytic common antigen)
- CD 68 (microglia, monocytes, macrophages)

Untersucher:

Prof. Dr. Oehmichen
Universitätsklinikum des Landes Schleswig-Holstein
Arnold-Heller-Str. 12
24105 Kiel
Tel. 0431-597 36 00

II. Immunhistochemie der Lunge und des Herzens

a) Ziele

Nachweis bzw. Ausschluß einer Myokarditis bzw. interstitiellen/alveolären Pneumonie als und Wertung vorbestehender Erkrankungen im Hinblick auf ihre todesursächliche Relevanz.

b) Antikörper

Herz: Antikörper gegen:

- CD 68 (Makrophagen)
- LCA (leucocyte common antigen)
- CD 45R0 (B-Lymphozyten)
- CD 3 (T-Lymphozyten)
- C_{5b-9} (Komplementkomplex als Nekrosemarker)

Lunge: Antikörper gegen:

- CD 68 (Makrophagen)
- CD 45R0 (B-Lymphozyten)
- CD 3 (T-Lymphozyten)
- MRP 14 (entzündlich aktivierte Monozyten, Makrophagen)

Untersucher:

PD Dr. Bajanowski

Institut für Rechtsmedizin

Uniklinikum Essen-Duisburg

Hufelandstr. 55

45122 Essen

III Mikrobiologie, Virologie

a) Hintergrund für die Untersuchungen

Plötzliche und unerwartete Todesfälle bei Kindern können durch Infektionen oder Entzündungsreaktionen nach Impfungen oder Infektionen verursacht sein. Für die Mehrzahl der Organe ist es jedoch unwahrscheinlich, dass eine Infektion oder Entzündungsreaktion innerhalb von sehr kurzer Zeit zum Tod führt und vor dem Tod oder bei der Obduktion keine Symptome festzustellen waren. Für Gehirn, Herz oder Lunge kann jedoch ein derart akutes Geschehen nicht ausgeschlossen werden. Das Gehirn kontrolliert sowohl die Atmung als auch andere lebenswichtige Funktionen. In einigen Fälle scheint SUD mit einem Hirnödem assoziiert gewesen zu sein. Herz und Lunge haben ebenfalls vitale Aufgaben in der Sauerstoffversorgung.

b) Mikrobiologische/virologische Untersuchungen des Respirationstraktes

Multiplex PCR (Asservate: Trachealabstrich und Lungengewebe) zum Nachweis folgender Erreger:

Influenza A-virus, Influenza B-Virus, RSV, Parainfluenzavirus (PIV) 1, PIV 2, PIV 3, PIV 4, Adenovirus, Corona-virus including SARS, Enterovirus, Rhinovirus, Reovirus (types 1, 2, 3), human Metapneumovirus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Bordetella pertussis, Bordetella parapertussis, Legionella.

Untersucher:

Prof. Dr. Heinz-J. Schmitt

Zentrum für Präventive Pädiatrie, Labor Bau 106
Langenbeckstr. 1

55101 Mainz

c) Mikrobiologische/virologische Untersuchungen des Gehirns, Herzens und des Liquors

PCR zum Nachweis der nachfolgend aufgeführten Mikroorganismen (Einzeltestung, bei positivem Ergebnis eventuell mit Sequenzierung):

Asservate:

1. Medulla oblongata oder wenn vorhanden, zusätzlich von veränderten Regionen
2. Myocard, linker Ventrikel
3. Liquor

Organism	**Comments**
Measles virus	Important since concomitant vaccination likely and disease still epidemic in Germany; if positive additional testing to distinguish vaccine virus from wild type virus
Mumps virus	As above
Rubella virus	As above
Herpes simplex virus	
Varicella zoster virus*	
Cytomegalovirus*	
Epstein Barr virus	
Enterovirus*	These organisms are part of multiplex PCR and in order to reduce costs will be tested for in Kiel from brain, CSF and myocardium
Parainfluenzavirus 1*	
Parainfluenzavirus 2	
Parainfluenzavirus 3*	
Parainfluenzavirus 4	
Adenovirus*	
Influenzavirus A*	
Influenzavirus B*	
Legionella*	
Mycoplasma pneumoniae*	
Chlamydia pneumoniae*	

*organism previously identified in SUD cases

d) Konventionelle Mikrobiologie (Bakterienkulturen)

Gewebeproben (wie unter Anlage 2 III.3.a aufgelistet -) der normalerweise sterilen Organe werden zur Anzüchtung von Bakterien kultiviert.

- Blutagar
- Schokoladenagar
- McConkey agar
- Sabouraud dextrose-Agar
- Thioglycolateboullion
- Brain heart infusion broth
- Schaedler-Agar für obligate anaerobe Bakterien

Stuhlproben

- zum Nachwesi TPE-Erregern in Routineagar.
- Spezieller Nachweis von Clostridien im Stuhl.
- Stuhlprobe und Serum will zum Nachweis von Clostridium botulinum Toxin.
- Nachweis von Superantigenen, falls erforderlich.
- Staph. Aureus mit Prüfung auf Toxinbildung (TSST-1, Enterotoxine)

Untersucher:

Dezentrale Untersuchung in den jeweiligen Rechtsmedizinischen Instituten

IV. Immunologische Untersuchungen

a) Serumfaktoren (1,5 ml Serum, tiefgefroren, -20°C)

- Superantigen-Spiegel (TSST-1, SEA, SEB, SEC, Pertussistoxin) 244,80
- CH50
- C3d
- Zytokine (IFN-γ, TNF-α, IL-1β, IL-6, IL-10, IL-18)
- Mastzell-Tryptase
- CRP
- IgM, IgG, IgA, IgD ($\rightarrow$ Hyper-IgM-Sysndrom, IgA-Defizienz, Hyper-IgD-Syndrom, Agammaglobulinämie)
- IgE (gesamt, spezifisch: Neomycin, Streptomycin, Polymyxin B, Tromethamol)

Für eventuell zeitversetzt durchzuführende, weitere Untersuchungen werden Probenbanken von Blut bzw. Serum angelegt.

b) Untersuchung von Polymorphismen immunregulatorischer Gene (1 Stück Milz, 1:1:0,5cm, tiefgefroren, - 20°C)

- TNF-A Promotor (SNP in Pos. -238 und-308)
- IL-6 Promotor (Pos. 174 G/C)
- IL-10 Promotor (ATA/ATA Genotyp- SNPs in Pos. -1082, -819, -592)
- IL-10 Mikrosatelliten (IL-10G und IL-10R)

Molekulargenetischer Nachweis weiterer Polymorphismen

- Serotonin-Transporter (Opdal SH Pediatics 2004; 114:e506)

c) molekulargenetischer Nachweis von Immunfefekten

Bare Lymphocyte Syndrome (CIITA Varianten)

Komplementdefekte C1q-Inhibitor , C2, C3, C4

V. Stoffwechselscreening

Das Stoffwechselscreening erfolgt mittels Tandem-MS-Analyse.

Untersuchunghsmaterial:

- zwei Tropfen Blut auf Filterpapier (kühl und trocken lagern),
- zwei Tropfen Galleflüssigkeit Filterpapier (kühl und trocken lagern).

Folgende Stoffwechselerkrankungen können nachgewiesen oder ausgeschlossen werden:

Störungen im Aminosäurestoffwechsel (Aminoazidopathien)

- Phenylketonurie
- Tyrosinämie
- Homocystinurie
- Ahornsirupkrankheit

Carnitinzyklus- und Fettsäureoxidations-Defekte

- CPT1- und CPT2-Mangel
- Carnitin-Translokase-Mangel
- MCAD-Mangel
- VLCAD-Mangel
- LCHAD-Mangel

- MAD-Mangel (Glutarazidurie Typ III)

- Störungen im Stoffwechsel organischer Säuren (Organoazidämien)
  - 3-MCC-Mangel
  - Isovalerianazidämie
  - Glutarazidurie Typ I
  - Propionazidämie
  - Methylmalonazidämie
  - HMG-CoA-Lyase-Mangel
  - b-Katecholase-mangel (3-Oxo-Thiolase-Mangel).

Untersuchungsort:
Labor Becker, Olgemöller & Kollegen
Führichstraße 70
81671 München

Manual related to the standardized autopsy protocol (SAP)

Anlage 5 - Manual für Standardautopsieprotokoll –

I Röntgenuntersuchung des Skeletts

Übersichtsaufnahme, falls erforderlich Spezialtechniken

II Leichenöffnung

Äußere Besichtigung

Innere Besichtigung

Erstellung des standardisierten Protokolls

III Asservation

1. Histologie

a) 4%iges, gepuffertes Formalin, Fixierung über 24 bis maximal 48 Stunden

Zunge, Uvula, Tonsillen, Larynx, Zungenbein, Schilddrüse, Oesophagus, Trachea

Gl. submandibularis, Gl. parotis

3 Cervicale Lymphknoten

4 Lunge: je Lappen 1x (right: □ 1<2<3; left: ∇ 4<5)
1 x zentraler Teil mit Bronchus (rechts)

5 Herz: Vorhof und oberer Teil der Ventrikel einschließlich Septum.

6 Thymus

7 Milz

8 Diaphragma (longitudinal)

9 Pylorus mit Duodenum

10 Pancreas, Kopf und Schwanz

11 Ileum, Zoekum, Appendix

12 Leber (beise Lappen, je 1 x)

13 Nieren (Querschnitt re., li. je 1 x)

14 Nebennieren

15 Magenschleimhaut

16 Hirnanhangdrüse

17 M. ileopsoas

18 Rippe (Knorpel-Knochen-Grenze)

19 Nasengänge, Gaumen,Siebbeinzellen

20 Teile des Gehirns (Cerebrum, Cerebellum, Pons, Medulla) und des Rückenmarks

21 Haut, ggf. von Impfstelle, hier auch mit Unterhautgewebe und Muskulatur

22 Felsenbein mit Anteil der Paukenhöhle

b) Tiefgefrorenes Material (Lagerung bei -20°C)

23 Bifurcatio tracheae

24a,b Lunge (je 1 x rechts, links)

25 Duodenum/jejunum (etwa 2cm)

26 höherer Teil des Gyrus frontalis, left side

27 Myocard, linker Ventrikel, 3 Proben

28 Thymus

29 Halslymphknoten

30 Milz

31 Tonsille

32 Leber

2. Neuropathologie

4%iges, gepuffertes Formalin, Fixierung über ca eine Woche

Teile des Gehirns

- Cerebrum
- Cerebellum
- Pons
- Medulla und Halsmark, wenn vorhanden auch Thorakal- und Lendenmark

3. Mikrobiologie, Virologie

a.) für dezentral durchgeführte konventionelle Mikrobiologie

- 0,5ml steril entnommenes Herzblut
- Stuhlprobe für Clostridien
- Abstriche von:
  - Darm
  - Herzblut
  - Leptomeninx
  - Lunge
  - Mittelohr
  - Trachea

b.) für extern durchgeführte Zusatzuntersuchungen

(sterile Entnahme, keine Lagerung, direkter Versand bei 4-8°C an: Prof. Dr. Heinz-J. Schmitt, Zentrum Präventive Pädiatrie, Labor Bau 106, Langenbeckstr. 1, 55101 Mainz)

- Liquor
- Gewebeproben in Epi (ca. 4:4:4 mm)
    - Medulla oblongata oder wenn vorhanden, zusätzlich von veränderten Regionen
    - Leber
    - Lunge (zentral) oder wenn vorhanden, zusätzlich von veränderten Regionen-
    - Myocard, linker Ventrikel

4. Immunologie

- 1,5 ml Serum (in 2 Portionen, tiefgefroren, -20° C)
- 1 Stück Milz, 1:1:0,5 cm (tiefgefroren, -20° C)

5. Toxikologie

a) Körperflüssigkeiten (Lagerung bei -20°C bis zur Untersuchung vor Ort)

- Liquor (ca. 1-2ml)
- Herzblut
- Femoralvenenblut
- Urin (wenn vorhanden)
- Augenkammerwasser
- Gallenflüssigkeit

b) Gewebeproben (Lagerung in Glasgefäßen bei -20°C)

- Leber (ca. 60 g in 2 Portionen)
- Niere (ca. 10 g)
- Mageninhalt (wenn vorhanden)
- Fettgewebe (ca. 10 g)

6. Stoffwechselscreening

- Zwei Tropfen Blut auf Filterpapier (kühl und trocken lagern)
- Zwei Tropfen Galleflüssigkeit auf Filterpapier (kühl und trocken lagern)

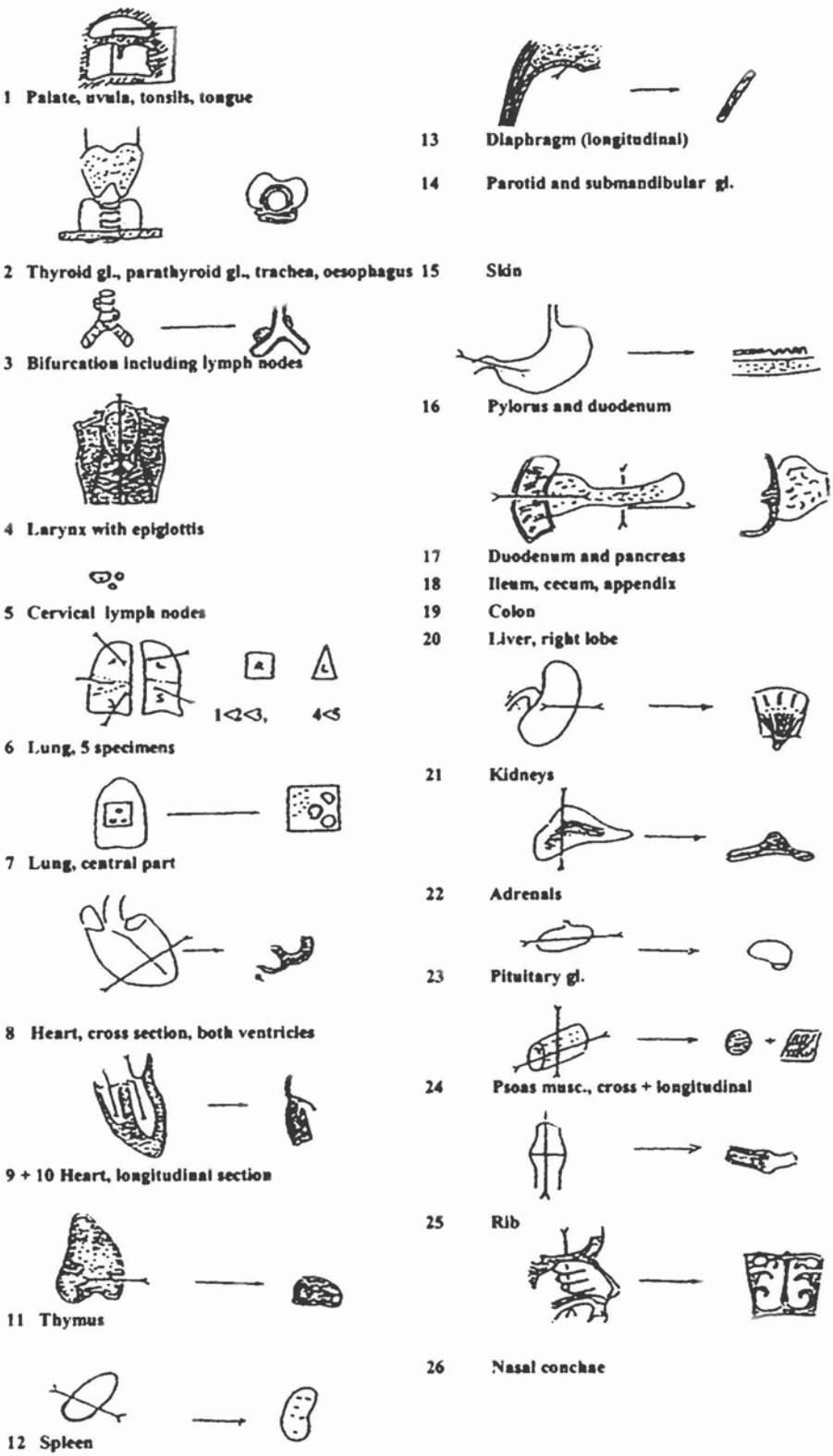
IV. Untersuchungen vor Ort im Institut für Rechtsmedizin

1. Histologie - Zuschneideschema und Färbungen

a) tabellarisch

1	Tonsille, Uvula, Zungenrand – HE
2	Querschnitt: Gl. thyreoidea, Trachea, Oesophagus. Parathyreoidea - HE
3	Bifurcatio tracheae - HE
4	Längsschnitt: Larynx einschließlich epiglottis - HE, EvG
5	Halslymphknoten - HE
6a-e	Lunge, (rechtst: □ 1<2<3; links: ∇ 4<5) - HE, Alcianblau-PAS, Berliner blau
7	zentraler Lungenblock (right) - HE, Alcianblau-PAS, Berlin blau
8a,b	Herz, Querschnitt Septum von vorn + Vorderwand beider Ventrikel - HE, EvG, Fett
9,10	Herz, längs durch Vorhof uns Ventrikel, beide Seiten - HE, EvG
11	Thymus - HE
12	Milz - HE, Berliner blau
13	Diaphragma (longitudinal) - HE
14	Gl. submandibularis und - parotiis - HE
15	Haut, evtl. mit Subcutis und Muskulatur - HE
16	Pylorus und Duodenum - HE
17a,b	Pankreas (Kopf und Schwanz)- HE
18	Ileum, Coecum, Appendix - HE
19	Colon - HE
20a,b	Leber, rechter Lappen - HE, Fett
21a,b	Nieren, beide - HE, PAS
22a,b	Nebennieren, beide (möglichst ohne Fettgewbe einbetten) - HE, Fett
23	Hirnanhangdrüse - HE
24a,b	M. Ileopsoas (längs und quer) - HE, Fett
25	Rippe (Knorpel-Knochen-Übergang - HE, Giemsa
26	Nasengänge – HE
27	Felsenbein (incl. Mittelohr)- HE
28	Impfstelle (Haut und Stichkanal)

b) Zuschnitt - schematisch



2. Toxikologie

Nachweis von:

- Ethanol, Methanol, Azeton, iso-Propanol im Femoralvenenblut
  (head-space GC, cut-off 20µg/ml)

- Co-Hb (Herzblut, photometrisch)

- Amphetamine, Cannabinoide, Kokain, Opiate (immunologisch nach Azetonextraktion aus dem Herzblut)

- *General unknown* Analyse zum Nachweis von Antiepileptika, Benzodiazepinen, Hypnotika, Antidepressiva, Neuroleptika, Opiaten und anderen Analgetika (Herzblut, Lebergewebe, Gc-MS)

3.) Konventionelle Mikrobiologie

- 0,5ml steril entnommenes Herzblut, 0,5ml Serum
- Stuhlprobe für Clostridien
- Abstriche von:
  - Darm
  - Herzblut
  - Leptomeninx
  - Lunge
  - Mittelohr
  - Trachea

Untersuchung unmittelbar nach der Obduktion in den Instituten für Mikrobiologie des jeweiligen Universitätsklinikums. Nachweis von:

a. Respirationstrakt, Blut, Leptomeninx

- Staphylokokken
- Streptokokken
- Pneumokokken
- Meningokokken
- Hämophilus
- Bordetella
- Klebsiellen
- Pseudomonas
- Chlamydien
- Mycoplasma

b. Magen-Darmtrakt
    - Salmonellen
    - Shigellen
    - Listerien
    - Camphylobacter
    - Coli
    - Bacillus cereus

c. anaerobe Bakterien
    - Clostridien

d. sonstige Untersuchungen wenn möglich
    - Candida Titer bei Hinweisen auf Pilzinfektion
    - eventuell Toxin-Nachweis
    - eventuell Nachweis von Superantigenen

V Material-/Befundversand

1. Neuropathologie

Teile des Gehirns (Cerebrum, Cerebellum, Pons, Medulla) fixiert über ca. 1 Woche in 4%igem, gepufferten Formalin

Prof. Dr. Oehmichen
Universitätsklinikum des Landes Schleswig Holstein
Arnold-Heller-str. 12
24105 Kiel

2. Mikrobiologie, Virologie

Sämtliche unter Ziffer III.3.b aufgelistete Proben (sterile Entnahme, keine Lagerung, direkter Versand bei 4-8°C)

Prof. Dr. Heinz-J. Schmitt

Zentrum für Präventive Pädiatrie, Labor Bau 106
Langenbeckstr. 1

55101 Mainz

3. Immunologie (tiefgefroren, -20° C)

- 1,5 ml Serum
- 1 Stück Milz, 1:1:0,5 cm

Prof. Dr. H. Grosse-Wilde

Institut für Immunologie
Universitätsklinikum Essen-Duisburg
Hufelandstr. 55
45122 Essen

4. Stoffwechselscreening

- zwei Tropfen Blut auf Filterpaier
- zwei Tropfen Galleflüssigkeit auf Filterpapier

Labor Becker, Olgemöller & Kollegen
Führichstraße 70
81671 München

5. Material für Immunhistochemie

a) tiefgefrorenes Material

(Lagerung bei -20°C in Epis, Versand auf Trockeneis)

23 Bifurcatio tracheae

24a,b Lunge (je 1 x rechts, links)

25 Duodenum/Jejunum (etwa 2cm)

26 höherer Teil des Gyrus frontalis, linke Seite

27 Myocard, linker Ventrikel, 3 Proben

b) Paraffinblöcke von Herz und Lunge

PD Dr. T. Bajanowski
Institut für Rechtsmedizin
Universitätsklinikum Essen-Duisburg
Hufelandstr. 55
45122 Essen

6. Befundversand

- Standardautopsieprotokoll
- Histologiebefund
- Toxikologiebefund
- Schnittpräparate Histologie (leihweise)

PD Dr. T. Bajanowski
Institut für Rechtsmedizin
Universitätsklinikum Essen-Duisburg
Hufelandstr. 55
45122 Essen

Information letter enclosed to the informed consent – epidemiological study part –

ROBERT KOCH INSTITUT

Liebe Eltern,

Sie erhalten von uns, dem Robert Koch-Institut in Berlin, diesen Brief über Ihr zuständiges Gesundheitsamt, da aus datenschutzrechtlichen Gründen nur Ihr Gesundheitsamt Ihren Namen und Ihre Anschrift kennt.

Sie haben vor kurzem den Verlust Ihres Kindes erlitten. Dazu sprechen wir Ihnen unser aufrichtiges Bedauern und Mitgefühl aus.

Mit diesem Brief möchten wir Sie bitten, eine wichtige wissenschaftliche Untersuchung zu unterstützen. Diese Untersuchung soll bisher unbekannte Risikofaktoren für einen frühen Tod erkennen (z. B. bestimmte Lebensumstände, problematische Schwangerschafts- und Geburtsverläufe, Erkrankungen, medizinische bzw. medikamentöse Behandlungen einschließlich Impfungen).

Gegenwärtig versterben in Deutschland jährlich etwa 1500 Kinder im ersten und zweiten Lebensjahr trotz moderner medizinischer Untersuchungs- und Behandlungsmöglichkeiten. Bekannte Todesursachen sind angeborene Fehlbildungen des Herzens oder anderer lebenswichtiger Organe, Krebserkrankungen, Unfälle und schwere Infektionen. In einigen Fällen bleibt die Todesursache jedoch unklar. Ihre Antworten werden uns helfen, bisher unbekannte Einflussfaktoren für solche ungeklärten Todesfälle zu erkennen. Ziel ist es, wirksame und sichere Vorsorgemaßnahmen zu entwickeln.

Das Robert Koch-Institut als Bundesinstitut auf dem Gebiet der Krankheitskontrolle und –vorsorge führt in Zusammenarbeit mit der Kinderklinik der Universität Magdeburg sowie dem Institut für Soziale Pädiatrie und Jugendmedizin der Ludwig-Maximilians-Universität in München diese Studie durch. Über das zuständige Gesundheitsamt haben wir erfahren, dass Ihr Kind verstorben ist; wir kennen jedoch aus datenschutzrechtlichen Gründen Ihren Namen und Ihre Anschrift nicht. Wenn Sie sich bereit erklären, an der Untersuchung teilzunehmen, sendet das Robert Koch-Institut Ihnen und – mit Ihrem Einverständnis – dem Kinderarzt Ihres verstorbenen Kindes einen Fragebogen zu. Bitte teilen Sie uns dazu Namen und Anschrift des Kinder- oder Hausarztes Ihres verstorbenen Kindes mit und geben Sie Ihr Einverständnis für die Übermittlung der ärztlichen Befunde.

Die Ethikkommission der Medizinischen Hochschule Hannover hat unsere wissenschaftliche Untersuchung genau geprüft und ist mit ihrer Durchführung einverstanden. Auch die Datenschutzbeauftragten des Bundes und der Länder haben unser Vorgehen überprüft, und wir haben deren datenschutzrechtliche Empfehlungen umgesetzt. Ihre Daten werden nur pseudonymisiert ausgewertet, d. h., wenn die von Ihnen und dem Kinderarzt Ihres Kindes ausgefüllten Fragebögen bei uns angekommen ist und wir die Angaben zu Ihrem Kind vollständig zusammengeführt haben, werden alle Namen und Adressen von den Fragebögen getrennt, durch eine fortlaufende Nummer ersetzt und spätestens 2 Jahre nach Abschluss der Studie vernichtet. So können später keinerlei Rückschlüsse auf Einzelpersonen mehr gezogen werden.

Ihre Teilnahme ist freiwillig, bei Nichtteilnahme oder unvollständigem Ausfüllen entstehen Ihnen keine Nachteile, und Sie können Ihre Einwilligung jederzeit widerrufen. Die zu Ihnen und Ihrem verstorbenen Kind gespeicherten Informationen werden dann gelöscht und nicht für diese Studie ausgewertet.

Bitte erklären Sie in der beigefügten Einwilligungserklärung (Blatt Nummer 1) durch Ihre Unterschrift, dass Sie über die Untersuchung informiert worden sind und Sie damit einverstanden sind, dass Ihre Angaben im Fragebogen durch die beteiligten Einrichtungen Robert Koch-Institut und der Kinderklinik der Universität Magdeburg gespeichert und wissenschaftlich ausgewertet werden dürfen. Eine Weitergabe von anonymisierten Daten kann auch im Rahmen von gesetzlichen Regelungen an die für die Zulassung von Arzneimitteln zuständigen in- und ausländischen Behörden (z. B. das Paul-Ehrlich Institut) erfolgen.

Wenn Sie nicht an der Untersuchung teilnehmen möchten, bitten wir Sie, uns dies auf der vorbereiteten Erklärung zur Nichtteilnahme an der Studie (Blatt Nummer 2) mitzuteilen. Bitte antworten Sie uns in jedem Fall. Wenn wir nichts von Ihnen hören, gehen wir davon aus, dass Sie unser Schreiben nicht erhalten haben oder vielleicht die Rücksendung der Einverständniserklärung vergessen haben, und Ihr Gesundheitsamt wird nach einiger Zeit versuchen, Sie erneut zu erreichen.

Wir wissen wohl, dass dieser Brief und Ihre Entscheidung für Sie nicht einfach sind. Dennoch bitten wir Sie sehr herzlich um Ihre Teilnahme an dieser Untersuchung, damit zukünftig solche Fälle hoffentlich verhindert werden können.

Sollten Sie unsicher sein, welche Entscheidung für Sie richtig ist, möchten wir Sie ermutigen, ein Gespräch mit dem Kinderarzt Ihres verstorbenen Kindes zu führen. Hilfe bei Ihrer Entscheidung oder auch zusätzliche Informationen über diese Studie können Sie auch bei den Mitarbeitern der Magdeburger Kinderklinik erhalten: Klinik für Allgemeine Pädiatrie und Neonatologie, PD Dr. Klaus Mohnike, Emanuel-Larisch-Weg 17 – 19, 39112 Magdeburg, Tel.: 03 91/67-1 71 01 Fax: 03 91/67-1 71 05.

Prof. Dr. Reinhard Kurth
Präsident
Robert Koch-Institut

Ansprechpartner der Studienleitung im Robert Koch-Institut:
Robert Koch-Institut
Abteilung für Epidemiologie und Gesundheitsberichterstattung
Fachgebiet ‚Gesundheit von Kindern und Jugendlichen, Präventionskonzepte'
Seestraße 10
13353 Berlin
Telefon 01888/754-3437 (Studienleiter: Priv. Doz. Dr. Martin Schlaud)
Telefon 01888/754-3193 (Studienkoordination: Dr. Christina Poethko-Müller)

Informed consent – epidemiological study part –

ROBERT KOCH INSTITUT

Blatt 1
Einverständniserklärung (BITTE ZURÜCKSENDEN)

Hiermit erkläre ich,

Frau _____

Herr _____

Adresse: _____

_____

Telefon _____Handy-Nummer_____

dass ich als Sorgeberechtigte/r von

_____, geboren am _____
(Vor- und Familienname des Kindes) Tag Monat Jahr

schriftlich über die ‚Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat' informiert und aufgeklärt wurde. Mit meiner Unterschrift willige ich ein, (Nichtzutreffendes bitte streichen) dass die

- Daten meines / unseres Kindes an Hand des Fragebogen erfasst und pseudonymisiert wissenschaftlich ausgewertet werden,
- Angaben auf dem amtlichen Totenschein im Rahmen der Studie pseudonymisiert wissenschaftlich ausgewertet werden,
- zusätzlich entbinde(n) ich/wir den behandelnden Kinder- oder Hausarzt meines / unseres Kindes:

- Frau/Herrn _____

  Adresse: _____

  _____

  Telefon: _____
- sowie andere Ärzte und Einrichtungen, deren Namen wir im Fragebogen angeben,

  von der Schweigepflicht und gestatten die Anforderung von Unterlagen zur medizinischen Vorgeschichte meines/unseres Kindes von diesen Ärzten und Krankenhäusern.

Ich weiß, dass alle an der Studie beteiligten Personen der Schweigepflicht unterliegen, dass keine persönlichen Informationen über mein Kind oder mich an Dritte weitergegeben werden, und gebe meine Einwilligung nur unter dieser Voraussetzung. Die Abgabe dieser Einverständniserklärung und die Teilnahme an der Studie sind freiwillig. Mir ist bekannt, dass ich meine Einwilligung bis zur Löschung meines Namens und meiner Adresse jederzeit ohne Angabe von Gründen widerrufen kann, ohne dass mir daraus Nachteile erwachsen. Die

zu mir und meinem verstorbenen Kind gespeicherten Informationen werden in diesem Fall gelöscht und nicht für die Studie ausgewertet. Mein Ansprechpartner dafür ist Priv.-Doz. Dr. med. Martin Schlaud, Fachgebiet 23 "Gesundheit von Kindern und Jugendlichen, Präventionskonzepte", Abteilung für Epidemiologie und Gesundheitsberichterstattung, Robert Koch-Institut Seestraße 10, 13353 Berlin, Telefon 01888/754-3437, Telefax 01888/154-3555). Alle Namen und Anschriften werden von den Fragebögen getrennt, bevor die Daten wissenschaftlich ausgewertet werden, vom Robert Koch-Institut verschlossen aufbewahrt und spätestens zwei Jahre nach Ende der Studie vernichtet. Die pseudonymisierten Fragebögen werden spätestens 10 Jahre nach Abschluss der Studie vernichtet.

_____	_____	_____
Ort	Datum	Unterschrift/en Sorgeberechtigte/r

Einverständniserklärung (Für Ihre Unterlagen)

Hiermit erkläre ich,

Frau _____

Herr _____

Adresse: _____

_____

Telefon _____Handy-Nummer_____

dass ich als Sorgeberechtigte/r von

_____, geboren am _____
(Vor- und Familienname des Kindes) Tag Monat Jahr

schriftlich über die ‚Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat' informiert und aufgeklärt wurde. Mit meiner Unterschrift willige ich ein, (Nichtzutreffendes bitte streichen) dass die

- Daten meines / unseres Kindes an Hand des Fragebogen erfasst und pseudonymisiert wissenschaftlich ausgewertet werden,
- Angaben auf dem amtlichen Totenschein im Rahmen der Studie pseudonymisiert wissenschaftlich ausgewertet werden,
- zusätzlich entbinde(n) ich/wir den behandelnden Kinder- oder Hausarzt meines / unseres Kindes:

- Frau/Herrn _____

  Adresse: _____

  _____

  Telefon: _____
- sowie andere Ärzte und Einrichtungen, deren Namen wir im Fragebogen angeben,

  von der Schweigepflicht und gestatten die Anforderung von Unterlagen zur medizinischen Vorgeschichte meines/unseres Kindes von diesen Ärzten und Krankenhäusern.

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_____	_____	_____
Ort	Datum	Unterschrift/en Sorgeberechtigte/r

Declaration not to take part in the study for parents – epidemiological study part –

ROBERT KOCH INSTITUT

Blatt 2
Erklärung über Nichtteilnahme an der
‚Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat'

Hiermit erkläre ich,

Frau _____

Herr _____

Adresse: _____

_____

dass ich als Sorgeberechtigte/r von

_____, geboren am _____
(Vor- und Familienname des Kindes) Tag Monat Jahr

nicht an der ‚Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat' teilnehmen möchte.

☐ ich bin damit einverstanden, dass mir ein Kurzfragebogen zugesendet wird.

_____ _____ _____
Ort Datum Unterschrift Sorgeberechtigte/r

Compilation of parental experiences with the study

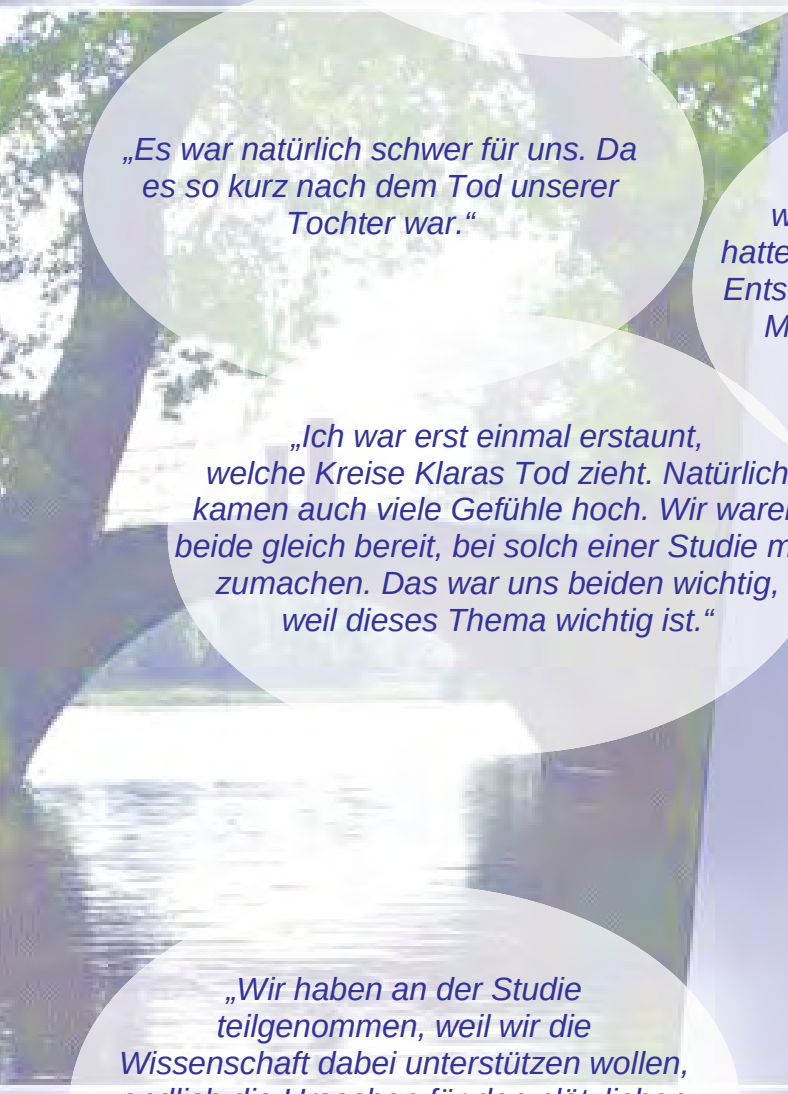
Eltern, die sich für die Studie entschieden haben, schildern ihre Gefühle und Eindrücke, um Ihnen Mut zu machen.

„Zuerst haben wir gotterbärmlich geheult. Dann haben wir uns gesagt, vielleicht hilft es ja, um anderen dieses Leid zu ersparen. Wir haben nicht groß nachgedacht, ob oder ob nicht, für uns war es eigentlich klar, mitzumachen.“

„… ich denke, jeder, der sein Kind verliert, möchte in irgendeiner Weise helfen, dass so etwas anderen Kindern nicht widerfährt.“

„Ja, aber der Zeitpunkt, wann Eltern den Fragebogen beantworten können, hängt von dem Seelenzustand jedes Einzelnen ab. Unserer Meinung nach sollten mind. 3 Monate seit dem Tod des Kindes vergangen sein.“

„Es war ein Gefühlschaos bei uns, da wir immer erinnerten was wir durchlebten oder noch durchmachen müssen!!!“



„Es war natürlich schwer für uns. Da es so kurz nach dem Tod unserer Tochter war.“

„Am Anfang war ich nicht daran interessiert, wollte vom Kindstod nichts wissen. Ich hatte dann darüber nachgedacht und bin zum Entschluss gekommen, ihn doch auszufüllen. Mich würde es schon interessieren was man machen kann, dass mir dies nicht noch einmal passiert.“

„Ich war erst einmal erstaunt, welche Kreise Klaras Tod zieht. Natürlich kamen auch viele Gefühle hoch. Wir waren beide gleich bereit, bei solch einer Studie mitzumachen. Das war uns beiden wichtig, weil dieses Thema wichtig ist.“

„Als wir nach dem Tod unserer Tochter diese Einladung zur Teilnahme erhielten waren mein Mann und ich überrascht, da wir bis dahin keine Ahnung hatten, dass es so etwas gibt. Der Tod unserer Tochter erschien nun nicht mehr als so sinnlos wie noch kurz zuvor. Wir haben die Hoffnung, dass Ihre Studie und damit verbundene Forschungen anderen Eltern ein ähnliches Schicksal erspart.“

„Wir haben an der Studie teilgenommen, weil wir die Wissenschaft dabei unterstützen wollen, endlich die Ursachen für den plötzlichen Kindstod zu finden. Andere Eltern sollen ihre Kinder nicht auch verlieren.“

„Wir halten die Studie für zumutbar, für andere mag es anders sein. Gut war, dass der Fragebogen relativ zeitnah beantwortet werden musste. Bei einer späteren Beantwortung wäre alles wieder aufgewühlt worden, was man mühsam versucht zu verarbeiten. Dann wäre unsere Entscheidung vielleicht anders ausgefallen.“

Accompanying letter with the parental questionnaire

ROBERT KOCH INSTITUT

Liebe Eltern,

Sie haben sich trotz des großen Verlusts, den Sie erlitten haben, freundlicherweise bereit erklärt, an einer Untersuchung über Todesfälle bei Säuglingen und Kleinkindern teilzunehmen. Wir danken Ihnen sehr für diese Bereitschaft. Wir wissen wohl, dass die Beantwortung unserer Fragen für Sie nicht einfach ist. Doch soll diese Untersuchung Daten und Erkenntnisse über die Ursachen dieses tragischen Ereignisses gewinnen und dadurch zukünftig helfen, solche Fälle zu verhindern.

Gegenwärtig versterben trotz moderner medizinischer Untersuchungs- und Behandlungsmöglichkeiten in Deutschland jährlich etwa 1500 Kinder im ersten und zweiten Lebensjahr. Bekannte Todesursachen sind angeborene Fehlbildungen des Herzens oder anderer lebenswichtiger Organe, Krebserkrankungen, Unfälle und schwere Infektionen. Ihre Antworten werden uns helfen, weitere bisher unbekannte Einflussfaktoren zu erkennen. Ziel ist es, wirksame und sichere Vorsorgemaßnahmen zu entwickeln.

Unsere Fragen an Sie finden Sie im beiliegenden Fragebogen. Ihre Antworten unterliegen den Vorschriften des Datenschutzes. Die Beauftragten für den Datenschutz haben unser Vorgehen überprüft, und wir haben die Empfehlungen umgesetzt. Ihre Angaben werden pseudonymisiert ausgewertet, d. h., wenn die von Ihnen und dem Kinderarzt Ihres Kindes ausgefüllten Fragebögen bei uns angekommen ist und wir die Angaben zu Ihrem Kind vollständig zusammengeführt haben, werden alle Namen und Adressen von den Fragebögen getrennt und spätestens 2 Jahre nach Abschluss der Studie vernichtet. Ihre persönlichen Unterlagen (Impfbuch und Kinderuntersuchungsheft) senden wir Ihnen schon vorher zurück. Niemand kann später feststellen, wer welche Angaben gemacht hat. Ihre Teilnahme ist freiwillig, bei Nichtausfüllen oder unvollständigem Ausfüllen entstehen Ihnen keine Nachteile, und Sie können Ihre Einwilligung jederzeit widerrufen. Die zu Ihnen und Ihrem verstorbenen Kind gespeicherten Informationen werden in diesem Fall gelöscht und nicht für die Studie ausgewertet.

Wenn Sie bei der Beantwortung unserer Fragen Hilfe benötigen, können Sie sich an die Kinderärztliche Abteilung der Universität Magdeburg wenden. Dorthin senden Sie bitte auch portofrei den ausgefüllten Fragebogen und das von uns benötigte Impfbuch sowie das gelbe Vorsorgeheft oder Kopien dieser Dokumente. Die Anschrift lautet: Klinik für Allgemeine Pädiatrie und Neonatologie: PD Dr. Klaus Mohnike, Emanuel-Larisch-Weg 17 - 19 , 39112 Magdeburg, Tel.: 03 91/67-1 71 01.

Haben Sie vielen Dank für Ihre wertvolle Unterstützung.

Prof. Dr. Reinhard Kurth
Präsident des Robert Koch-Instituts

Informed consent

- Pathological study part -

ROBERT KOCH INSTITUT

Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat

A1 Aufklärung (für betroffene Eltern)
Zum Verbleib bei den Eltern

Liebe Eltern,

Sie haben vor kurzem den Verlust Ihres Kindes erlitten. Dazu sprechen wir Ihnen unser aufrichtiges Bedauern und Mitgefühl aus.

Mit diesem Brief möchten wir Sie bitten, eine wichtige wissenschaftliche Untersuchung zu unterstützen. Diese Untersuchung soll bisher unbekannte Risikofaktoren für einen frühen Tod erkennen.

Gegenwärtig versterben in Deutschland jährlich etwa 1500 Kinder im ersten und zweiten Lebensjahr trotz moderner medizinischer Untersuchungs- und Behandlungsmöglichkeiten. Bekannte Todesursachen sind angeborene Fehlbildungen des Herzens oder anderer lebenswichtiger Organe, Krebserkrankungen, Unfälle und schwere Infektionen. In einigen Fällen bleibt die Todesursache jedoch unklar. Ihre Antworten werden uns helfen, bisher unbekannte Einflussfaktoren für solche ungeklärten Todesfälle zu erkennen. Ziel ist es, wirksame und sichere Vorsorgemaßnahmen zu entwickeln.

Das Robert Koch-Institut als Bundesinstitut auf dem Gebiet der Krankheitskontrolle und Krankheitsvorsorge führt in Zusammenarbeit mit der Kinderklinik der Universität Magdeburg, dem Institut für Rechtsmedizin der Universität Essen-Duisburg sowie dem Institut für Soziale Pädiatrie und Jugendmedizin der Ludwig-Maximilians-Universität in München diese Studie durch. Wenn Sie sich bereit erklären, an der Untersuchung teilzunehmen, sendet das Robert Koch-Institut Ihnen und – mit Ihrem Einverständnis – dem Kinderarzt Ihres verstorbenen Kindes einen Fragebogen zu. Bitte teilen Sie uns dazu Namen und Anschrift des Kinder- oder Hausarztes Ihres verstorbenen Kindes mit und geben Sie Ihr Einverständnis für die Übermittlung der ärztlichen Befunde.

Diese Untersuchungen können außer für die Allgemeinheit unter Umständen auch für Sie als die betroffenen Eltern von Bedeutung sein, wenn Sie an dieser Studie teilnehmen. Wenn für den Tod Ihres Kindes eindeutige Ursachen festgestellt werden, kann dies möglicherweise von quälenden Fragen oder unnötigen Selbstvorwürfen befreien. Der Ausschluss innerer Fehlbildungen und Erbkrankheiten, kann Ihnen vielleicht bei der künftigen Familienplanung eine Entscheidung erleichtern.

Die Studie knüpft an die gerichtliche Obduktion Ihres verstorbenen Kindes an. Im Rahmen dieser Studie soll, sobald die zuständige Staatsanwaltschaft ebenfalls ihr Einverständnis erklärt, die Todesursache noch genauer untersucht werden. Zu diesem Zweck bitten wir Sie um Zustimmung zu folgendem Vorgehen:

I. Gewebeuntersuchungen

1. Bei der gerichtlichen Obduktion Ihres verstorbenen Kindes sind Teile oder Gewebeproben von allen inneren Organen, auch Teile des Gehirns und des Herzens sowie Körperflüssigkeiten und Abstriche zurückbehalten worden. Diese Teile sollen nun weiter untersucht werden. Dabei werden die bei der Obduktion getroffenen Feststellungen in diese Untersuchungen einbezogen und ausgewertet.

2. Die bei diesen Untersuchungen angefertigten mikroskopischen Präparate und – unter Umständen – auch Teile des Gehirns, der Lunge und des Herzens, werden zur weiteren Klärung der Todesursache auch in anderen Instituten untersucht und aufbewahrt, damit später eventuell notwendig werdende Nachuntersuchungen durchgeführt werden können.

Alle zuvor genannten Untersuchungen erfolgen ausschließlich zu dem Zweck, die Ursache und Risikofaktoren des plötzlichen Todes zu ermitteln. Alle Proben, mikroskopischen Präparate, Organteile und Zellkulturen werden pseudonymisiert. Das bedeutet, dass sie unter einer Code-Nummer ohne Namensangabe aufbewahrt und gegebenenfalls weiter untersucht werden. Alle Namens- und Adressenangaben werden von den Proben getrennt und die Namensliste spätestens 2 Jahre nach Abschluss der Studie vernichtet. Spätestens 10 Jahre nach Abschluss der Studie werden sämtliche mikroskopischen Präparate, Organteile und Zellkulturen eingeäschert.

II. Medizinische Unterlagen

Medizinische Angaben zu Ihrem verstorbenen Kind werden durch die Kinderklinik der Universität Magdeburg von dem betreuenden (Kinder-) Arzt und ggf. von Kinderklinik/en mittels eines Fragebogens erhoben. Für diese Zwecke bitten wir, dass Sie die betreffenden Ärzte von ihrer Schweigepflicht entbinden. Die Auswertungen erfolgen nur zu dem Zweck, die Ursachen und Risikofaktoren für den plötzlichen Kindestod zu ermitteln.

Auch diese Fragebögen und Unterlagen werden in der Studienzentrale mit Code-Nummern versehen und nur pseudonymisiert ausgewertet. Das bedeutet, wenn die ausgefüllten Fragebögen und Unterlagen angekommen ist und die Angaben zu Ihrem Kind vollständig zusammengeführt wurden, werden alle Namen und Adressen von den Fragebögen getrennt und die Namensliste spätestens 2 Jahre nach Abschluss der Studie vernichtet. Die in der Studienzentrale aufbewahrten Fragebogen und Unterlagen werden spätestens 10 Jahre nach Abschluss der Studie vernichtet.

III. Fragebogen

Im Auftrage der Studienleitung wird Ihnen ein Fragebogen zugesendet, der Fragen über die Lebensumstände und die Entwicklung Ihres Kindes sowie zu durchgeführten Behandlun-

gen und Impfungen enthält. Alle Ihre Angaben bei dieser Befragung unterliegen der Schweigepflicht. Sie werden nur in pseudonymisierter Form, d. h. mit Code-Nummer, ohne Namensangabe durch die beteiligten Studienzentren wissenschaftlich ausgewertet. Alle Namens- und Adressenangaben werden von den Fragebogen getrennt und die Namensliste spätestens 2 Jahre nach Abschluss der Studie vernichtet.

IV. Gespräche

Nach Abschluss der Untersuchungen an den Gewebeproben, d. h. in etwa einem Vierteljahr nach diesem Aufklärungsgespräch, wird sich, sofern Sie das wünschen, ein Arzt des untersuchenden rechtsmedizinischen Instituts oder eines Studienzentrums mit Ihnen in Verbindung setzen, um Sie über die Untersuchungsergebnisse in Bezug auf den Tod Ihres Kindes zu informieren und Ihnen eventuell weitere Fragen beantworten.

V. Datenschutz

Die Ethikkommission der Medizinischen Hochschule Hannover hat unsere wissenschaftliche Untersuchung genau geprüft und ist mit ihrer Durchführung einverstanden. Auch die Beauftragten für den Datenschutz haben unser Vorgehen überprüft, und wir haben deren datenschutzrechtliche Empfehlungen umgesetzt. Ihre Daten werden nur pseudonymisiert ausgewertet, so dass aus den Ergebnissen keinerlei Rückschlüsse auf Einzelpersonen mehr möglich sein werden. Soweit für diese Studie Pseudonymisierungen erfolgt sind, d. h. bei mikroskopischen Präparaten, Organteilen und Zellkulturen (oben I.) sowie medizinischen Unterlagen oder Fragebögen (oben II und III.), werden diese unter den Code-Nummern aufbewahrt und ausgewertet. Ein Bezug zum Namen des Kindes und der Eltern kann nur anhand von Zuordnungslisten erfolgen, die bei der Studienleitung im Robert Koch-Institut verschlossen aufbewahrt werden. Ein solches “Aufbrechen des Codes” kann nur auf Anweisung der Studienleitung durch die ärztlichen Mitarbeiter/innen der Studienzentrale erfolgen, wenn dies erforderlich ist, z. B. um Sie über das Untersuchungsergebnis bezüglich Ihres verstorbenen Kindes zu informieren. Spätestens zwei Jahre nach Abschluss der Studie wird das Robert-Koch Institut alle Namen und Adressen vernichten. Eine Weitergabe von pseudonymisierten Daten (ohne Namen und Adressen) kann auch im Rahmen von gesetzlichen Regelungen an die für die Zulassung von Arzneimitteln und Medizinprodukten zuständigen in- und ausländischen Behörden (z.B. das Paul-Ehrlich Institut) erfolgen.

VI. Freiwilligkeit

Die Teilnahme an dieser Studie ist freiwillig. Es steht Ihnen auch frei, nur zu Teilen der Studie Ihre Zustimmung zu geben oder einzelne Fragen des Fragebogens (oben III) nicht zu beantworten. Sie können Ihr Einverständnis zur Studienteilnahme selbstverständlich auch noch nach Untersuchungsbeginn bis zur Löschung Ihres Namens und Ihrer Adresse jederzeit und ohne Angaben von Gründen ganz oder teilweise widerrufen. Ihr Ansprechpartner hierfür ist Priv.-Doz. Dr. med. Martin Schlaud, Fachgebiet 23 "Gesundheit von Kindern und Jugendlichen, Präventionskonzepte", Abteilung für Epidemiologie und Gesundheitsberichterstattung, Robert Koch-Institut, Seestraße 10, 13353 Berlin, Telefon 01888/754-3437, Telefax 01888/154-3555. Es werden dann die gespeicherten Informationen ganz oder teilweise gelöscht und nicht für die Studie ausgewertet. Je nach Umfang des Widerrufs werden die noch aufbewahrten mikroskopischen Präparate, Organteile oder Zellkulturen eingeäschert.

VI. Weitere Fragen
Bei weiteren Fragen wenden Sie sich bitte an das Institut für Rechtsmedizin der Universitätsklinik Essen-Duisburg, Hufelandstr. 55, 45122 Essen, Tel. 0201/723 3600.

Bitte erklären Sie in der beigefügten Einwilligungserklärung durch Ihre Unterschrift, dass Sie über die Untersuchung informiert worden sind und Sie damit einverstanden sind, dass Ihre Angaben im Fragebogen und aus den Obduktionsergebnissen durch die beteiligten wissenschaftlichen Einrichtungen Robert Koch-Institut, Kinderklinik der Universität Magdeburg (nur Fragebogendaten) und der Ludwig-Maximilians-Universität in München gespeichert und ausgewertet werden dürfen.

Wir wissen wohl, dass dieser Brief und Ihre Entscheidung für Sie nicht einfach ist. Dennoch bitten wir Sie sehr herzlich um Ihre Teilnahme an dieser Untersuchung, damit zukünftig solche Fälle hoffentlich verhindert werden können.

Prof. Dr. Reinhard Kurth
Präsident
Robert Koch-Institut

ROBERT KOCH INSTITUT

Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat

A2 Einverständniserklärung (für betroffene Eltern**)**
Zum Verbleib bei den Eltern

Hiermit erkläre ich,

Frau _____

Herr _____

Adresse: _____

_____

Telefon _____Handy-Nummer_____

dass ich als Sorgeberechtigte/r von

_____, geboren am _____
(Vor- und Familienname des Kindes) Tag Monat Jahr

schriftlich über die ‚Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat' informiert und aufgeklärt wurde. Ich/wir haben auch das mir/uns übergebene Aufklärungsformular zu dieser Studie in Ruhe gelesen. Den Inhalt der schriftlichen Aufklärung habe/n ich/wir verstanden und habe/n keine weiteren Fragen mehr.

Mit meiner Unterschrift willige ich ein, dass
(Nichtzutreffendes bitte streichen)

- eine Obduktion im schriftlich erläuterten Umfang durchgeführt wird und die Organe dabei untersucht werden,

- bei der Obduktion Teile des Herzens und des Gehirns, Gewebeproben von den übrigen Organen sowie Körperflüssigkeiten und Abstriche zur weiteren Klärung der Todesursache entnommen und untersucht werden,

- die bei diesen Weiteruntersuchungen angefertigten mikroskopischen Präparate und unter Umständen auch Teile des Gehirns und des Herzens an andere Institute gesandt und aufbewahrt werden, damit später eventuell Nachuntersuchungen durch-

geführt werden können. Diese Präparate werden bis maximal 10 Jahre nach Beendigung der Studie, d.h. bis zum Jahr 2018 aufbewahrt und dann eingeäschert.

- medizinische Angaben und Unterlagen meines Kindes von dem Kinderarzt und der/den Kinderklinik/en angefordert und ausgewertet werden. Zu diesem Zweck entbinde ich den behandelnden Kinder- oder Hausarzt meines/unseres Kindes:

Frau/Herrn _____

Adresse: _____

_____

Telefon _____

sowie andere Ärzte und Einrichtungen, deren Namen wir im Fragebogen angeben, von der Schweigepflicht und gestatten die Anforderung von Unterlagen zur medizinischen Vorgeschichte meines/unseres Kindes von diesen Ärzten und Krankenhäusern.

- mir Mitarbeiter der Kinderklinik der Universität Magdeburg einen Fragebogen zusenden
- sich ein Arzt des untersuchenden rechtsmedizinischen Instituts oder eines Studienzentrums mit mir in Verbindung setzt, um mich über die Untersuchungsergebnisse in Bezug auf den Tod meines Kindes zu informieren.

Die medizinischen Unterlagen und Obduktionsbefunde werden ebenso wie die Fragebögen nur mit Codenummer versehen in der Studienzentrale im Robert-Koch-Institut aufbewahrt und spätestens 10 Jahre nach Beendigung der Studie vernichtet. Ein Bezug zum Namen des Kindes und der Eltern kann nur anhand von Zuordnungslisten erfolgen, die bei der Studienleitung im Robert Koch-Institut verschlossen aufbewahrt werden. Ein solches "Aufbrechen des Codes" kann nur auf Anweisung der Studienleitung durch die ärztlichen Mitarbeiter/innen der Studienzentrale erfolgen, wenn dies erforderlich ist, z. B. um Sie über das Untersuchungsergebnis bezüglich Ihres verstorbenen Kindes zu informieren. Spätestens zwei Jahre nach Abschluss der Studie wird das Robert-Koch Institut alle Namen und Adressen vernichten. Eine Weitergabe von pseudonymisierten Daten kann auch im Rahmen von gesetzlichen Regelungen an die für die Zulassung von Arzneimitteln und Medizinprodukten zuständigen in- und ausländischen Behörden (z.B. das Paul-Ehrlich Institut) erfolgen. **Ich bin darüber informiert, dass ich das Einverständnis bis zur Löschung meines Namens und meiner Adresse jederzeit, auch zu einzelnen Punkten, ohne Angabe von Gründen Widerrufen kann.** Die zu mir und meinem verstorbenen Kind gespeicherten Informationen werden in diesem Fall gelöscht und nicht für die Studie ausgewertet.

_____, den _____
(Ort) (Datum)

_____
Unterschrift/en Sorgeberechtigte/r

ROBERT KOCH INSTITUT

Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat

A2 Einverständniserklärung (für betroffene Eltern**)**
Zum Verbleib im Studienzentrum

Hiermit erkläre ich,

Frau _____

Herr _____

Adresse: _____

_____

Telefon _____Handy-Nummer_____

dass ich als Sorgeberechtigte/r von

_____, geboren am _____
(Vor- und Familienname des Kindes) Tag Monat Jahr

schriftlich über die ‚Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat' informiert und aufgeklärt wurde. Ich/wir haben auch das mir/uns übergebene Aufklärungsformular zu dieser Studie in Ruhe gelesen. Den Inhalt der schriftlichen Aufklärung habe/n ich/wir verstanden und habe/n keine weiteren Fragen mehr.

Mit meiner Unterschrift willige ich ein, dass
(Nichtzutreffendes bitte streichen)

- eine Obduktion im schriftlich erläuterten Umfang durchgeführt wird und die Organe dabei untersucht werden,

- bei der Obduktion Teile des Herzens und des Gehirns, Gewebeproben von den übrigen Organen sowie Körperflüssigkeiten und Abstriche zur weiteren Klärung der Todesursache entnommen und untersucht werden,

- die bei diesen Weiteruntersuchungen angefertigten mikroskopischen Präparate und unter Umständen auch Teile des Gehirns und des Herzens an andere Institute gesandt und aufbewahrt werden, damit später eventuell Nachuntersuchungen durchgeführt werden können. Diese Präparate werden bis maximal 10 Jahre nach Beendigung der Studie, d.h. bis zum Jahr 2018 aufbewahrt und dann eingeäschert.

- medizinische Angaben und Unterlagen meines Kindes von dem Kinderarzt und der/den Kinderklinik/en angefordert und ausgewertet werden. Zu diesem Zweck entbinde ich den behandelnden Kinder- oder Hausarzt meines/unseres Kindes:

Frau/Herrn _____

Adresse: _____

_____

Telefon _____

sowie andere Ärzte und Einrichtungen, deren Namen wir im Fragebogen angeben, von der Schweigepflicht und gestatten die Anforderung von Unterlagen zur medizinischen Vorgeschichte meines/unseres Kindes von diesen Ärzten und Krankenhäusern.

- mir Mitarbeiter der Kinderklinik der Universität Magdeburg einen Fragebogen zusenden
- sich ein Arzt des untersuchenden rechtsmedizinischen Instituts oder eines Studienzentrums mit mir in Verbindung setzt, um mich über die Untersuchungsergebnisse in Bezug auf den Tod meines Kindes zu informieren.

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_____, den _____
(Ort) (Datum)

_____
Unterschrift/en Sorgeberechtigte/r

Accompanying letter with the physician questionnaire

ROBERT KOCH INSTITUT

Sehr geehrte Frau Kollegin,
sehr geehrter Herr Kollege,

mit diesem Brief möchten wir Sie bitten, uns bei einer wissenschaftlichen Untersuchung zur Erfassung der Todesursachen im ersten und zweiten Lebensjahr zu unterstützen.
Gegenwärtig versterben jährlich etwa 1500 Kinder im ersten und zweiten Lebensjahr nach Vollendung des ersten Lebensmonats in Deutschland trotz moderner medizinischer Diagnostik- und Behandlungsmöglichkeiten. Neben den bekannten Todesursachen wie angeborene Fehlbildungen des Herzens oder anderer lebenswichtiger Organe, Krebserkrankungen, Unfälle und schwere Infektionen sind einige Todesfälle bisher ätiologisch nur unzureichend oder nicht zu klären.

Einige dieser Todesfälle haben sich in auffälliger zeitlicher Nähe zu Impfungen ereignet. Dies führt dazu, dass eine Verunsicherung der Bevölkerung hervorgerufen wird und medizinische Maßnahmen wie Impfungen in Frage gestellt werden. Eine Aussage darüber, ob der beobachtete zeitliche Zusammenhang zufällig ist oder tatsächlich eine überzufällige Häufung dieser Todesfälle in engem zeitlichen Zusammenhang nach bestimmten Impfungen auftritt, kann nur geklärt werden, wenn alle Todesfälle im Rahmen einer epidemiologischen Studie standardisiert erfasst und untersucht werden. Dabei ist die Erhebung von zuverlässigen und sehr detaillierten Daten über Vorerkrankungen, medikamentöse Therapien und Impfungen von herausragender Bedeutung. Hier sind wir auf Ihre Mithilfe angewiesen und bitten Sie sehr um Ihr Engagement! Als Entschädigung für Ihren Aufwand können wir Ihnen den Betrag von 30 Euro anbieten. Dafür geben Sie bitte auf der letzten Seite des Fragebogens Ihre Bankverbindung an.

Familie ..... hat Sie als Arzt des Vertrauens genannt und von der Schweigepflicht für das von Ihnen behandelte Kind ....., geb. ..... entbunden. Beiliegend eine Kopie der Schweigepflichtentbindung.

Für die Erfassung der notwendigen Daten haben wir einen Fragebogen beigelegt, der sich wesentlich an den dokumentierten Impfungen und anamnestischen Angaben orientiert. Falls Ihnen weitere ärztliche Befunde vorliegen, wären wir für diese zusätzlichen Informationen sehr dankbar.

Diese Studie wird durchgeführt vom **Robert Koch-Institut** als zentraler Forschungseinrichtung des Bundesministeriums für Gesundheit und soziale

Sicherung auf dem Gebiet der Krankheitskontrolle und –prävention in Kooperation mit

- der Klinik für Allgemeine Pädiatrie und Neonatologie der Universität Magdeburg,
- dem Institut für Soziale Pädiatrie und Jugendmedizin der Ludwig-Maximilians-Universität in München.

Die Ethikkommission der Medizinischen Hochschule Hannover (MHH) hat der Durchführung der Untersuchung zugestimmt. Die Beauftragten des Datenschutzes haben unser Vorgehen überprüft und wir haben die Empfehlungen der Beauftragten für Datenschutz umgesetzt. Ihre Angaben werden pseudonymisiert ausgewertet, d.h., wenn die von Ihnen und den Eltern des Kindes ausgefüllten Fragebögen bei uns angekommen ist und wir die Angaben zu dem verstorbenen Kind vollständig zusammengeführt haben, werden wir Namen und Adresse von den Daten trennen, gesichert verwahren und spätestens nach zwei Jahren vernichten. Es kann dann später weder ein Bezug zu dem verstorbenen Kind noch zu Ihnen als behandelndem Arzt hergestellt werden. Wir bitten Sie auch aus Gründen des Datenschutzes die erste Seite des Fragebogens, die den Namen des Kindes enthält, vor der Rücksendung abzutrennen. Ihre Teilnahme ist freiwillig, bei Nichtausfüllen oder unvollständigem Ausfüllen entstehen Ihnen keine Nachteile.

Gerne stehen wir Ihnen für weitere Fragen zur Verfügung (Klinik für Allgemeine Pädiatrie und Neonatologie: PD Dr. Klaus Mohnike, Emanuel-Larisch-Weg 17 - 19 , 39112 Magdeburg, Tel.: 03 91/67-1 71 01).

Wir bedanken uns bei Ihnen und verbleiben
Mit freundlichen Grüßen

Prof. Dr. Reinhard Kurth
Präsident des Robert Koch-Instituts

Data protection issues

Darstellung der Maßnahmen zur Gewährleistung des Datenschutzes ‚Studie über Todesfälle bei Kindern im 2. – 24. Lebensmonat' TOKEN

Epidemiologischer Studienteil

1. Initial erfolgt für jeden Todesfall im 2.-24. Lebensmonat die Übermittlung aller leichenschauärztlichen Angaben sowie von Geburts- und Todesdatum durch das öffentliche Gesundheitsamt an die Studienleitung im Robert-Koch-Institut.

    a. Zu diesem Zeitpunkt sind die personenidentifizierenden Angaben (Name, Anschrift) auf der Kopie des Totenscheins geschwärzt und eine laufende Nummer durch das jeweilige Gesundheitsamt vergeben, die eine eindeutige Zuordnung des Falls in der Kommunikation mit dem RKI ermöglicht. Erst nach Einholung des informierten Einverständnisses der Eltern durch das öffentliche Gesundheitsamt (bzw. den obduzierenden Rechtsmediziner) liegen dem RKI die personenidentifizierenden Daten vor.

2. Eine laufende Fallnummer wird durch das RKI vergeben.

3. Das RKI sendet eine Kopie des informierten Einverständnisses und der Erklärung über die Entbindung von der ärztlichen Schweigepflicht an die Studiengruppe in Magdeburg (MD).

4. Das RKI führt eine Liste, auf der die Fallnummern den Namen der Probanden zugeordnet werden. Diese Zuordnungsliste wird fortlaufend aktualisiert und vom RKI in einem abgeschlossenen, gesicherten Ort (Stahlschrank nach DIN-Norm) hinterlegt. Alle zur Dateneingabe vorgesehenen Dokumente tragen nur noch die nicht sprechende Fallnummer. Von diesem Zeitpunkt an ist in der Daten eingebenden und Daten auswertenden Stelle RKI die Pseudonymisierung vollzogen. Die Zuordnungslisten werden im Fall einer Rücknahme der Einverständniserklärung durch einzelne Eltern verwendet, um die Fallnummer zu ermitteln, so dass die Daten auf Wunsch der Eltern gelöscht werden können.

5. MD sendet den mit der Fallnummer versehenen Elternfragebogen an die Eltern. Die Eltern füllen ihn aus, senden ihn zusammen mit einer Kopie des Impfbuchs an Magdeburg zurück. Eine Schwärzung der personenidentifizierenden Angaben auf der Kopie des Impfbuchs und die alleinige Kennzeichnung mit der Fallnummer bereits durch die Eltern wird nicht für dienlich gehalten, da MD zu diesem Zeitpunkt ohnehin noch mit den persönlichen Angaben aus Fragebogen und informiertem Einverständnis arbeitet (zum Beispiel wird bei der elterlichen Angabe von zusätzlichen Ärzten auf der vom Elternfragebogen abzutrennenden Seite 17/18 diesen Ärzten mit Hinweis auf den Namen und den Todestag des Kindes ebenfalls ein Arztfragebogen zugesendet). Magdeburg führt erste Qualitätskontrollen durch (Vollständigkeit, Lesbarkeit, medizinische Plausibilität), schwärzt alle personenidentifizierende Angaben auf der Kopie des Impfbuchs, versieht diese mit der Fallnummer und sendet dann alle Unterlagen an das RKI zur Dateneingabe und Auswertung (vorher: Kopie). Nach Bestätigung des Eingangs der Unterlagen beim RKI vernichtet Magdeburg die Kopie des informierten Einverständnisses und bewahrt nur noch die Kopie des mit der Fallnummer versehenen Fragebogens auf. Diese Kopie wird nach Eingabe der Daten in die Datenbank (RKI) ebenfalls vernichtet.

6. MD sendet einen mit der Fallnummer versehenen Arztfragebogen an die Ärzte. Die vom Arzt benötigten personenidentifzierenden Angaben zum Kind sind auf dem (abzutrennenden) Deckblatt aufgeführt. Die Ärzte senden den Fragebogen an MD zurück, nachdem sie das Deckblatt entfernt und zu ihren Unterlagen genommen haben.

MD trennt den Abschnitt mit den Angaben zur Kontoverbindung vom Fragebogen und sendet diesen mit getrennter Post an das RKI, so dass über diese Angaben kein Bezug zwischen dem Arzt und dem Todesfall hergestellt werden kann. Magdeburg führt erste Qualitätskontrollen durch (Vollständigkeit, Lesbarkeit) und sendet dann alle Unterlagen ans RKI zur Dateneingabe und Auswertung (vorher: Kopie). Über die Kontoinformationen kann später lediglich nachvollzogen werden, welche Ärzte überhaupt an der Studie teilgenommen haben.

7. Das RKI gibt die pseudomymisierten Daten ein und wertet sie aus.
8. Nach vollständiger Zusammenführung und Eingabe der Daten, spätestens zwei Jahre nach Abschluss der Fallerfassungsphase werden alle personenidentifizierenden Daten (Einverständniserklärung und Zuordnungslisten) definitiv vernichtet. Die pseudonymisierten Dokumente (Fragebögen etc.) und Daten werden frühestens 10 Jahre nach Abschluss der Studie vernichtet.

Rechtsmedizinischer Studienteil

1. Initial erfolgt die Übermittlung aller leichenschauärztlichen Angaben, Name. Adresse, Geburts- und Todesdatum sowie der internen Autopsienummer zusammen mit einer Kopie des informierten Einverständnisses durch die obduzierenden Rechtsmedizinischen Institute an die Studienleitung im Robert-Koch-Institut.
2. weiter wie unter 2. – 8. des epidemiologischen Studienteils
3. parallel zu Schritt drei informiert das RKI die LMU über die vergebende Fallnummer und die dazugehörenden internen Autopsienummern.
4. LMU sammelt Daten von Obduktionen und Zusatzuntersuchungen unter Fallnummern

Ablaufschema

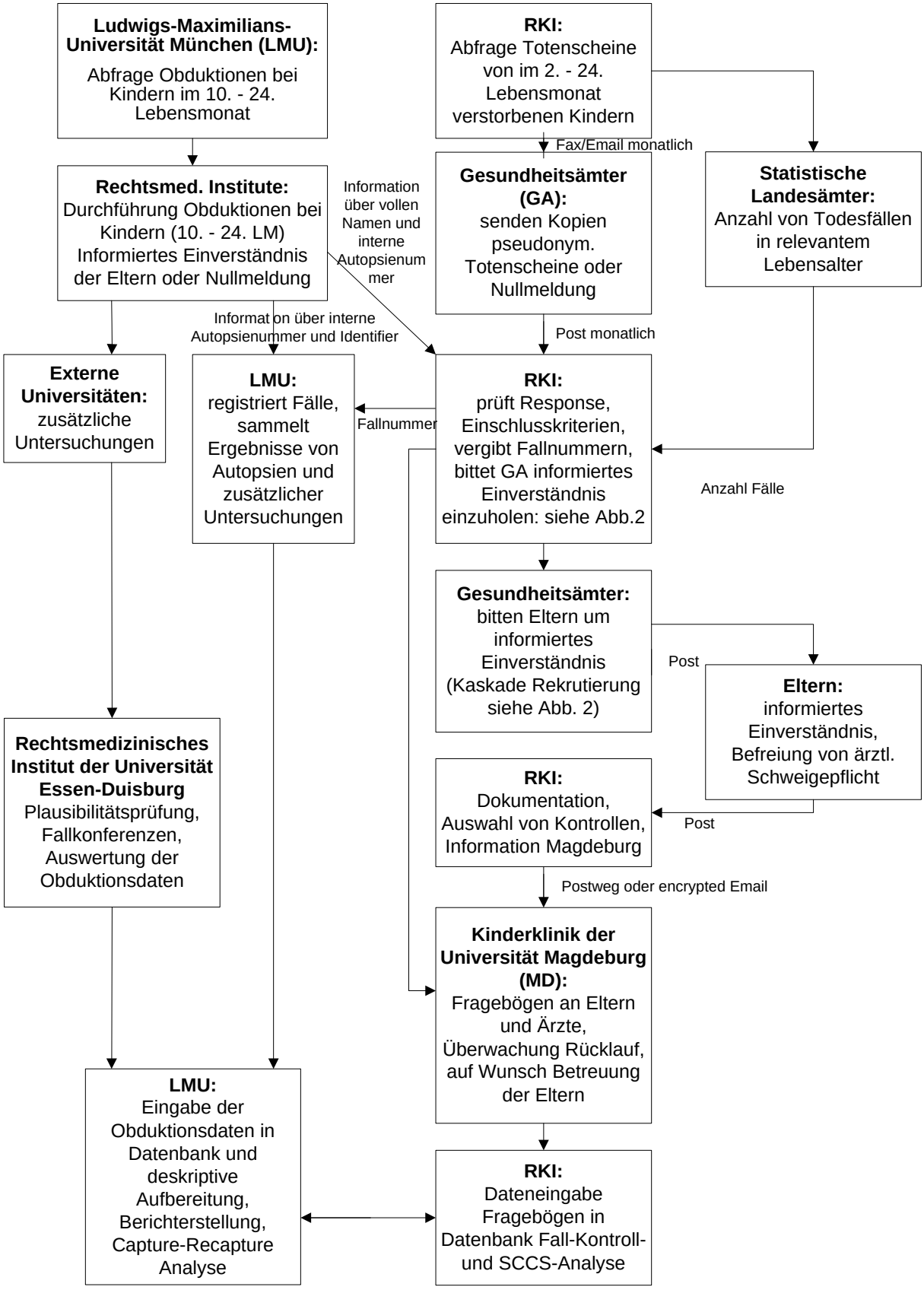

Abbildung 1: Ablaufdiagramm

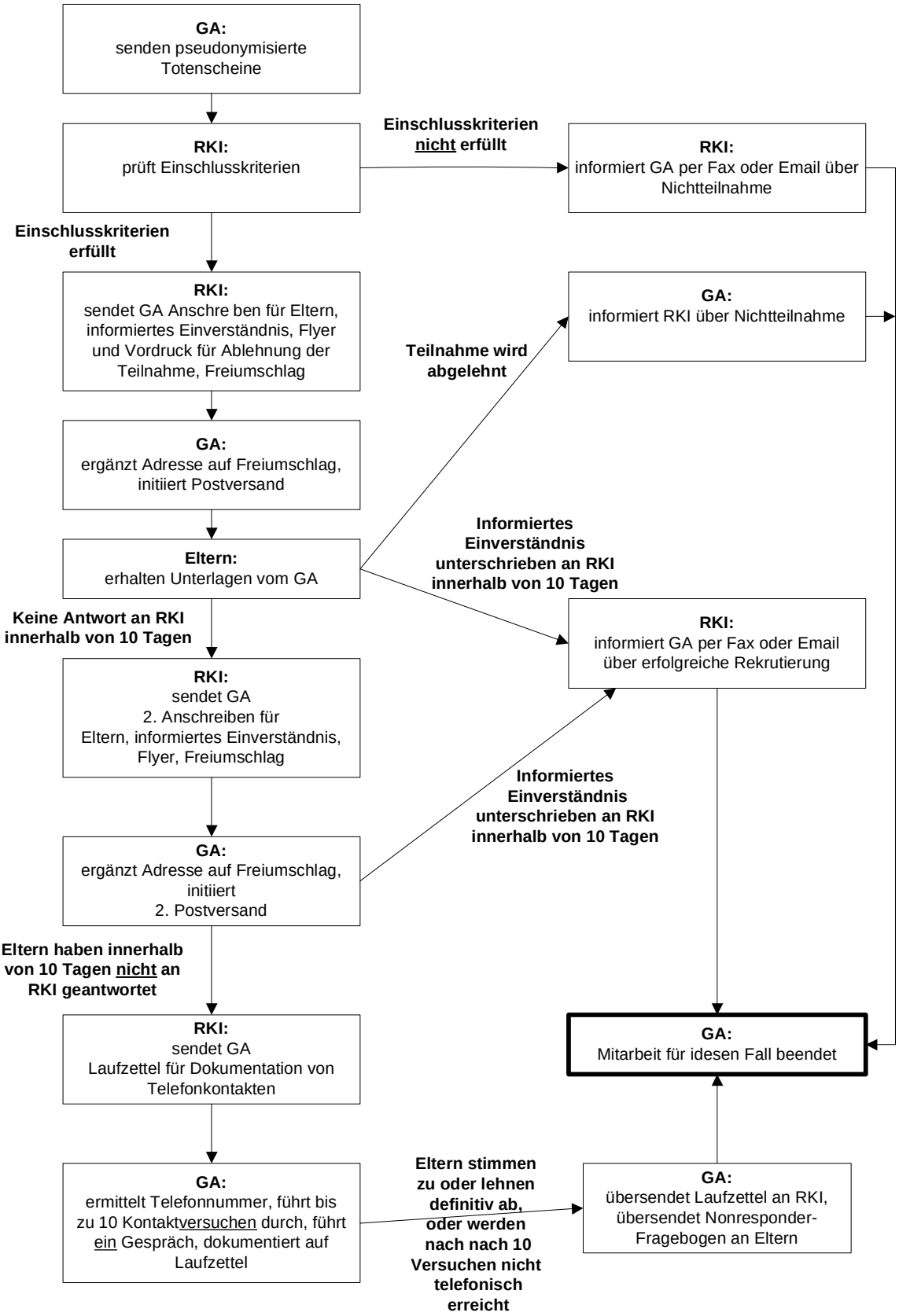

Abbildung 2: Maßnahmen zur Teilnahmegewinnung

Approval of the federal data protection officer

Der
Bundesbeauftragte
für den Datenschutz

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Robert Koch Institut
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BEARBEITET VON Walter
NTERNET www.datenschutz.bund.de

DATUM Bonn, 24.03.2005

GESCHÄFTSZ. **IV-401/008#0008**

BETREFF **Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat**
BEZUG Ihr Schreiben vom 23.02.05, AZ: FG23/Sd/TOKEN

Nach Durchsicht der mir zugesandten Unterlagen bestehen aus meiner Sicht keine grundsätzlichen Bedenken gegen die Durchführung der geplanten Studie. Die Einzelheiten der Durchführung auf Lä n-derebene müssen Sie allerdings mit den zuständ igen Landesbeauftragten für Datenschutz abstimmen. Aus datenschutzrechtlichen Gründen ist darauf zu achten, dass das von Ihnen geschilderte - und von mir bereits mehrmals akzeptierte - Pseudonymisierungsverfahren strikt eingehalten wird und die daran beteiligten Mitarbeiter über die Konsequenzen von Verstößen informiert we rden.

Darüber hinaus sollte Sie in den Aufklärungsunterlagen und den Einwilligungserklärungen die hier unzutreffenden Bezeichnungen "anonymisiert" usw. durch "pseudonymisiert" ersetzen.
Zusätzlich ist in diesen Papieren kurz die Wirkung des Widerrufs der Einwilligung au fzunehmen.

Im Auftrag
gez.
Walter

Approval of the ethics committee

MEDIZINISCHE HOCHSCHULE HANNOVER
Ethik-Kommission

MHH – Ethik-Kommission - 30623 Hannover

Frau
Dr. Christina Poethko-Müller
Robert Koch-Institut
Abt. für Epidemiologie und
Gesundheitsberichterstattung
Postfach 65 02 61
13302 Berlin

E-Mail	Mein Zeichen	Telefon	Fax	Hannover
Landowski.Rita@MH-Hannover.de	Trö/L	0511/532-3443	0511/532-5423	21.03.05

Nr. 3879 Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat

Sehr geehrte Frau Kollegin Poethko-Müller,

die Mitglieder der Ethikkommission haben auf ihrer Sitzung am 16.03.05 über o.g. Antrag beraten. Es bestehen keine Bedenken gegenüber der Durchführung der Studie.

Bei Abschluss der Studie bittet die Kommission um Nachricht und einen Bericht, im Falle von Publikationen um einen Sonderdruck.
Eine Genehmigung des Forschungsvorhabens erfolgt vorbehaltlich der im Protokoll erläuterten Erkenntnislage. Falls die Studie eine längere Anlaufzeit benötigt und sich die Erkenntnislage in der Zwischenzeit geändert hat, ist eine Wiedervorlage vor Beginn bei der Ethikkommission erforderlich.
Die Ethikkommission bestätigt ferner, dass ihre Zusammensetzung und Arbeitsweise den gesetzlichen Vorschriften bzw. den für die Arbeitsweise der Ethikkommission relevanten ICH-GCP-Empfehlungen zur Nutzen-Risiko-Abwägung entspricht.
Die an der Beratung des o.g. Antrages beteiligten Mitglieder der Ethikkommission sind unten aufgeführt.

Mit den besten Grüßen bin ich
Ihr

Prof. Dr. H.D. Tröger
Vorsitzender der Ethik-Kommission

Folgende Mitglieder haben an der Beratung des o.g. Antrages am 16.03.05 mitgewirkt:

Prof. Dr. Alfred Berger, em. Leiter der PHW Oststadt-Krankenhaus
Prof. Dr. Dr. h.c. E. Deutsch, Abt. für Arzt- und Arzneimittelrecht, Universität Göttingen
Prof. Dr. J. Frölich, em. Leiter der Abt. Klin. Pharmakologie der MHH
Dr. J. Graubner, Arzt f. Allgemeinmedizin
Prof. Dr. H. Hecker, Komm. Leiter der Abt. Biometrie der MHH
Dr. J.L. Hülsemann, Rheumatologie der MHH
Prof. Dr. Christoph Klein, Abt. Päd. Onkologie der MHH
Frau Prof. Dr. B. Lohff, Leiterin der Abt. Geschichte, Ethik und Philosophie der Medizin der MHH
Prof. Dr. H. D. Tröger (Vorsitzender), Leiter der Abt. Rechtsmedizin der MHH

Der Bundesbeauftragte
für den Datenschutz und
die Informationsfreiheit

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DATUM Bonn, 12.03.2007
GESCHÄFTSZ. IV-401/008#0008

Robert Koch - Institut	Präs
	1462 i.V. 22/3
Eing. 21. MRZ 2007 FF	FG23
Aktenzeichen: 3904-00	
Tagebuch-Nr.: 537	

BETREFF **Studie über Todesfälle bei Kindern im 2. bis 24. Lebensmonat**

Sehr geehrte Frau Dr. Poethko-Müller,

nach Durchsicht der mir zugesandten Änderungen im Studienablauf bestehen aus meiner Sicht auch weiterhin keine Bedenken gegen die Durchführung der geplanten Studie. Da die Änderungen auch die Durchführung auf Länderebene betreffen, sollten Sie sich gegebenenfalls mit den zuständigen Landesbeauftragten für Datenschutz abstimmen.

Ich wünsche Ihnen viel Erfolg bei der Durchführung der Studie.

Mit freundlichen Grüßen
Im Auftrag

Walter

ZUSTELL- UND LIEFERANSCHRIFT Husarenstraße 30, 53117 Bonn
VERKEHRSANBINDUNG Straßenbahn 61, Finanzministerium

Parental questionnaire
- control group -

ROBERT KOCH INSTITUT

Studie über Risikofaktoren bei Kindern im 2. bis 24. Lebensmonat

Elternfragebogen

Liebe Eltern,

Sie haben sich bereit erklärt, an unserer Untersuchung über Risikofaktoren bei Säuglingen und Kleinkindern teilzunehmen.

Dafür danken wir Ihnen sehr. Diese Untersuchung soll Erkenntnisse über Ursachen von frühen Todesfällen gewinnen und dadurch helfen, zukünftig solche Fälle zu verhindern.

Wir befragen Sie zunächst kurz zu Ihren Lebensumständen und möchten auch wissen, wer diesen Bogen ausfüllt. Es werden dann Fragen zu Schwangerschaft, Geburt, medizinischen Behandlungen und Impfungen Ihres Kindes gestellt. Anschließend bitten wir Sie um einige Angaben zu Ihren Lebensgewohnheiten und Lebensbedingungen.

- Bitte beantworten Sie alle Fragen vollständig! Sie können zwar Fragen auslassen, die Ihnen unangenehm sind, allerdings würde das die wissenschaftlichen Ergebnisse dieser Untersuchung sehr beeinträchtigen.
- Kreuzen Sie bitte bei jeder Frage an, was auf Sie oder Ihr Kind am besten zutrifft.
- **Bitte senden Sie uns dann im bereits frankierten Briefumschlag den Fragebogen zusammen mit einer <u>Kopie des Impfbuchs</u> Ihres Kindes zu.**

Die Adresse für die portofreie Rücksendung und unsere Kontaktadresse bei Fragen und Unklarheiten lautet:

Robert Koch – Institut
Fachgebiet 23
- Gesundheit von Kindern und Jugendlichen, Präventionskonzepte -
Dr. med. Christina Poethko-Müller
Seestraße 10
13353 Berlin
Tel.. 030 18754 3193 (Ortstarif)

Angaben der Eltern

1. Bitte tragen Sie das heutige Datum ein: ☐☐.☐☐.☐☐☐☐

(TT.MM.JJJJ, z. B. 28.09.2007)

2. Wer beantwortet diesen Fragebogen?

Leibliche Mutter . . . . . ☐

Leiblicher Vater . . . . . ☐

Mutter und Vater . . . . . ☐

Großeltern, andere Verwandte . . . . . ☐

Pflegeeltern/Adoptiveltern . . . . . ☐

Betreuer . . . . . ☐

3. Wie alt sind Sie?
Bitte für beide Elternteile angeben!

Leibliche Mutter	**Leiblicher Vater**
☐☐ Jahre	☐☐ Jahre

4. In welchem Land sind Sie geboren?
Bitte für beide Elternteile angeben!

Leibliche Mutter

In Deutschland ☐ In einem anderen Land: ☐

In welchem anderen Land? _____

Weiß nicht ☐

Leiblicher Vater

In Deutschland ☐ In einem anderen Land: ☐

In welchem anderen Land? _____

Weiß nicht ☐

Angaben der Eltern

5. Welchen Familienstand haben Sie?
Bitte für beide Elternteile angeben!

	Leibliche Mutter	Leiblicher Vater
Alleinlebend	☐	☐
Zusammenlebend in häuslicher Partnerschaft oder Ehe	☐	☐
Weiß nicht	☐	☐

Angaben zu den Lebensumständen des Kindes

6. Wann ist Ihr Kind geboren? ☐☐.☐☐.☐☐☐☐

(TT.MM.JJJJ, z. B. 28.03.2006)

7. Welches Geschlecht hat Ihr Kind?

männlich ☐ weiblich ☐

8. Bei wem lebt Ihr Kind hauptsächlich? (Hier bitte nur **ein** Kreuz machen!)

Das Kind lebt hauptsächlich bei

- leiblichen Eltern ☐
- Mutter und ihrem Partner ☐
- Vater und seiner Partnerin ☐
- alleinlebender Mutter ☐
- alleinlebendem Vater ☐
- Großeltern oder anderen Verwandten ☐
- Pflegeeltern/Adoptiveltern ☐
- In einem Heim ☐
- Weiß nicht ☐

Angaben zu den Lebensumständen des Kindes

9. Mit wie vielen älteren und jüngeren Geschwistern lebt Ihr Kind zusammen?
Gemeint sind in diesem Fall auch Halbgeschwister und angeheiratete Geschwister.

Mein Kind lebt mit keinen Geschwistern zusammen . . . . . ☐

Mein Kind lebt mit einem (1) Geschwisterkind zusammen . . . . . ☐

Mein Kind lebt mit zwei (2) Geschwisterkindern zusammen . . . . . ☐

Mein Kind lebt mit drei (3) Geschwisterkindern zusammen . . . . . ☐

Mein Kind lebt mit mehr als drei Geschwisterkindern zusammen . . . . . ☐

Weiß nicht . . . . . ☐

10. Wie groß ist die Wohnung, in der Ihr Kind hauptsächlich lebt?

☐☐☐ m² Weiß nicht ☐

11. Wie viele Personen leben außer Ihrem Kind in dieser Wohnung?

☐☐ Personen Weiß nicht ☐

12. Wird oder wurde Ihr Kind gestillt?

Nein . . . . . ☐

Wenn ihr Kind nicht gestillt wurde, weiter mit Frage 14.

Ja, es wurde bis zum ☐☐. Lebensmonat gestillt ☐

Wird zurzeit noch gestillt . . . . . ☐

Weiß nicht . . . . . ☐

Angaben zu den Lebensumständen des Kindes

13. Wie lange wurde Ihr Kind ausschließlich gestillt?

Es wurde nie ausschließlich gestillt . . . . . ☐

Es wird zurzeit noch ausschließlich gestillt . . . . . ☐

Es wurde bis zum ☐☐. Lebensmonat ausschließlich gestillt ☐

Weiß nicht . . . . . ☐

14. Wird in der Gegenwart Ihres Kindes in der Wohnung geraucht?

Täglich . . . . . ☐

Mehrmals pro Woche . . . . . ☐

Einmal pro Woche . . . . . ☐

Seltener . . . . . ☐

Nie . . . . . ☐

Weiß nicht . . . . . ☐

Schwangerschaft und Geburt

Die folgenden Fragen zur Schwangerschaft richten sich an die Mutter des Kindes. Kann die Mutter den Frageboen nicht ausfüllen, so bitten wir die oder den Ausfüllende/n die Fragen so genau wie möglich zu beantworten.

15. War die Geburt Ihres Kindes eine Mehrlingsgeburt?

Ja . . . . . ☐

Nein . . . . . ☐

Weiß nicht . . . . . ☐

Schwangerschaft und Geburt

16. Wie viele (Lebend-) Geburten hatten Sie <u>vor</u> der Geburt des Kindes?

☐☐ Geburten Weiß nicht ☐

17. Haben Sie während der Schwangerschaft Ihres Kindes geraucht?

Ja, täglich über 10 Zigaretten . . . . . ☐

Ja, täglich bis zu 10 Zigaretten . . . . . ☐

Ja, gelegentlich . . . . . ☐

Nein, nie . . . . . ☐

Weiß nicht . . . . . ☐

18. Wenn Sie mehrere Kinder geboren haben, ist eines Ihrer Kinder im Alter unter 24 Monaten verstorben?

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, in welchem Lebensmonat ist das Kind verstorben?

Im ☐☐. Lebensmonat

Wenn ja, welches war die Todesursache?

Schwangerschaft und Geburt

19. In welcher Schwangerschaftswoche wurde Ihr Kind geboren?

☐☐ . Schwangerschaftswoche Weiß nicht ☐

Falls Sie sich daran nicht mehr erinnern können:

Mein Kind wurde

zu früh geboren . . . . . ☐
(mehr als 3 Wochen vor dem errechneten Geburtstermin)

termingerecht geboren . . . . . ☐
(bis zu 3 Wochen vor und bis zu 2 Wochen nach dem errechneten Geburtstermin)

zu spät geboren . . . . . ☐
(mehr als 2 Wochen nach dem errechneten Geburtstermin)

20. Wie schwer und wie groß war Ihr Kind bei der Geburt?

ca. ☐☐☐☐ Gramm schwer Weiß nicht ☐

ca. ☐☐☐ Zentimeter lang Weiß nicht ☐

Neugeborenenzeit

21. Sind bei Ihrem Kind in den ersten 4 Lebenswochen nach der Geburt Probleme aufgetreten?

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, welche? (Hier sind mehrere Antworten möglich.)

Schwierigkeiten bei der Atmung, Anpassungsstörungen . . . . . ☐

Infektion . . . . . ☐

Neugeborengelbsucht . . . . . ☐

Untergewicht, Frühgeburt . . . . . ☐

Sonstige . . . . . ☐

Verlegung in eine Kinderklinik . . . . . ☐

Wie lange lag es dort? ☐☐☐ Nächte

Krankheiten

22. Hat oder hatte Ihr Kind jemals folgende Krankheiten?

Angeborene Fehlbildungen

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, welche?

Andere angeborene Erkrankungen

z. B. Stoffwechsel-Störungen, hormonelle Störungen wie z. B. Schilddrüsen-unterfunktion, Blutkrankheiten

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, welche?

Körperliche oder geistige Entwicklungsstörungen

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, welche?

Herzerkrankungen

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, welche?

Krankheiten

Fortsetzung Frage 22:
Hat oder hatte Ihr Kind jemals folgende Krankheiten?

Atemwegserkrankungen
z.B. Asthma, obstruktive Bronchitis

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, welche?

Erkrankungen des Nervensystems
z. B. Bewegungsstörungen, Lähmungen

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, welche?

Anfallsleiden (Fallsucht, Epilepsie)

Ja ☐ Nein ☐ Weiß nicht ☐

Bösartige Tumorerkrankung
z. B. Hirntumor, Leukämie, Knochenkrebs, Neuroblastom

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, welche?

---

23. Ist oder war Ihr Kind ein so genanntes "Schreibaby", das vermehrt (d.h. über mehrere Wochen täglich oder fast täglich mehrere Stunden ohne erkenntlichen Grund) **geschrien hat und nicht oder kaum zu trösten war?**

Ja ☐ Nein ☐ Weiß nicht ☐

Krankheiten

24. Haben Sie Ihr Kind schon einmal scheinbar leblos aufgefunden (mit Atemstillstand, schlaffer Muskulatur, blasser oder bläulicher Hautfarbe und stark verlangsamtem Herzschlag "ALTE", von dem es sich erst nach heftigem Schütteln (Stimulation) oder Wiederbelebung erholte)**?**

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, wann?

☐☐.☐☐.☐☐☐☐ (Datum)

(TT.MM.JJJJ, z. B. 28.09.2005)

Wenn ja, ist Ihr Kind damals von einem Arzt oder in einem Krankenhaus nachuntersucht worden?

Ja ☐ Nein ☐ Weiß nicht ☐

Medizinische Behandlungen und Impfungen

25. Wurde Ihr Kind jemals wegen einer Verletzung beim Arzt oder in der Notaufnahme eines Krankenhauses behandelt?

Ja ☐ Nein ☐ Weiß nicht ☐

26. Wurde Ihr Kind in den letzten 4 Wochen vor dem %GENGEB <u>regelmäßig</u> mit Medikamenten behandelt?

Ja ☐ Nein ☐ Weiß nicht ☐

<u>Wenn ja</u>, mit welchen? (Bitte geben Sie möglichst auch die Dosierung an.)

Medizinische Behandlungen und Impfungen

! Bitte beantworten Sie die folgenden Fragen unbedingt so gut es geht. Bitte fügen Sie zusätzlich eine Kopie des Impfausweises bei.

27. Wurde Ihr Kind jemals geimpft?

Ja ☐ Nein ☐ Weiß nicht ☐

28. Hatten Sie Gründe, Ihrem Kind Impfungen nicht oder noch nicht geben zu lassen?

Ja ☐ Nein ☐

Wenn ja, welche Gründe hatten Sie?

Mein Kind ist noch zu jung . . . . . ☐

Mein Kind hat/hatte Erkrankungen, wegen derer die Impfung aufgeschoben/verhindert wurde . . . . . ☐

Angst vor Nebenwirkungen . . . . . ☐

Ich halte für mein Kind das Durchmachen der Krankheiten für besser als die entsprechende Impfung . . . . . ☐

Ich war über die Notwendigkeit der Impfung nicht informiert . . . . . ☐

Der Arzt hat von der Impfung abgeraten . . . . . ☐

Die Impfung wurde vergessen . . . . . ☐

Sonstiges:

Wenn Ihr Kind nie geimpft wurde, bitte weiter mit Frage 32.

Medizinische Behandlungen und Impfungen

Bitte nehmen Sie jetzt den **Impfausweis** Ihres Kindes zu Hand und übertragen Sie die Angaben zu den **letzten beiden Impfungen** vor dem **%GENGEB** aus dem Impfausweis in die Tabelle.

29. Wenn Ihr Kind je geimpft wurde, welches waren die letzte und vorletzte Impfung vor dem %GENGEB ?

Bitte übertragen Sie Handelsnamen und Chargennummern möglichst genau!

Datum	Handelsname und Chargen-nummer (Ch.-B.:) des Impfstoffes	Tetanus	Diphtherie	Pertussis	Haemophilus influenzae b (Hib)	Hepatitis B	Poliomyelitis	Pneumokokken	Masern	Mumps	Röteln	Varizellen	Meningokokken
__.__.____		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
__.__.____		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Medizinische Behandlungen und Impfungen

30. Bitte geben Sie möglichst genau das Datum und die Uhrzeit der letzten Impfung des Kindes vor dem %GENGEBU an:

Die letzte Impfung des Kindes vor dem %GENGEBU fand statt am

☐☐.☐☐.☐☐☐☐ (Datum)

(TT.MM.JJJJ, z. B. 28.09.2007)

um ☐☐.☐☐ Uhr (z.B. 09.15 Uhr)

Weiß nicht ☐

31. Hat Ihr Kind diese Impfung gut vertragen?

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn nein, welche Schwierigkeiten gab es?

Wurde im Zusammenhang mit der letzten Impfung ein Medikament verabreicht (z.B. ein fiebersenkendes Arzneimittel) wenn ja, welches?

---

32. War das Kind seit seiner Geburt in einer Klinik?

Ja ☐ Nein ☐ Weiß nicht ☐

Wenn ja, warum?

Schlafgewohnheiten

33. Bitte erinnern Sie sich, in welche Liegeposition Ihr Kind in den letzten vier Wochen vor dem %GENGEB vorwiegend zum Schlafen hingelegt wurde?

- Auf den Rücken . . . . . ☐
- Auf den Bauch, Gesicht nach unten . . . . . ☐
- Auf den Bauch, Gesicht zur Seite . . . . . ☐
- Auf die Seite . . . . . ☐
- Weiß nicht . . . . . ☐

34. Veränderte Ihr Kind in den letzten 4 Wochen vor dem %GENGEB selbstständig seine Schlafposition?

Ja ☐ Nein ☐ Weiß nicht ☐

35. Welche Schlafposition nahm es dann überwiegend selbstständig ein?

- Rückenlage . . . . . ☐
- Bauchlage, Gesicht nach unten . . . . . ☐
- Bauchlage, Gesicht zur Seite . . . . . ☐
- Seitenlage . . . . . ☐
- Wechselnd . . . . . ☐
- Weiß nicht . . . . . ☐

Schlafgewohnheiten

36. Wurde Ihr Kind während des Schlafens in den letzten 4 Wochen vor dem %GENGEB von außen gewärmt? (z.B. Heizdecke, Wärmestrahler, Wärmflasche)

Ja . . . . . ☐

Gelegentlich . . . . . ☐

Einmal . . . . . ☐

Nein . . . . . ☐

Weiß nicht . . . . . ☐

Wenn ja, wodurch wurde Ihr Kind gewärmt?

Wärmflasche . . . . . ☐

Elektrisches Heizkissen . . . . . ☐

Das Bett befand sich in unmittelbarer Nähe
einer eingeschalteten Heizung . . . . . ☐

Wärmestrahler . . . . . ☐

Andere Formen direkter Wärme . . . . . ☐

Wenn ja, welche?

Angaben zu den Eltern

Die folgenden Fragen betreffen die Beschreibung der Lebenssituation des Kindes. Mit der Rubrik "Mutter" und "Vater" sind jetzt auch diejenigen Personen gemeint, die möglicherweise für das Kind diese Funktion übernehmen, wie z.B. der Lebenspartner der Mutter (für "Vater") oder die Lebenspartnerin des Vaters (für "Mutter") oder sonstige Personen, falls das Kind nicht bei den leiblichen Eltern lebt.

37. Rauchen Sie zurzeit?
Bitte für beide Elternteile angeben!

	Mutter	Vater
Ja, täglich über 20 Zigaretten	☐	☐
Ja, täglich bis zu 20 Zigaretten	☐	☐
Ja, aber nicht täglich	☐	☐
Nein	☐	☐
Weiß nicht	☐	☐

38. Welchen Schulabschluss haben Sie? Nennen Sie bitte nur den höchsten Abschluss. Bitte für beide Elternteile angeben!

	Mutter	Vater
Hauptschulabschluss/Volksschulabschluss	☐	☐
Realschulabschluss (Mittlere Reife)	☐	☐
Abschluss Polytechnische Oberschule (POS, 10. Klasse)	☐	☐
Fachhochschulreife (Abschluss einer Fachoberschule)	☐	☐
Abitur (Gymnasium bzw. EOS)	☐	☐
Anderer Schulabschluss	☐	☐
Schule beendet ohne Schulabschluss	☐	☐
(Noch) keinen Schulabschluss	☐	☐
Weiß nicht	☐	☐

Angaben zu den Eltern

39. Haben Sie eine abgeschlossene Berufsausbildung? Wenn ja, welche?
Nennen Sie bitte nur den höchsten Abschluss. Bitte für beide Elternteile angeben!

	Mutter	Vater
Lehre (beruflich-betriebliche Ausbildung)	☐	☐
Berufsschule, Handelsschule (beruflich-schulische Ausbildung)	☐	☐
Fachschule (z. B. Meister-Technikerschule Berufs- oder Fachakademie)	☐	☐
Fachhochschule, Ingenieurschule	☐	☐
Universität, Hochschule	☐	☐
Anderer Ausbilungsabschluss	☐	☐
Kein beruflicher Abschluss (und auch nicht in der Ausbildung)	☐	☐
In beruflicher Ausbildung (Auszubildender, Student)	☐	☐
Weiß nicht	☐	☐

Lebensumstände der Eltern

40. Welche der folgenden Angaben trifft auf Sie zu?

	Mutter	Vater
Zurzeit...		
nicht berufstätig (Rentner, Student usw.)	☐	☐
arbeitslos	☐	☐
vorübergehende Freistellung (z.B. Erziehungsurlaub)	☐	☐
Teilzeit oder stundenweise berufstätig	☐	☐
voll berufstätig	☐	☐
Auszubildener (z. B. Lehrling)	☐	☐
Weiß nicht	☐	☐

Lebensumstände der Eltern

41. Wie hoch ist Ihr <u>durchschnittliches</u> monatliches Haushaltseinkommen, d.h. das Nettoeinkommen, das alle Haushaltsmitglieder zusammen nach Abzug von Steuern und Sozialabgaben haben?(Einschließlich Erziehungs- und Kindergeld)

Unter 500 € . . . . . ☐

500 bis unter 1000 € . . . . . ☐

1000 bis unter 2000 € . . . . . ☐

2000 bis unter 4000 € . . . . . ☐

4000 € und mehr . . . . . ☐

Weiß nicht . . . . . ☐

Vielen Dank, Sie haben unsere Fragen jetzt beantwortet. Gibt es vielleicht noch etwas, das Sie uns gerne mitteilen möchten?

Vielen Dank für die Beantwortung der Fragen!

Bitte prüfen Sie Ihre Angaben noch einmal auf

Vollständigkeit.

Bitte senden Sie dann den Fragebogen zusammen mit der

Kopie des Impfbuchs

im beiliegenden Freiumschlag portofrei an:

Robert Koch – Institut
Fachgebiet 23
- Gesundheit von Kindern und Jugendlichen, Präventionskonzepte -
Dr. med. Christina Poethko-Müller
Seestraße 10
13353 Berlin

Non-responder questionnaire
- control group -

ROBERT KOCH INSTITUT

Robert Koch-Institut | Seestraße 10 | 13353 Berlin

Kurzfragebogen-Studie über Risikofaktoren bei Kindern im 2. – 24. Lebensmonat

Unser Zeichen : >Fallnummer<

1. **Aus welchen Gründen möchten bzw. können Sie an der Studie nicht teilnehmen?** (Mehrfachantworten möglich)

   Nehme grundsätzlich nicht an Studien teil ..... ☐
   Sehe für mich keinen Nutzen ..... ☐
   Aus zeitlichen Gründen ..... ☐

   Sonstige Gründe, ... ☐

   und zwar (*bitte eintragen!*): _____

2. **Welches Geschlecht hat Ihr Kind?** Junge ... ☐ Mädchen ... ☐

3. **Bei wem lebt Ihr Kind hauptsächlich?** (Hier bitte nur ein Kreuz machen!)

   Leibliche Eltern ..... ☐
   Mutter und ihrem Partner ..... ☐
   Vater und seiner Partnerin ..... ☐
   Mutter ..... ☐
   Vater ..... ☐
   Großeltern oder anderen Verwandten . ☐
   Pflegeeltern/Adoptiveltern ..... ☐
   In einem Heim ..... ☐

4. **Wer beantwortet diesen Kurzfragebogen?**

   Mutter ..... ☐
   Vater ..... ☐
   Sonstige Person ... ☐
   Lebenspartner der Mutter .... ☐
   Lebenspartnerin des Vaters . ☐

5. **Wie alt sind Sie?** (Bitte für beide angeben)

   Mutter... ☐☐ (Jahre) **Vater**... ☐☐ (Jahre)

6. **Rauchen Sie zurzeit?** (Bitte für beide angeben)

   Mutter: Ja ... ☐ Nein ... ☐ **Vater:** Ja ... ☐ Nein ... ☐

7. **Wie viele Tage vor dem >*Referencedate*< wurde Ihr Kind das letzte Mal geimpft?**

☐☐ Tage wenn nicht bekannt oder länger her als 7 Tage : ☐☐ Wochen

8. Wogegen wurde Ihr Kind vor dem >*Referencedate*< das letzte Mal geimpft?

Mein Kind war noch nie geimpft worden	☐	
5-fach Impfung	☐	welches Impfpräparat?_____
6-fach Impfung	☐	welches Impfpräparat?_____
Masern, Mumps, Röteln	☐	welches Impfpräparat?_____
Windpocken	☐	welches Impfpräparat?_____
Sonstige Impfung	☐	

und zwar (*bitte eintragen!*):

_____

9. **Welche Staatsangehörigkeit haben Sie?**

Mutter: deutsch .... ☐ andere ... ☐ welche? _____

Vater: deutsch .... ☐ andere ... ☐ welche? _____

10. **Welchen Schulabschluss haben Sie?**
(Wenn Sie mehrere Abschlüsse haben, nennen Sie bitte nur den höchsten!)

	Mutter	**Vater**
Hauptschulabschluss / Volksschulabschluss	☐	☐
Realschulabschluss (Mittlere Reife)	☐	☐
Abschluss Polytechnische Oberschule (POS) 10.Klasse	☐	☐
Fachhochschulreife (Abschluss Fachoberschule)	☐	☐
Abitur (Gymnasium bzw. EOS)	☐	☐
Anderer Schulabschluss	☐	☐
Schule beendet ohne Schulabschluss	☐	☐
(Noch) keinen Schulabschluss	☐	☐

11. Welche der folgenden Angaben zur Berufstätigkeit trifft auf Sie zu?

	Mutter	**Vater**
Zurzeit nicht berufstätig (Rentner, Student usw.)	☐	☐
Arbeitslos	☐	☐
Vorübergehende Freistellung (z.B. Erziehungsurlaub)	☐	☐
Teilzeit oder stundenweise berufstätig	☐	☐
Voll berufstätig	☐	☐
Auszubildender (z.B. Lehrling)	☐	☐

Vielen Dank für Ihre Mitarbeit!

Study report

Pathological study part of the TOKEN study

TOKEN Study

Pathology study part

– Final report –

Institute of Legal Medicine, University Duisburg-Essen
Institute of Legal Medicine, Westfälische Wilhelms-University Münster
Institute for Transfusion Medicine, University Duisburg-Essen
Institute of Neuropathology, RWTH Aachen

Essen, 16 February 2010

Abbreviations

ILM	Institute of Legal Medicine
LMU	Ludwig Maximilians University
SIDS	Sudden Infant Death Syndrome
SUDI	Sudden Unexpected Death in Infancy
UCD	Underlying Cause of death

1 Introduction

SIDS (Sudden Infant Death Syndrome) is the most important cause of death in the first year of life (ICD-10 code: R95) after the neonatal period. Apart from SIDS, a number of infants die with the diagnosis of unknown causes and need to be put together in the same category of SUDI (Sudden Unexpected Death in Infancy). The number of SIDS infants has declined within the last two decades in Germany from 1283 infants (1.4 per 1000 live births) in the year 1990 to 228 infants (0.33 per 1000 live births) in the year 2007. However, the number of SUDI cases in the first and second year of life has not changed substantially over the last 10 years. Compared to other countries, the incidence of SIDS and SUDI is relatively high (Figure 1) in Germany.
The TOKEN study is a three-year (2005-2008) active epidemiological surveillance study. Its main objective is to investigate a potential temporal association between vaccination and sudden death in young children. There are two parts, the ‘epidemiological approach’ and the ‘pathological approach’. We hereby only refer to the pathological approach.

The pathology part of the TOKEN study was initiated in order to answer the following study question: Is there a common pathological mechanism for cases of sudden death following vaccination?

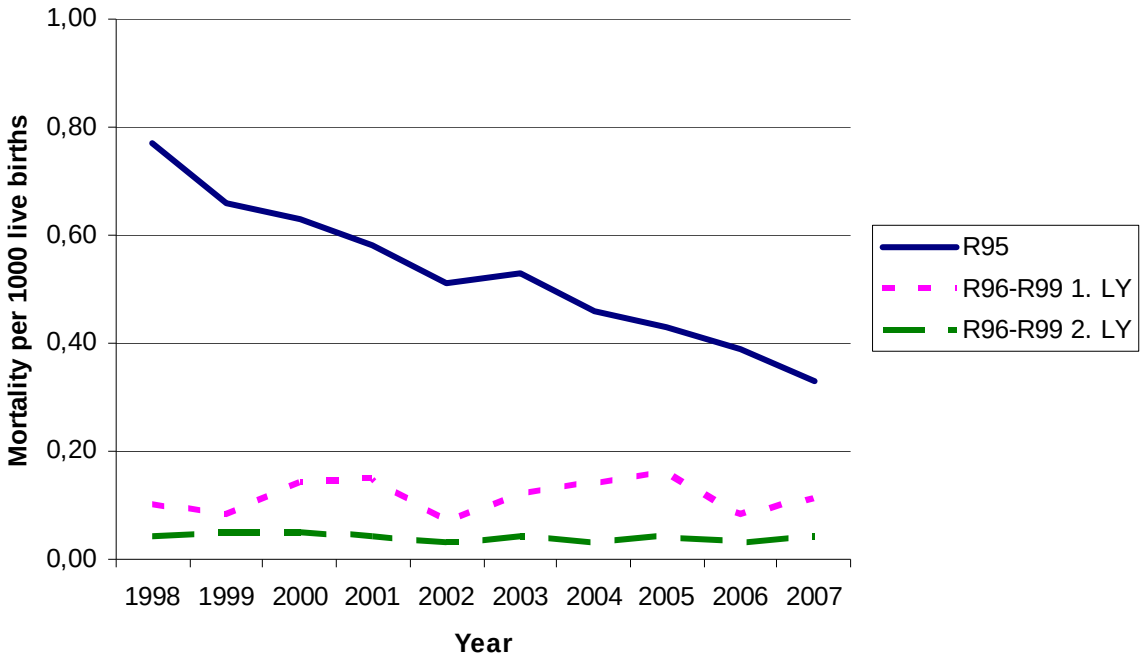

Figure 1: SIDS mortality rates (per 1000 live births per year) in Germany between 1998 and 2007, source: German Federal Bureau of Statistics.

In the study protocol of the pathological part, the recruitment of cases was defined as: Complete ascertainment of sudden and unexpected deaths occurring during the tenth to 24th month of life for which post mortem examinations have been carried out is aspired. All institutes of legal medicine and pathology in Germany were informed in advance and agreement for collaboration was sought. Copies of the study protocol, informed consent forms and case report forms were provided to collaborating institutes of legal medicine and pathology. This collaboration required that children deceased between the tenth and 24th month of life were autopsied and specimens processed according to the study protocol. With the aim to exclude any natural cause of death and detect possibly unknown pathomechanisms, there were additional neuropathological, immunohistochemical, bacteriological, virological and immunological investigations and also investigations for predisposing genetic factors. The institutes were to identify eligible cases, ask parents for informed consent and pass the case report forms and the informed consents to the RKI.

The inclusion criteria were: all infants between the completion of their 9th months of life and the completion of the 24th months of life, who had died suddenly and unexpectedly, were to be included in the study. The exclusion criteria were: age at death does not meet inclusion criteria or informed consent of parents or guardian not obtained. At the beginning of 2006 the study protocol was changed: inclusion criteria were changed and infants in the 2nd-9th month of life, who were vaccinated within seven days prior to death, were included.

At the beginning of the study, all public and university institutes of legal medicine (ILMs) in Germany were contacted and asked for participation. They were asked to notify the study centre in Munich of each case of sudden and unexpected infant death anonymously and to perform a standardised autopsy.

Twenty-five out of 31 ILMs consented to participate, covering about 60% of the German territory. Since July 2007 the Berlin institute participated but never reported a case to the study centre in Munich.

The participating ILMs were contacted on a monthly basis either by e-mail or telefax. The following information was collected:

- The number of autopsied children who had died in their 2^{nd}-9^{th} month of life and had been vaccinated within 7 days before death and
- The number of all autopsied children who had died in their 10^{th} -24^{th} month of life.

Furthermore, information on sex and diagnosis of death of each deceased child was obtained. Inclusion criteria were

- children who had died suddenly and unexpectedly in their 2^{nd}-9^{th} month of life and had been vaccinated within 7 days before death and
- any children who had died suddenly and unexpectedly in their 10^{th} -24^{th} month of life

Then the parents or guardians of these children were asked to give their informed consent that the autopsy data and the results of the additional investigations may be used for the study.

Participating ILMs were asked to report every death of a child who had died in their 2^{nd} and 24^{th} month of life to the study centre in Munich, to make sure that no case was missed. With the eligible cases, the institutes undertook standardised post mortem examinations[1], histology, microbiology and toxicology. Neuropathological examinations were done by the University of Aachen. All information was entered into an ACCESS database and then transferred into SAS 9.1.

2 Methods and case reporting

The response proportion of the institutes was, apart from the beginning of the study, stable at 100%. The participating ILMs reported 365 cases from August 1^{st}, 2005 to August 31^{st}, 2008. The

[1] The SAP (standardised autopsy protocol) is in accordance with the European guidelines for medico-legal autopsies. (Brinkmann B. Harmonisation of medico-legal autopsy rules. Int J Legal Med 1999; 113:1-14.

institutes in Kiel and Lübeck were reorganized and combined to one institute in the year 2000 and therefore reported their cases together.

2.1 Participating institutes of legal medicine

Six of the 31 ILMs in Germany refused to participate for various reasons. The participating institutes (Table 1) reported monthly all cases of sudden and unexpected death that had died in their 2nd to 24th month of life. All cases for the forensic part were to be autopsied according to the standard autopsy protocol (SAP). For some cases, however, adherence to the SAP was not possible for various reasons (long interval between death and autopsy, not enough material to investigate, mistakes in the participating institutes).

Table 1: Participating public and university institutes of legal medicine in Germany.

Place of institute	**Type of institute**
BERLIN	University Institute of Legal Medicine
BONN	University Institute of Legal Medicine
BREMEN*	Institute of Legal Medicine
DORTMUND*	Institute of Legal Medicine
DUISBURG*	Institute of Legal Medicine
DÜSSELDORF	University Institute of Legal Medicine
ESSEN	University Institute of Legal Medicine
FRANKFURT am Main	University Institute of Legal Medicine
FREIBURG	University Institute of Legal Medicine
GIESSEN	University Institute of Legal Medicine
GÖTTINGEN	University Institute of Legal Medicine
HAMBURG	University Institute of Legal Medicine
HANNOVER	University Institute of Legal Medicine
HEIDELBERG	University Institute of Legal Medicine
HOMBURG	University Institute of Legal Medicine
JENA	University Institute of Legal Medicine
KIEL/LÜBECK	University Institute of Legal Medicine
KÖLN	University Institute of Legal Medicine
LEIPZIG	University Institute of Legal Medicine
MAGDEBURG	University Institute of Legal Medicine
MAINZ	University Institute of Legal Medicine
MÜNSTER	University Institute of Legal Medicine
ROSTOCK	University Institute of Legal Medicine
ULM	University Institute of Legal Medicine
WÜRZBURG	University Institute of Legal Medicine
	In addition 2 cases of non-participating institutes were reported:
Trier	Private practice of Legal Medicine
Dresden	University Institute of Pathology

* - Municipal institute of legal medicine

2.1.1 Area covered by the institutes

Figure 2 shows the area of the German territory that is covered by Institutes of Legal Medicine that participated in the TOKEN study. The study area covers about 60% of the area of the Federal Republic of Germany with about 50 million inhabitants out of 82 million with about 400,000 live births (2006).

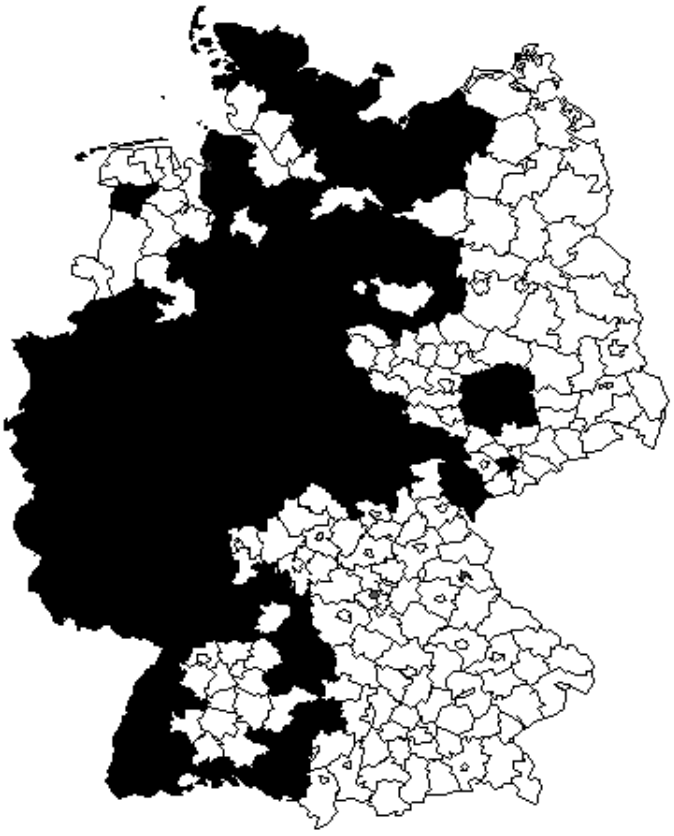

Figure 2: The study area is marked by black colour.

2.2 Response proportion of the participating ILMs

After some problems at the beginning of the study, 100% of the institutes responded to the monthly queries (Figure 3).

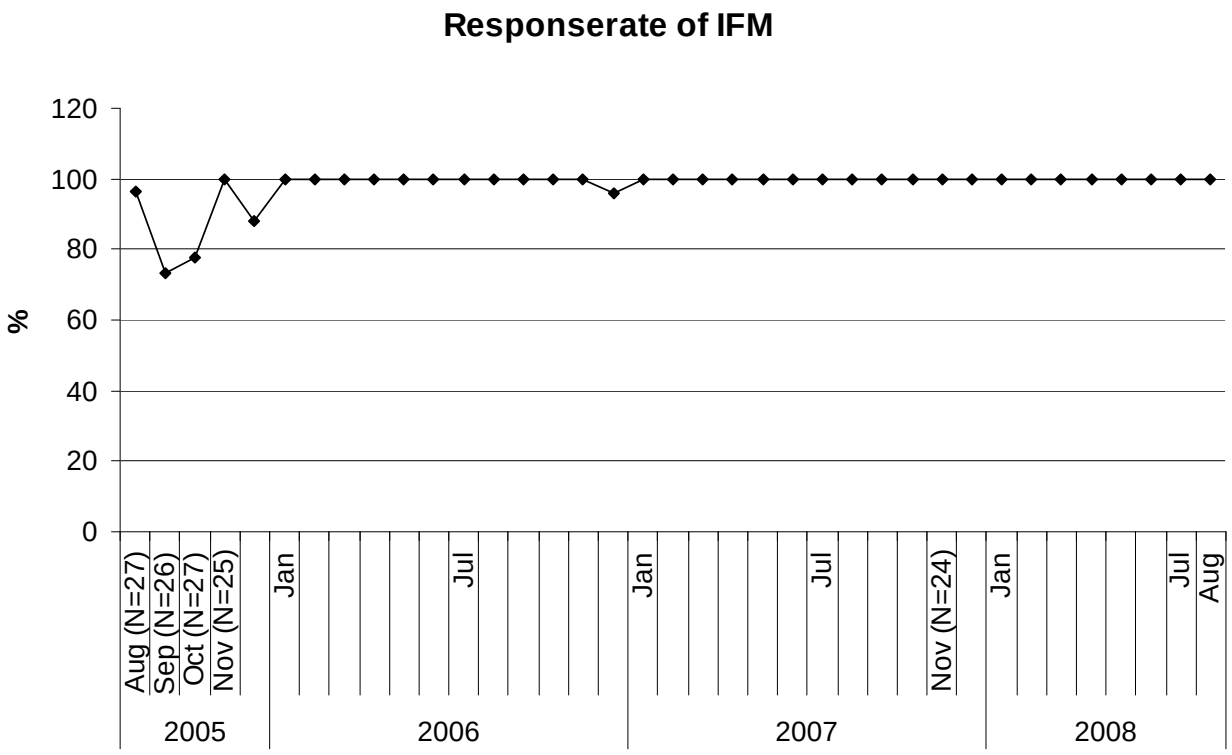

Figure 3: Percentage of participating institutes of legal medicine responding to monthly queries.

2.3 Reported cases by institutes

Three hundred and sixty-five cases were reported by the ILMs between August 2005 and August 2008. Of these, 222 were in the wrong age group, 32 cases were unnatural deaths and in 10 cases no autopsy was performed (Figure 4). In 43 of the remaining 101 eligible cases (Figure 5), an informed consent of the parents could be obtained (42.5%).

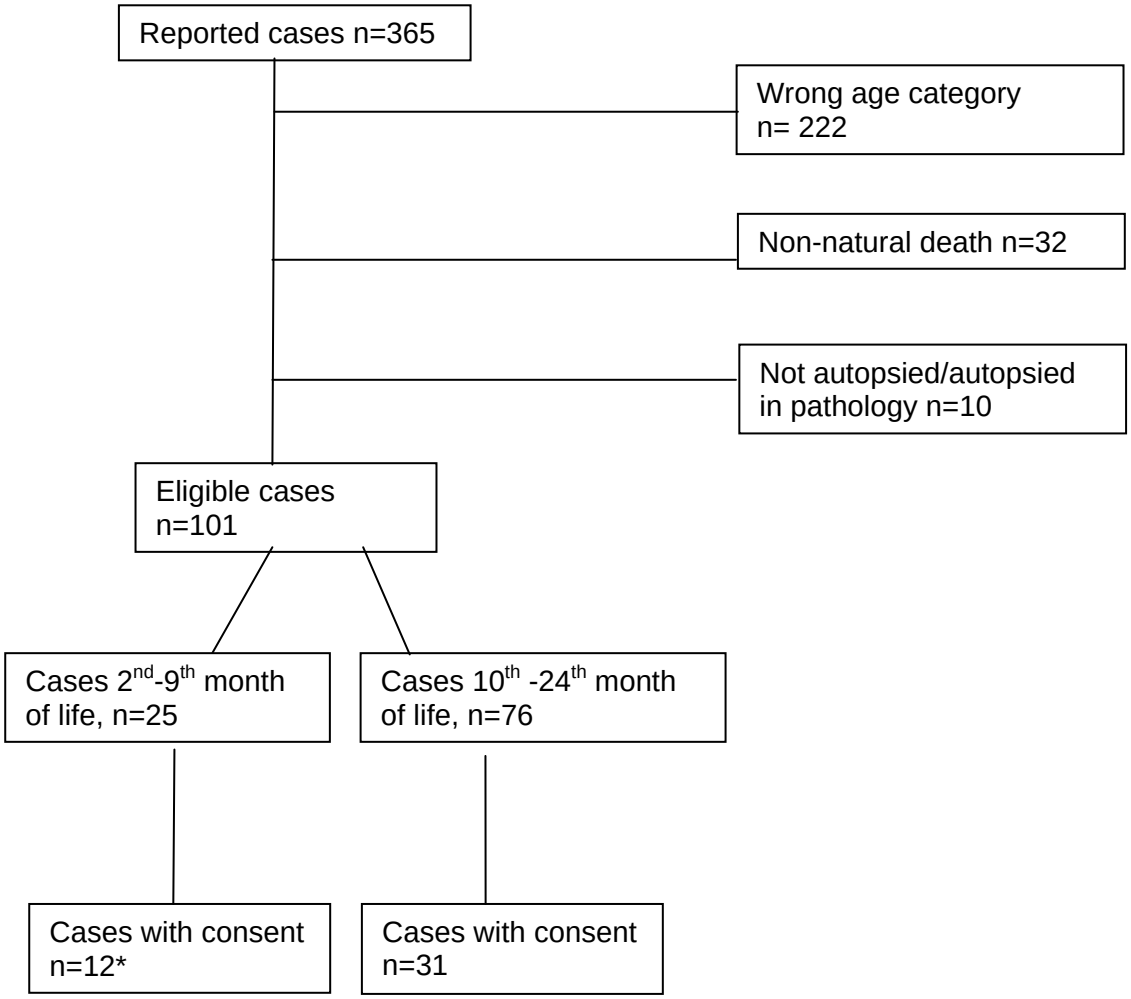

Figure 4: Reported/eligible cases.

***** Including one infant (2^{nd}-9^{th} months) who had died >7 days after vaccination but had the onset of the final event <7 days after vaccination.

One hundred and one cases fulfilled the inclusion criteria, 25 cases had died in their 2^{nd}-to 9^{th} month of life and 76 cases were ≥ 9 months old. From nearly half of these cases (43/101), parental informed consent to study participation could be obtained.

Finally, 43 cases (12 in age group 2^{nd}-to 9^{th} month and 31 in age group 10^{th} to 24^{th} month) met the inclusion criteria and were included in the final analyses

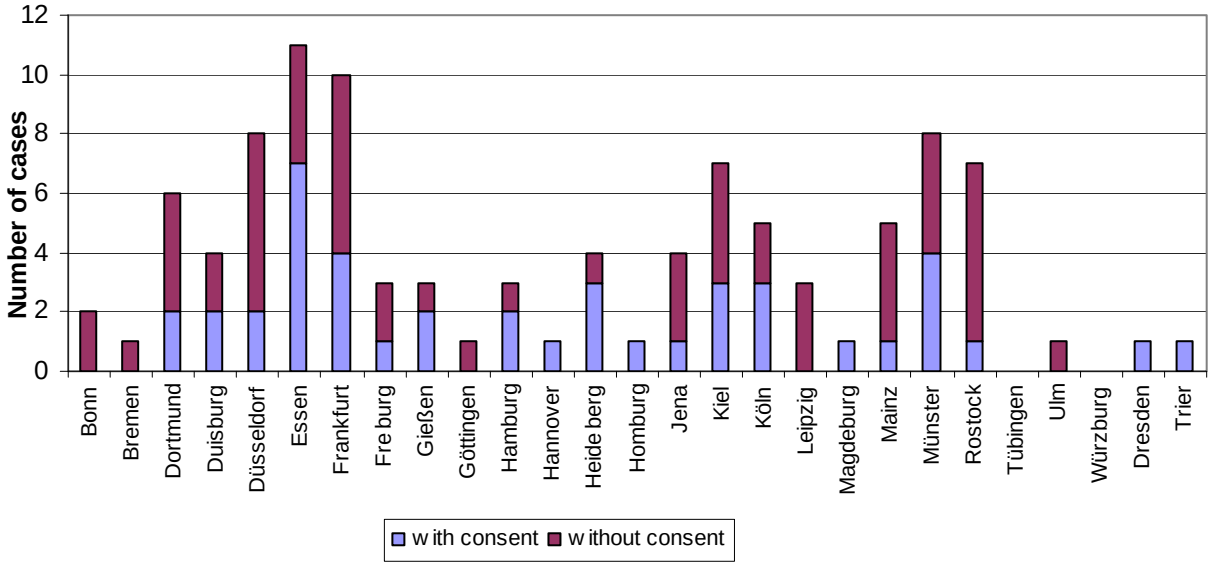

Figure 5: Number of eligible cases by institute of legal medicine

The highest numbers were reported in the state of North-Rhine Westphalia, which has both the highest population density and the highest infant mortality rate in Germany.

2.4 Expected versus reported cases

Based on the year 2003 with 372 SIDS cases, we expected 10% of cases to occur at ages ≥9 months (this corresponds to the age distribution of the German SIDS Study). The number of unexpected deaths in the second year of life is relatively stable at about 25 cases per year. As the SIDS rate fell further during the study period to 228 in the year 2007, an expected number of 27 SIDS cases seemed more realistic. Therefore, 81 cases were expected during the study period. The institutes reported 101 cases and 43 parents agreed to participate (31 of cases aged ≥9 months).

2.5 Standardised autopsy protocol

A standardised autopsy protocol (SAP) was introduced to all study centres involved. This SAP is in accordance with the European guidelines for medico-legal autopsies [2] and closely reflects the international standardised autopsy protocol [3] as well as protocols used in other studies on SIDS

[2] Brinkmann B (1999) Harmonisation of medico-legal autopsy rules. Int J Legal Med 113:1–14

[3] Krous H (1996) Instruction and reference manual for the international standardised autopsy protocol for sudden unexpected infant death. J SIDS Infant Mortal 1:203–246

including the GeSID study [4,5,6]. The autopsy included a thorough external examination, a complete internal examination, extensive histology, immunohistochemistry of the lungs and the myocardium, a full analytical toxicology scheme, and microbiology and virology. Furthermore, neuropathology was done for most of the cases at the Institute of Neuropathology of the Aachen University Hospital. For some cases these investigation were done decentralised. Finally a metabolic screening was organised to be performed by the Laboratory Olgemöller & Becker in Munich using tandem-MS spectrometry. The diagnostic procedure is in accordance with international recommendations published in 2007 [7].

Data management and statistics

All data were entered with a case-related code number. Data recording was performed at the study centre in Munich using a Microsoft Access data base. The data were then transferred into SAS (Statistical Analysis System, version 9.01) software in Muenster.

Case conferences

The cases of the pathology study part were discussed during case conferences held at the RKI in Berlin. The review committee consisted of one paediatric pathologist, one forensic pathologist, two paediatricians, and two epidemiologists. The committee reviewed all cases to determine the underlying causes of death (UCD) and to assign the cases without a morphologically defined UCD to a specific group (R95 – R99), using the same classification introduced for the GeSID study and considering the Brighton criteria [8].

---

[4] Mitchell EA, Scragg R, Stewart AW et al. (1991) Cot death supplement: results from the first year of the New Zealand cot death study. NZ Med J:71–76

[5] L'Hoir MP, Engelberts AC, van Well GTJ, Bajanowski T, Helweg-Larsen K, Huber J (1998) Sudden unexpected death in infancy; epidemiology determined risk factors related to a pathology classification. Acta Paediatr 87:1279–1287

[6] Findeisen M, Vennemann M, Brinkmann B, Ortmann C, Röse I, Köpcke W, Jorch G, Bajanowski T (2003) German study on sudden infant death (GeSID): design, epidemiological and pathological profile. Int J Legal Med 118: 163-169

[7] Bajanowski T, Vege A, Byard RW, Krous HF, Arnestad M, Bachs L, Banner J, Blair PS, Borthne A, Dettmeyer R, Fleming P, Gaustad P, Gregersen M, Groogard J, Holter E, Isaksen CV, Jorgensen JV, de Lange C, Madea B, Moore I, Morland J, Opdal SH, Rasten-Almqvist P, Schlaud M, Sidebotham P, Skullerud K, Stoltenburg-Didinger G, Stray-Pedersen A, Sveum L, Rognum TO (2007) Sudden infant death syndrome (SIDS)--standardised investigations and classification: recommendations. Forensic Sci Int 165(2-3):129-143

[8] Jorch G, Tapiainen T, Bonhoeffer J, Fischer TK, Heininger U, Hoet B, Kohl KS, Lewis EM, Meyer C, Nelson T, Sandbu S, Schlaud M, Schwartz A, Varricchio F, Wise RP; Brighton Collaboration Unexplained Sudden Death Working Group (2007) Unexplained sudden death, including sudden infant death syndrome (SIDS), in the first and second years of life: case definition and guidelines for collection, analysis, and presentation immunization safety data. Vaccine 25: 5707-5716

3 General characteristics of cases

In the following, all infants vaccinated within 6 days prior to death will be referred to as “vaccinated”, while infants vaccinated more than 1 week prior to death or never vaccinated will be referred to as “not vaccinated” (Figure 6). The mean age of the 15 vaccinated infants is 5.8 months (range 2nd to 24th month), the mean age of the not vaccinated infants 14.5 (range 10th - 23thmonth). The difference in mean age is due to the study design (see page 5). Of the vaccinated infants, 12 had died in the 2nd to 9th month of life, one in the 10th to 12th month of life and two were older than 12 months of age. Twenty-seven infants are male and 16 female. This gender distribution is generally found in SIDS cases worldwide.

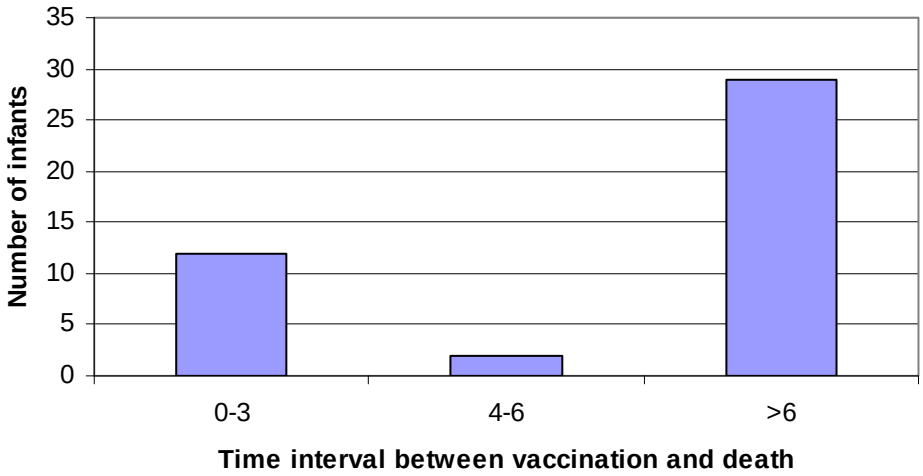

Figure 6: Distribution of cases by time interval between immunisation and death

4 Results with regard to the causes of death

The cases were investigated according to the standard autopsy protocol. The results of the investigations were used to make final diagnoses for the UCD. If any of the planned diagnostic steps could not be done or was missed for other reasons, this was considered in the final diagnosis as a level of decreased diagnostic certainty.

4.1 Causes of death

Twenty-five percent of infants in the younger age group had died due to explained causes. Of the remaining cases, the UCD remained "unexplained" in 25%, because of incomplete investigations and/or additional findings not typical for SIDS, while the other 50% showed typical SIDS findings.

Table 2: Causes of death and mean age of infants deceased in their 2nd to 9th month of life.

Cause of death	N	Mean age in months
SIDS (R95)	6	4.3
Unknown (R 96-99)	3	2.5
Explained cause of death	3	4.0

Table 3: Causes of death and mean age of infants deceased in their 10th to 24th month of life

Cause of death	N	Mean age in months
SIDS (10-12 months old)	0	
Unknown (R96-99 including "SIDS-like")	18 (2 vaccinated)	16.0
Explained cause of death	13 (1 vaccinated)	15.8

Seventy-five percent (3 out of 4) of infants who had died in their 10h to 12th month of life were SIDS/SID cases, showing a similar "SIDS" frequency compared to the younger group. In the second year of life, an explained UCD was found in 40%.

4.2 Immunohistochemistry

4.2.1 Lungs

In addition to conventional histology, immunohistochemistry (IHC) is an important method to characterise inflammatory changes of the lung. In the present study, 4 different antibodies were used to describe the quality of inflammatory cells which are located in the blood vessels, the interstitium and in the alveoli. This additional diagnostic procedure was introduced to improve the diagnosis of interstitial pneumonia and other virus related diseases.

The **CD68** antibody reacts with a 110 kDa glycoprotein expressed primarily as an intracellular molecule. It stains macrophages in a wide variety of human tissues, including lung alveoli. Therefore the CD68 antibody can be used as pan macrophage marker which is in particular suitable to detect macrophages in alveoli. These macrophages *phagocyte excessively produced surfactant* [9].

The **CD20** antibody is specific to a 33 kDa polypeptide present on the majority of B cells in peripheral blood and lymphoid tissue. No reactivity with other haematopoietic cells has been observed. The CD20 antigen is present on human pre B lymphocytes and on B lymphocytes at all stages of maturation, except on plasma cells [10].

The **CD45** antibody reacts with a protein tyrosine phosphatase (PTP) located in hematopoietic cells except for erythrocytes and platelets. CD45 is also called the common leukocyte antigen. It is nonreactive with epithelium and connective tissues. The PD7/26 and 2B11antibody have been assigned to the CD45 cluster at the 6th International Workshop on Human Leukocyte Differentiation [11]. The protein tyrosine kinases constitute a family of receptor-like enzymes that catalyze the dephosphorylation of phosphotyrosine residues and are characterized by homologous catalytic domains [12]. It is well suited for formalin-fixed paraffin-embedded tissues and is used as a pan lymphocyte screener.

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[9] Kunisch E, Fuhrmann R, Roth A, Winter R, Lungershausen W, Kinne RW. Macrophage specificity of three anti-CD68 monoclonal antibodies (KP1, EBM11, and PGM1) widely used for immunohistochemistry and flow cytometry. Ann Rheum Dis. 63(2003): 774-784.

[10] Polyak MJ, Li H, Shariat N, Deans JP. CD20 Homo-oligomers Physically Associate with the B Cell Antigen Receptor: Dissociation upon receptor engagement and recruitment of phosphoproteins and calmodulin-binding proteins.*J Biol Chem* 283 (2008): 18545-52.

[11] Sewell WA, Cooley MA, Hegen M. NL6. CD45 workshop panel report. In: Kishimoto T, Kikutani H, von dem Borne AEG, Goyert SM, Mason DY, Miyasaka M, et al., editors. Leucocyte typing VI. White cell differentiation antigens. Proceedings of the 6th International Workshop and Conference; 1996 Nov 10-14; Kobe, Japan. New York, London: Garland Publishing Inc.; 1997. p. 499-502.

[12] Braford, D., Flint, A.J., Tonks, N.K., Crystal structure of human phosphotase 1B. 1994. Science 11:253(5152):1373.

The antibody **MRP14** reacts with peripheral blood monocytes, neutrophils and keratinocytes (mature). The antigen expression is lost on tissue maturation of monocytes to macrophages. MRP14 may be associated with monocyte and neutrophil activation and the accumulation of these cells in inflammatory sites. The antibody MRP14 can be used as an early stage inflammatory marker of activated macrophages and monocytes [13].

In 31 cases the investigation of the lungs could be done. All cases showed positive staining results for CD68, mainly for cells in the lung periphery. These cells can therefore be diagnosed as alveolar macrophages which occur physiologically in lungs in the investigated age group. CD20-positive B lymphocytes were detected in small numbers in 10% of the cases mainly located in the alveolar interstitium, indicating mild forms of interstitial pneumonia. In 20% of the cases CD45 positive lymphocytes were found. The cells were localised in the alveolar walls as well as in blood vessels. In the interstitium, the cells indicate the presence of interstitial pneumonia. MRP14 was detected in a small number of cells in each case. In two cases the density of positive cells was higher compared to the average rate indicating acute inflammation. In one case the intensity of the changes were sufficient to explain the death. In the other case the inflammation was judged to be contributory to death.

4.2.2 Myocardium

In addition to conventional histology, immunohistochemistry (IHC) can help to detect inflammatory changes associated to myocarditis [14] and is therefore recommended in international protocols [15]. To improve the diagnosis of myocarditis, we decide to use the following set of antibodies to detect necrosis and to differentiate cell types:

C5b-9 is also known as the terminal complement complex (TCC). The TCC consists of C5b, C6, C7, C8 and C9 and forms the membrane attack complex (MAC) as well as the non-lytic fluid-phase SC5b-9 complex (with protein S). The MAC forms channels in target cell membranes leading to cell lysis by osmotic leakage. The complexes contain neoantigens that are absent from the

[13] Sorg C. The calcium binding proteins MRP8 and MRP14 in acute and chronic inflammation. Behring Inst Mitt (1992) 91: 126-137

[14] Dettmeyer R, Schlamann M, Madea B (1999) Immunohistochemical techniques improve the diagnosis of myocarditis in cases of suspected sudden infant death syndrome (SIDS). For Sci Int 105: 83-94.

[15] Bajanowski T, Vege A, Byard RW, Krous HF, Arnestad M, Bachs L, Banner J, Blair PS, Borthne A, Dettmeyer R, Fleming P, Gaustad P, Gregersen M, Groogard J, Holter E, Isaksen CV, Jorgensen JV, de Lange C, Madea B, Moore I, Morland J, Opdal SH, Rasten-Almqvist P, Schlaud M, Sidebotham P, Skullerud K, Stoltenburg-Didinger G, Stray-Pedersen A, Sveum L, Rognum TO (2007) Sudden infant death syndrome (SIDS)--standardised investigations and classification: recommendations. Forensic Sci Int 165(2-3):129-143

individual native components from which they are formed and is directed against a neoepitope exposed on C9 when incorporated into the TCC.

Thomsen, Schulz and Bhakdi developed a technique for antibody application on routine paraffin sections: C5b-9 Complement Complex is particularly well-suited for the exact and autolytically insensitive **presentation of disseminated necroses** of fibre bundles and single fibres of myocardium [16]. The application of the technique on paraffin sections lead to the use of this technique in forensic medicine routine diagnostics of early ischemic myocardial lesions, even in cases of "sudden" cardiac death.

The **CD68** antibody reacts with a 110 kD glycoprotein expressed primarily as an intracellular molecule. It stains **macrophages** in a wide variety of human tissues, including Kupffers cells and macrophages in the spleen, gut, and lung alveoli and in bone marrow. Peripheral blood monocytes, large lymphocytes and basophiles and mast cells are positive but neutrophils stain very weakly.

The **CD20** antibody is specific to a 33 kDa polypeptide present on the majority of B cells in peripheral blood and lymphoid tissue. No reactivity with other haematopoietic cells has been observed. The CD20 antigen is present on human pre B lymphocytes and on B lymphocytes at all stages of maturation, except on plasma cells. The CD20 molecule is involved in regulation of B cell differentiation, presumably via its reported function as a Ca++ channel subunit.

CD45R0 (UCHL1) is a member of leukocyte common antigen family. It reacts with an epitope unique for CD45R0. The antibody labels most thymocytes, a subpopulation of resting T cells within both CD4 and CD8 subsets, and mature, activated T cells [17]. It is effective on formalin-fixed, paraffin-embedded tissue sections, and is an excellent marker of reactive T cells and T-cell neoplasm when only routinely processed material is available.

The anti-LCA antibody (leukocyte common antigen) recognizes a molecule present on the cell surface of human leukocytes (CD45). It is a transmembrane glycoprotein expressed on most nucleated cells of haematopoietic origin. CD45, encoded by a single gene mapped to chromosome 1, has various isoforms based on differential splicing of exons 4, 5 and 6. On human leucocytes, five different isoforms of CD45, named ABC, AB, BC, B and 0, have been identified. These isoforms are recognized by CD45RA, CD45RB, CD45RC and CD45R0 antibodies. All the CD45

[16] Thomsen H, Schulz A, Bhakdi S (1990) Immunohistochemical C5b-9 complement complex demonstration in early stages of myocardial necroses using paraffin sections. Z Rechtsmed 103: 199-206

[17] Berti E, Aversa GG, Soligo D, Cattoretti G, Delia D, Aiello A, Parravicini C, Hall BM, Caputo R (1991) A6 – a new 45RO monoclonal antibody for immunostaining of paraffin-embedded tissues.Am J Clin Pathol 95:188-193.

isoforms share the same intracellular segment, which has been shown to have tyrosine phosphatase activity. Various leucocytes express characteristic CD45 isoforms, thus T cells express CD45 isoforms corresponding to their development and activation, B cells predominantly express the ABC isoform, and monocytes and dendritic cells predominantly express the B and 0 isoforms. Granulocytes principally express only the B and 0 isoforms [18].

In two out of 42 cases, positive results were obtained: Case *HGI 30806* showed single cell necrosis and an increased number of leucocytes in the myocardium by histology. IHC showed positive staining using C5b-9, indicating acute myocytolysis. Furthermore an increased number of LCA positive cells were present which could be characterised as T-cells (CD45R0). Therefore we diagnosed myocarditis and classified this (in combination with severe acute bronchitis/bronchiolitis) as UCD.

Case *HGI 18206* was inconspicuous in histology, but showed positive reaction for LCA and CD45R0. Because of the number of inflammatory cells and the quality of the infiltrates the case was diagnosed as viral myocarditis. Cellular necrosis was not present. Therefore the findings cannot be judged as sufficient UCD, and the case was classified as borderline SIDS.

18 Thomas ML (1989) The leukocyte common antigen family. Ann Rev Immunol 7: 339-369

4.3 Screening for metabolic disorders

The classical and simple post-mortem screening method for metabolic disorders in corpses of infants and young children is the histological investigation of liver specimens stained for fatty degeneration of liver cells. Nevertheless, this method is unspecific. Therefore in the present study tandem mass spectrometry was used to perform this metabolic screening (Labour Becker & Olgemöller, Munich). The method is suitable to quantify amino acids, carnitines, and acylcarnitines [19].

The following disturbances of metabolism can be diagnosed/excluded:

- Disturbances of amino acid metabolism
  - Phenylketonuria
  - Tyrosinemia
  - Homocysteinuria
  - Maple syrup urine disease
- Disturbances of the carnitin cycle and fatty acid oxidation
  - Carnitin Palmitoyl Transferase1 (*CPT1*) Deficiency
  - Carnitin Palmitoyl Transferase2 (*CPT2*) Deficiency
  - Carnitin Translokase Deficiency
  - MCAD-Deficiency
  - VLCAD-Deficiency
  - LHCAD-Deficiency
  - Myoadenylate Deaminase Deficiency
- Disturbances of the metabolism of organic acids
  - 3-MCC deficiency
  - Isovaleric acidemia
  - Glutaric acidemia Type I
  - Propion academia
  - Methylmalon academia
  - HMG-CoA lyase deficiency
  - b-ketothiolase deficiency.

In none of the investigated 43 cases, positive findings were made by tandem mass spectrometry. This means that all the above listed disturbances/disorders can be excluded in the investigated cases.

[19] Sweetman L. (1996) Newborn screening by tandem mass spectrometry (MS-MS). Clin Chem 42:3456.

4.4 Final diagnosis for the underlying cause of death

A summary of the causes of death in both age groups is given in Tables 4 and 5.

Table 4: Causes of death in the younger age group (2 – 9 months) using ICD 10 codes.

Cause of death	Number of cases
R95	6
R98/99	3
B34.9	1
Q21.2	1
A88.8	1

Table 5: Causes of death in infants/children who had died in their 10th to 24th month of life using ICD 10 codes.

Cause of death	Number of cases
R98/99	18
W78.0	1
J21.9	1
Q20.5	1
Y65.4	1
A08.0	1
B99	1
I42.4	1
G93.9	1
A39.1	1
Q04.8	1
Q04.3	1
I42.0	1
P27.1	1

In the older children, an explained UCD could be found in 13 out of 31 (41.9%). This proportion is nearly twice as high as in the younger group (25%). In the older group there are 18 cases showing findings as known for SIDS. These were diagnosed as “SIDS like” using the ICD-10 codes R98, R99.

5 Results with regard to possible pathomechanisms leading to death in vaccinated infants/children

5.1 Brain oedema

Some recently reported cases rose the suspicion that brain swelling and brain oedema could be one mechanism contribution to death after vaccination using hexavalent vaccines [20]. Therefore we looked at brain oedema in the cases of this study. Although neuropathological investigations have been performed, it is very difficult to quantify brain oedema. Brain oedema can occur focally and in such cases the functional significance depends on the region where it is present and on the centres which could be affected by the oedema. Focal brain oedema cannot be quantified sufficiently by conventional neuropathological investigation. As a marker of a more generalised oedema, the age-related brain weight can be measured with regard to the body weight. This method is an approximation, but easy to do during autopsy. To exclude death-related changes in brain weight, a suitable control group has to be defined. As a part of the German SIDS study (GeSID), the brain weight in 231 SIDS cases was recorded and analysed with regard to body weight and age [21]. These results could be used as reference values in the age group younger than one year. From these results it is obvious that the relative brain weight decreases during the first year of life from about 15% of body weight in the first month of life to 11% at the age of one year (Table 6).

[20] Zinka B, Rauch E, Buettner A, Ruëff F, Penning R (2006) Unexplained cases of sudden infant death shortly after hexavalent vaccination. Vaccine 24: 5779-5780.

[21] Fracasso T, Brinkmann B, Bajanowski T, Vennemann M (2009) Organ weights in cases of SIDS. A German study. Am J Forensic Med Pathol, in press

Table 6: Brain and body weight in SIDS cases. Results from the GeSID study are used as references [21].

Month of death	N	Mean body weight [g]	95% CI	Mean brain weight [g]	95% CI	Brain weight as a percentage of body weight [g]	95% CI
1	11	3306	2855-3757	482	441-523	14.4	13.4-15.8
2	29	4445	4155-4735	540	508-572	12.1	11.2-13.1
3	52	4984	4779-5189	611	595-627	12.3	11.4-13.2
4	27	5837	5516-6158	680	654-706	11.7	10.8-12.5
5	27	6784	6305-7263	775	741-809	11.4	10.7-12.2
6	27	6791	6367-7215	801	773-829	11.8	11.0-12.6
7	11	6531	5920-7142	795	734-855	12.2	11.4-13.0
8	13	8170	7618-8722	932	891-973	11.4	10.7-12.1
9	16	8472	7762-9182	935	886-984	11.0	10.4-11.7
10	4	9185	8063-10306	1010	858-1162	11.0	10.4-11.6
11	10	8875	8248-9502	987	908-1048	11.1	10.5-11.8
12	4	9113	7879-10346	967	907-1027	10.6	9.9-11.3

In the immunized cases with explained UCD (Table 7), there are three relative brain weights which are outside the 95% confidence interval (CI), as calculated from the GeSID study (Table 6). Two relative brain weights are too low and one exceeds the upper 95% confidence limit. All results may be explained by the diseases and circumstances leading to death. Interestingly, in the 2 cases with decreased relative brain weight, the body weight is outside the upper 95% confidence limit of the GeSID study. The brain weights of the children who had died within the second year of life cannot be compared to the SIDS group because of the differences in age.

In immunized cases with unexplained UCD, 4 out of 11 cases show increased relative brain weights compared to the GeSID cases while the relative brain weight is reduced in one case (Table 8). Therefore, a mild brain oedema can be postulated for three cases. Case No 10 is a child who had died at the age of 2 month and for whom a brain weight of 1560 g was noted in the autopsy protocol. As it is not noted in the protocol that the child had a very severe brain oedema or any other abnormalities, it is very likely that it is a typing error. A brain weight of 560 g is more probable. However, this cannot be verified in the institute where the child was autopsied as no other documentation was done and the brain was not examined in Aachen.

The relative brain weights of children who had died within the second year of life varied between 8% and 12% (Table 8). Although no data on brain weight from a suitable control group are available for this age group, these values are most probably within a normal range.

Table 7: Brain weight as percent of body weight in children with explained causes of death. One case is missing, due to missing data. Cases with relative brain weights outside the age-dependent 95% CI are marked in bold.

No	Brain weight	Age in months	Gender	Body weight	Brain weight as percent of body weight	Cause of death	Vaccination Status
1	1050	7	male	8030	13%	A 88.8	Vaccinated
4	**632**	**2**	**male**	**6200**	**10%**	**B 34.9**	**Vaccinated**
11	**630**	**2**	**female**	**4500**	**14%**	**Q21.2**	**Vaccinated**
15	**985**	**11**	**female**	**10700**	**9%**	**W 78.0**	**Vaccinated**
20	1035	12	male	8000	13%	J21.9	Non vaccinated
22	833	13	female	6800	12%	Q20.5	Non vaccinated
23	900	13	female	11200	8%	Y65.4	Non vaccinated
24	1235	13	male	10300	12%	B99	Non vaccinated
27	1100	13	female	11230	10%	I42.4	Non vaccinated
32	1170	17	male	10000	12%	A39.1	Non vaccinated
33	840	18	female	6430	13%	Q04.8	Non vaccinated
35	555	20	male	9200	6%	Q04.3	Non vaccinated
39	930	23	female	13200	7%	I42.0	Non vaccinated
41	924	13	Male	Not recorded		A08.0	Non vaccinated
42	520	14	Male	5740	9%	G93.9	Non vaccinated

Table 8: Brain weight as percent of body weight in SIDS cases and in cases with unknown UCD (R95-R99). Cases with relative brain weights outside the age-dependent 95% CI are marked in bold.

No	Brain weight [g]	Age in months	Gender	Body weight [g]	Brain weight as percent of body weight	Cause of death	Vaccination Status
2	580	2	female	6800	9%	R 98	Vaccinated
3	**920**	**8**	**male**	**6570**	**14%**	**R 95**	**Vaccinated**
5	570	13	Male	6780	8%	R 99	Vaccinated
6	711	3	male	5923	12%	R 95	Vaccinated
7	**790**	**4**	**female**	**6300**	**13%**	**R 95**	**Vaccinated**
8	**720**	**4**	**male**	**5600**	**13%**	**R 95**	**Vaccinated**
9	1010	14	female	not recorded		R 98	Vaccinated
10	**1560**	**2**	**male**	**5580**	**28%**	**R 99**	**Vaccinated**
12	562	3	female	4510	12%	R 98	Vaccinated
13	660	3	female	5700	12%	R 95	Vaccinated
14	**5621**	**1**	**male**	**5320**	**11%**	**R 95**	**Vaccinated**
16	**986**	**10**	**male**	**10000**	**10%**	**R98**	**Non vaccinated**
17	**980**	**11**	**male**	**11200**	**9%**	**R98**	**Non vaccinated**
18	**800**	**11**	**female**	**8500**	**9%**	**R98**	**Non vaccinated**
19	1310	12	male	11500	11%	R99	Non vaccinated
21	985	13	male	8100	12%	R98	Non vaccinated
25	570	14	female	6780	8%	R99	Non vaccinated
26	970	13	female	11900	8%	R98	Non vaccinated
28	1184	14	male	10000	12%	R98	Non vaccinated
29	1130	16	female	8600	13%	R98	Non vaccinated
30	1135	16	male	11000	10%	R98	Non vaccinated
31	1165	16	male	11000	11%	R99	Non vaccinated
34	1340	19	male	13400	10%	R98	Non vaccinated
36	1360	20	male	11500	12%	R99	Non vaccinated
37	1295	20	male	12585	10%	R99	Non vaccinated
38	1120	22	female	10000	11%	R98	Non vaccinated
40	1215	24	male	Not recorded		R99	Non vaccinated

While one case (No 10) is regarded as an outlier due to incorrect documentation, data of remaining cases do not support the view that vaccination may be associated with severe brain oedema or that severe brain oedema may be a common pathomechanism leading to death.

5.2 Parameters characterizing the immune system

Measurements were done in 13 immunised and 14 not immunised cases. In some cases not all of the subsequently described parameters could be determined quantitatively due to an insufficient amount of serum available during autopsy. In the remaining 16 cases there was definitely not enough material to do these measurements, or in some cases the serum was haemolytic due to putrefaction. In the following the results of vaccinated and unvaccinated cases stratified by explained/unexplained UCD are reported.

5.2.1 Immunoglobulins

Immunoglobulins are important components of the humoral immune system. They play a central role in immune defence mechanisms. Therefore, IgG, IgM, IgD, and IgA concentrations were quantitatively determined by radial immunodiffusion and (total) IgE concentrations by ELISA method. In addition, the concentrations of specific antibodies (IgE) against components of vaccines were determined using ImmunoCAP technology. IgE is involved in Type I (or immediate type) hypersensitivities and can be detected by different methods. A semi-quantitative radioimmunoassay was developed for the detection of specific IgE in serum. Since then, *in vitro* IgE testing (i.e. “RAST”) has gained an important role worldwide [22] and a number of technical and procedural modifications have been introduced, especially the ImmunoCAP. These changes have increased the sensitivity of the test, without a significant decrease in specificity. This method uses as the solid phase a flexible, hydrophobic cellulosic polymer to which allergen has been covalently linked. The advantage of this system is that it has a very high antigen binding capacity when compared to other systems and it has minimal non-specific binding with high total IgE [23].
As components of vaccines, Streptomycin, Neomycin, Polymyxin B, and Tromethanol were identified and selected for the test. The results can be given in kU/l. Concentrations can be assigned to different CAP classes as given in the following (Table 9).

[22] Hamilton R, Adkinson NF (1983) Quantitation of allergen-specific IgE in serum using the RAST. Clin Immunoassay 6: 147-154.

[23] Corey JP, Mamikoglu B, Akbar I, Houser SM, Gungor A (2000) ImmunoCAP and HY*TEC enzyme immunoassays in the detection of allergen-specific IgE compared with serial skin end-point titration by receiver operating characteristic analysis. Otolaryngol Head Neck Surg. 2000 122: 64-70.

Table 9: CAP classes of specific IgE.

Class	IgE (kU/l)	Comment
CAP 0	< 0.1	negative
CAP 0/1	0.10 – 0.34	low positive
CAP 1	0.35 – 0.69	Moderately positive
CAP 6	>100	Very high

In particular, for allergens with rare exposure (as it is true in our study), figures ranging between 0.1 and 0.34 (CAP 0/1) give evidence that the individual has been sensitized [24].

In the following the cases are differentiated with regards to the UCD (either explained or unexplained according to ICD-10 codes 95-99) and with regards to the vaccination status (vaccinated within 6 days prior to death or not vaccinated within this time frame). Median values and standard deviations (SD) are calculated if parameters are available of four or more cases.

[24] Raulf-Heimsoth M, Rihs HP, Rozynek P, Cremer R, Gaspar A, Pires G, Yeang HY, Arif SA, Hamilton RG, Sander I, Lundberg M, Brüning T (2007) Quantitative analysis of immunoglobulin E reactivity profiles in patients allergic or sensitized to natural rubber latex (Hevea brasiliensis). Clin Exp Allergy 37: 1657-1667.

IgG

IgG molecules are glycoproteins excreted by B-lymphocytes and plasma cells in reaction to antigen contact. IgG molecules take part in acute immune reaction. Increased concentrations can be observed in acute infection, and in mono- or polyclonal gammopathy. Lack of antibodies can be caused by a decreased immune activity.

In 4 cases with an unexplained UCD, no IgG molecules were found (Table 10). This could be due to haemolytic serum as a result of putrefaction. For all other cases, increased concentrations were determined. IgG concentrations in the group of explained UCD are higher compared to cases of unexplained UCD. This phenomenon may be explained by the fact that causes of death were severe infections in this group.

Table 10: Total IgG concentrations, broken down by vaccination status and UCD. * Normal values are given for living children who are younger than two years of age.

	Arithmetic mean (mg/l)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=2)	7540	6650-8430			139 - 1139	100
Explained UCD, not vaccinated (N=4)	9844	7980-10300	9835	1096	139 - 1139	100
Unexplained UCD, vaccinated (N=8)	5433	0-10800	5090	3043	139 - 1139	100
Unexplained UCD, not vaccinated (N=8)	5379	0-17400	5379	5914	139 - 1139	100

IgM

IgM molecules were produced as the earliest reaction to antigen contact. IgM molecules activate the complement system. In acute infection IgM levels are increased. Decreased figures are associated with disturbed immune reaction and weakness of the immune system.

IgM concentrations in cases with explained UCD are much higher that in cases with unexplained UCD (Table 11). The explanation may be the same as for IgG concentrations. Four out of 16 cases of unexplained UCD showed IgM concentrations of 0 mg/l. This can be due to post-mortem changes (haemolysis). The increased values observed are not associated with vaccination status.

Table 11: IgM concentrations, broken down by vaccination status and UCD

* Normal values are given for living children who are younger than two years of age.

	Arithmetic mean (mg/l)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=2)	1604	977-2230			16 - 229	100
Explained UCD, not vaccinated (N=4)	1544	916-2310	1475	651	16 - 229	100
Unexplained UCD, vaccinated (N=8)	662	0-1100	775	435	16 - 229	100
Unexplained UCD, not vaccinated (N=8)	533	0-1160	439	432	16 - 229	100

IgD

IgD molecules are present on the surface of mature B-cells. IgD can be found in serum in very low concentration. The function is not well understood at present. IgD concentration is increased in chronic infection, and hyper-IgD syndrome. The significance of decreased levels is unknown.

In the present study no increased IgD concentration was seen. This is in accordance with the fact that no chronic infection was found in the cases neither by autopsy nor by histology. In 7 cases of unexplained UCD, IgD could not be determined, maybe due to post-mortem changes (2 cases were vaccinated prior to death).

Table 12: IgD concentrations, broken down by vaccination status and UCD

* Normal values are given for living adults.

	Arithmetic mean (mg/l)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=2)	16.6	16.6-16.6			1.3 – 152.7	0
Explained UCD, not vaccinated (N=4)	37.6	16.6-67.9	32.9	24.6	1.3 – 152.7	0
Unexplained UCD, vaccinated (N=8)	23.9	0-100	11	34.1	1.3 – 152.7	25
Unexplained UCD, not vaccinated (N=8)	10.9	0-49.6	0	18.1	1.3 – 152.7	62

IgA

IgA antibodies do mainly occur in body fluids and on mucous membranes. Selective IgA deficiency is the most common immunodeficiency among Caucasians showing variable clinical symptoms. Negative results of the determination of IgA concentrations can be explained by post-mortem haemolysis.

All cases with an explained UCD are characterised by increased IgA concentrations, independently of vaccination status (Table 13). In the group of unexplained UCD, 5 cases show increased levels compared to normal values, while IgA concentrations were not detectable in the remaining case. Therefore, all concentrations are outside the normal range given for living children younger than two years of age. Cases with explained UCD show higher concentrations compared to cases with unexplained UCD. However, the first group comprises of only 6 cases and no meaningful comparison can be done due to small sample sizes. Nevertheless, the results obtained do not indicate immunodeficiency in any case.

Table 13: IgA concentrations, broken down by vaccination status and UCD
* Normal values are given for living children who are younger than two years of age.

	Arithmetic mean (mg/l)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=2)	962	605-1320			3 - 102	100
Explained UCD, not vaccinated (N=4)	1024	605-1410	1040	361	3 - 102	100
Unexplained UCD, vaccinated (N=8)	252	0-1410	0	514	3 - 102	100
Unexplained UCD, not vaccinated (N=8)	279	0-859	0	392	3 - 102	100

IgE (total)

IgE can be found on the membrane of mast cells. The concentration in serum is very low. In case of antigen contact it stimulates mast cells and granulocytes to excrete histamine leading to mast cell degranulation as part of immediate allergic reaction. Increased IgE figures are found in allergic reactions, T-cell defects, and IgE-plasmocytoma. Decreased values can be found in immune deficiency and cases of Ataxia teleangiectatica.

IgE concentrations of both groups (explained UCD, unexplained UCD) are very similar and within the normal range, except for one case (Table 14). An increased IgE concentration was found in

one case with an unexplained UCD. The cause of this increase is not clear. Neither the result of the autopsy nor of the additional investigations explain the increased IgE concentration in this case.

Table 14: Total IgE concentrations, broken down by vaccination status and UCD
* Normal values are given for living children who are younger than two years of age.

	Arithmetic mean (IE/ml)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=2)	4	3.9-4.1			0 - 60	0
Explained UCD, not vaccinated (N=4)	7.8	1.5-21.8	4	9.4	0 - 60	0
Unexplained UCD, vaccinated (N=8)	15.6	1.3-107.9	2.2	37.3	0 - 60	12.5
Unexplained UCD, not vaccinated (N=8)	5.5	0.7-21.0	3.0	6.5	0 - 60	0

IgE (specific)

After antigen contact, specific antibodies can be detected by special detection methods (RAST). In this investigation, the concentration of specific antibodies to Streptomycin, Neomycin, Polymyxin B, and Tromethanol was determined. All these substances can be found in vaccines.

Only in one case (unexplained UCD), concentrations of specific IgE (Streptomycin, Neomycin, and Polymyxin B) were increased compared to normal values (Table 15). This case has to be attributed to CAP class 0/1 (“low positive”, see Table 9), while all other cases showed concentrations <0.1 kU/ml (CAP class 0). This positive finding is indicative for some contact with an allergen prior to death. Interestingly, the antibody concentrations detected differ for the various antigens investigated. It can be assumed that the antigenicity of the substances differs. The highest values were determined for Polymyxin B antibodies which were present in all cases.

Table 15: Specific IgE concentrations, broken down by vaccination status and UCD

	Arithmetic mean (kU/ml)	Range	Median	Standard deviation	Normal range	Values out of normal range (%)
Streptomycin						
Explained UCD, vaccinated (N=3)	0				< 0.1	0
Explained UCD, not vaccinated (N=4)	0	0	0	0	< 0.1	0
Unexplained UCD, vaccinated (N=10)	0	0	0	0	< 0.1	0
Unexplained UCD, not vaccinated (N=9)	0.0014	0-0.11	0	0.039	< 0.1	12.5
Neomycin						
Explained UCD, vaccinated (N=3)	0				< 0.1	0
Explained UCD, not vaccinated (N=4)	0	0	0	0	< 0.1	0
Unexplained UCD, vaccinated (N=10)	0.002	0-0.01	0	0.004	< 0.1	0
Unexplained UCD, not vaccinated (N=9)	0.019	0-0.14	0	0.046	< 0.1	11
Polymyxin B						
Explained UCD, vaccinated (N=3)	0.057	0.04-0.07			< 0.1	0
Explained UCD, not vaccinated (N=4)	0.06	0.05-0.057	0.06	0.008	< 0.1	0
Unexplained UCD, vaccinated (N=9)	0.068	0.04-0.1	0.07	0.024	< 0.1	11
Unexplained UCD, not vaccinated (N=9)	0.076	0.05-0.15	0.07	0.031	< 0.1	11
Tromethanol						
Explained UCD, vaccinated (N=3)	0	0			< 0.1	0
Explained UCD, not vaccinated (N=4)	0.005	0-0.08	0.005	0.006	< 0.1	0
Unexplained UCD, vaccinated (N=8)	0.004	0-0.01	0	0.007	< 0.1	0
Unexplained UCD, not vaccinated (N=8)	0.01	0-0.02	0.01	0.009	< 0.1	0

5.2.2 The complement system

The complement system, a well-known component of the innate immune system, significantly influences the adaptive immune response via direct cell–cell interaction and maintenance of lymphoid organ structure. Complement is vital for protecting individuals against pathogens and any disturbance of homeostasis associated with appearance of foreign antigens. Four antenna molecules seek for putative danger and subsequently start three activation pathways to eliminate the hostile triggering signal. To achieve this task, the complement system contains soluble plasma factors as well as membrane-bound receptor molecules. Complement participates to construct an immunological network with extensive links to innate immunity, but also to the adaptive immune system. The body supports the complement activity with a high level of complement production. Nevertheless, it is important to regulate this immunological regiment by establishing a tight surveillance composed of redundantly acting regulator molecules [25]. The complement sequence consists of classical and alternate [Properdin] pathways which may be activated sequentially by a number of different causes. In general, the classic pathway is activated by antigen-antibody and cell-antibody complexes and the alternate pathway by bacteria, fungi and some immune complexes. The sequence of activation in the classical pathway is C1, C4, C2, C3 and C5 to C9. In the alternate pathway C1, C4 and C2 are bypassed and C3 is activated by an initiating factor (IF), and two substances called Properdin Factors D and B. Functionally active components of the complement system were determined by radial immunodiffusion.

C1 inactivator

The first complement component to act in the activation of complement system is called C1. This is a calcium-dependent complex made up of three subcomponents. When the intact C1 binds to at least two antibodies, C1r and C1s are sequentially activated, leading to an activation of the complement cascade [26]. C1-inactivator is the main inhibitor of the classical pathway of the complement system (C1s and C1r), of the contact activation system (factor XIIa and kallikrein) and of the intrinsic pathway of coagulation (factor XIa). A decrease in the concentration of C1-inactivator can be caused by the hereditary angioedema leading to overwhelming complement activation [27].

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[25] Rambach G, Würzner R, Speth C (2008) Complement: an efficient sword of innate immunity. Contrib Microbiol 15: 78-100.

[26] Rambach G, Würzner R, Speth C (2008) Complement: an efficient sword of innate immunity. Contrib Microbiol 15: 78-100.

[27] Zeerleder S, Caliezi C, Redondo M, Devay J, Wuillemin WA (1999) Activation of the plasmatic cascade systems in sepsis: role of C1-inhibitor. Schweiz Med Wochenschr 129:1410–1417.

More than 50% of the cases showed concentrations of C1 inactivator outside the normal range (Table 16). Among the cases outside the normal range, increased as well as decreased concentrations were measured. The increased concentrations show that no overwhelming complement activation was present in these cases. Only one vaccinated case showed a clearly decreased concentration (65 mg/l). No obvious cause for this finding could be established. Neither autopsy nor histology provided results of an angio-oedema. Seven cases of unexplained UCD showed decreased levels (two infants were vaccinated prior to death). The figures were only slightly decreased. Four out of these 7 children showed mild airway infection not adequate to explain the death, but may be sufficient to explain the increased figures of C1 inactivator.

Table 16: Concentration of C1 inactivator, broken down by vaccination status and UCD. *Normal values are available for living adults only.

	Arithmetic mean (mg/l)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=2)	293	181-406			195 - 345	100
Explained UCD, not vaccinated (N=4)	387	265-496	393	120	195 - 345	50
Unexplained UCD, vaccinated (N=8)	267	65-473	243	126	195 - 345	50
Unexplained UCD, not vaccinated (N=8)	237	102-428	169	131	195 - 345	75

C3

C3 is a glycoprotein with central importance in both the classical and the alternative pathway of complement activation. C3 can be cleaved into C3a and C3b spontaneously at low level or by C3 convertase at high level. The smaller fragment C3a is an anaphylatoxin and mediator of local inflammatory reaction. The larger fragment C3b binds with C3 convertase to form C5 convertase [28].

In one vaccinated case and one not vaccinated child in the group with explained UCD C3 concentrations higher the normal value were determined. Both infants had severe infections, which may explain the increased C3 concentrations. Normal values were found in 5 children, while the remaining 15 (3 explained UCD, 12 unexplained UCD) showed decreased concentrations. The

[28] Janssen BJ, Huizinga EG, Raaijmakers HC, Roos A, Daha MR, Nilsson-Ekdahl K, Nilsson B, Gros P (2005) Structures of complement component C3 provide insights into the function and evolution of immunity. *Nature* 437: 505–511

arithmetic mean of the C3 concentration is obviously higher in children who had died due to explained causes of death. This can be due to the presence of inflammatory diseases in these cases. With regard to decreased concentrations, it can only be supposed that complement factors become instable within some hours after death leading to decreased concentrations compared to the normal values which are given for living children.

Table 17: C3 concentrations, broken down by vaccination status and UCD
* Normal values are available for living children younger than 2 years.

	Arithmetic mean (mg/l)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=2)	1081	171-1990			800 - 1700	50
Explained UCD, not vaccinated (N=4)	945	194-1840	874	772	800 - 1700	75
Unexplained UCD, vaccinated (N=8)	479	0-1240	208	481	800 - 1700	62.5
Unexplained UCD, not vaccinated (N=8)	242	0-1200	36.6	414	800 - 1700	87.5

C4

In the absence of C4, immune complexes will not be cleared by C3 activation peptides, but bacterial infections can still be defended via the alternative pathway. C4 may be decreased in systemic Lupus erythematosus (SLE), early glomerulonephritis, immune complex disease, cryoglobulinaemia, hereditary angioedema, and congenital C4 deficiency.

One child (explained UCD, vaccinated) who had died due to severe infection showed an increased C4 concentration compared to age related normal values [29](Table 18). In fife cases out of the group with unexplained UCD, decreased figures were determined (one vaccinated, 4 not vaccinated). Signs associated with one of the above listed diseases were not found in any case. Therefore we suppose that concentrations could be influenced by post-mortem changes.

[29] : http://www.med4you.at/laborbefunde/referenzwerte/referenzbereiche_c3_c4_ch50.htm#C3

Table 18: C4 concentrations, broken down by vaccination status and UCD.
*Normal values are available for children younger two years of age.

	Arithmetic mean (mg/l)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=2)	410	171-650			70 - 400	50
Explained UCD, not vaccinated (N=4)	262	171-418	230	111	70 - 400	25
Unexplained UCD, vaccinated (N=8)	184	0-292	206	92	70 - 400	12.5
Unexplained UCD, not vaccinated (N=8)	136	0-374	36.6	170	70 - 400	50

5.2.3 Cytokine concentrations

TNFα

Tumour necrosis factor α (TNFα) is produced mainly by macrophages, but also by lymphocytes, mast cells, endothelial cells, fibroblasts, and neuronal tissue. Large amounts of TNFα are released in response to lipopolysaccharide, other bacterial products, and IL-1.

It is responsible for a number of actions on various organ systems, generally together with IL-1 and IL-6. The stimulation of acute phase responses in the liver is important, leading to an increase in C-reactive protein and a number of other mediators. Furthermore it induces insulin resistance by promoting serine-phosphorylation of insulin receptor substrate-1 (IRS-1), which impairs insulin signalling. It stimulates the phagocytotic activity of macrophages and the production of IL-1 oxidants and the inflammatory lipid prostaglandin E2 $PGE_{2.}$

A local increase in concentration of TNF will cause the cardinal signs of inflammation (heat, swelling, redness, and pain). High concentrations of TNFα induce shock-like symptoms. A prolonged exposure to low concentrations of TNFα can result in cachexia. This can be found, for example, in tumour patients [30,31,32].

[30] Locksley RM, Killeen N, Lenardo MJ (2001) The TNF and TNF receptor superfamilies: integrating mammalian biology. Cell 104: 487–501.

[31] Wajant H, Pfizenmaier K, Scheurich P (2003) Tumor necrosis factor signaling. Cell Death Differ 10: 45–65.

[32] Old LJ (1985) Tumor necrosis factor (TNF). Science 230: 630–632.

TNFα concentrations were increased in 3 respectively 9 cases of both groups (Table 19). In the cases with defined cause of death this increase is the expression of the severe inflammation leading to death (one was vaccinated prior to death). In the cases with unexplained UCD more or less severe inflammatory changes were present in 75%, but these changes were judged to be not sufficient to explain the death. Such inflammatory changes are typical findings in a considerable number of SIDS cases [33]. A TNF-induced shock cannot be assumed on these results.

Table 19: TNFα concentrations, broken down by vaccination status and UCD
*Normal values are available for living adults only.

	Arithmetic mean (pg/ml)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=3)	16.0	0-46.0			0 – 18.9	33.3
Explained UCD, not vaccinated (N=4)	138	9.5-274	134	145	0 – 18.9	50
Unexplained UCD, vaccinated (N=10)	36.3	0-264	5.1	36.3	0 – 18.9	50
Unexplained UCD, not vaccinated (N=10)	23.1	0-74	21.2	22.7	0 – 18.9	62.5

IFN-γ

Interferon gamma (IFN-γ) mediates activation of macrophages, leads to increased production of nitric oxide (NO), and suppresses T cell activation [34]. The involvement of NO in apoptosis of thymocytes and macrophages has also been documented [35,36] and NO markedly inhibits the induction of IL-2 promoter, which can account for most of the reduction in IL-2 production, and weakly increases the activation of IL-4 promoter [37]. This mechanism could be involved in the down regulation of IL-2 gene expression [38].

[33] Entrup M, Brinkmann B (1990) Histologic findings in the lung in sudden infant death. Z Rechtsmed 103:25-33

[34] Abrahamsohn IA, Coffman RL (1995) Cytokine and nitric oxide regulation of the immunosuppression in Trypanosoma cruzi infection. J Immunol 155: 3955–3963.

[35] Fehsel K, Kroncke K-D, Meyer KL, Huber H, Wahn V, Kolb-Bachofen V (1995) Nitric oxide induces apoptosis in mouse thymocytes. J Immunol 155: 2858–2865.

[36] Albina JE, Cui S, Mateo RB, Reichner JS (1993) Nitric oxide-mediated apoptosis inmurine peritonealmacrophages. J Immunol 150: 5080–5085.

[37] Chang R-H, Lin Feng M-H, Liu W-H, Lai MZ (1997) Nitric oxide increased interleukin-4 expression in T lymphocytes. Immunology 90: 364–369.

[38] Soong L, Tarleton RL (1994) Trypanosoma cruzi infection suppresses nuclear factors that bind to specific sites on the interleukin-2 enhancer. Eur J Immunol 24: 16–23.

In five cases of the first (explained UCD) and 18 cases of the second group, IFN concentrations could not be measured (Table 20). In the remaining cases the concentrations were within the normal range (for living adults). Two explanations are possible: 1. normal ranges could have age-related differences; 2. the results could be influenced by post-mortem processes. Furthermore, the measurements can indicate that down-regulation of IL-2 gene expression did not occur, because the down-regulating of IL-2 would lead to an increase in IFN-γ (not investigated in the present study).

Table 20: Concentrations of IFN-γ, broken down by vaccination status and UCD
* Normal values are available for living adults only. red. – reduced (below normal range).

	Arithmetic mean (pg/ml)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=3)	0	0			1.6 – 56.2	100
Explained UCD, not vaccinated (N=4)	1.6	0-4.7	0.8	2.2	1.6 – 56.2	50
Unexplained UCD, vaccinated (N=10)	3.4	0-33.7	0	10.7	1.6 – 56.2	90 (red.)
Unexplained UCD, not vaccinated (N=10)	2.0	0-20.1	0	6.4	1.6 – 56.2	95 (red.)

IL-1ß

Interleukin-1ß is a highly effective cytokine with a number of different functions. In endothelial cells, it triggers the transduction of cyclooxygenase-2 and induces the synthesis of prostaglandine-E2 [39]. During inflammatory reaction it stimulates neurons of the hypothalamus to excrete corticotropin releasing hormone which leads to ACTH stimulation, and cortisone excretion. Furthermore it triggers the IL-6 excretion, the formation and excretion of neutrophil granulocytes in bone marrow, and the formation of CD14 [40].

Seventeen cases (6 explained UCD, 11 unexplained UCD) showed IL-1ß concentration higher than normal (Table 21). One case (UCD: severe infection) showed a very high IL-1ß concentration of >62500 pg/ml. Therefore a cytokine shock has to be discussed in this case. Interestingly, the

[39] Rivest S et al. (2000) How the blood talks to the brain parenchyma and the paraventricular nucleus of the hypothalmus during systemic inflammatory and infectious stimuli. Proc Soc Exp Biol Med 223:22-38.

[40] Dinarello CA (2005) Blocking IL-1 in systemic inflammation. J Exp Med 201:1355-1359.

concentrations of IL-6 and IL-10 are also extremely increased in this case (see Tables 22 and 23). Cases with an explained cause of death are characterised by a higher proportion of cases with increased IL-1ß concentrations as well as a higher average concentration. As a pro-inflammatory cytokine IL-1ß is increased in cases showing more or less severe inflammation which is true for a number of cases of both groups. The IL-1ß concentrations in vaccinated cases are lower than in unvaccinated cases.

Table 21: IL-1 ß concentrations, broken down by vaccination status and UCD.
* Normal values are available for living adults only. [a] One case shows an extremely high concentration which is outside the quantification range of the method (limit: 62500pg/ml).

	Arithmetic mean (pg/ml)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=3)	47	24-80			0 – 34.3	66.6
Explained UCD, not vaccinated (N=4)	15683	51-62479 [a]	91	31209	0 – 34.3	100
Unexplained UCD, vaccinated (N=10)	57	20-201	57	36	0 – 34.3	60
Unexplained UCD, not vaccinated (N=10)	281	0-2418	39	751	0 – 34.3	60

IL-6

Interleukin-6 is one of the interleukins which regulates inflammatory reactions. In the inflammatory pathway it is secondary to TNFα. IL-6 should have a key position for the gateway from inborn to acquired immunity. It should activate the production of acute phase proteins and can act as lymphocyte stimulating factor. In acute inflammation, sIL-6R increases and limits the accumulation of neutrophil granulocytes as well as the immigration of $CD3^+$-T-lymphocytes [41]. This step marks the transformation from inborn to acquired immune reaction [42]. Further functions are the regulation of

- the apoptosis of leukocytes,
- differentiation and proliferation of B-lymphocytes,
- IgG-secretion of B-lymphocytes, and
- differentiation of monocytes [43].

In all cases the IL-6 concentrations measured were highly increased. In some cases this could be the expression of an inflammatory reaction (Table 22). In the cases without inflammation, we do not have a clear explanation. We assume that a mild increase could be due to unspecific agonal expression. Finally, it has to be considered that the normal values are given for living adults. In one case the concentration measured was extraordinarily high (>6030000 pg/ml). Interestingly, the vaccinated children (explained and unexplained UCD) showed lower levels compared to the unvaccinated.

Tsokos et al. [44] found significantly elevated IL-6 concentrations in septic patients compared to a control group (acute myocardial infarction, coronary heart disease, trauma, acute alcohol intoxication were recorded as causes of death in the controls). The authors concluded that post-mortem IL-6 serum levels above 1500 pg/ml indicate septicaemia. Furthermore, the group investigated the time course of post-mortem IL-6 levels and found a time dependent post-mortem increase in 62.5% of the sepsis cases as well as in 38% of the controls. They hypothesized that

[41] Heinrich PC et al. (2003) Principles of interleukin-(IL)-6 type signalling and its regulation. Biochem J 374:1-20.

[42] Jones SA (2005) Directing transition from innate to acquired immunity: defining a role for IL-6.. J Immunol 175:3463-3468.

[43] Fischer CP (2006) Interleukin-6 in acute exercise and training: what is the biological relevance? Exerc Immunol Rev 12:6-33.

[44] Tsokos M, Reichelt U, Jung R, Nierhaus A, Püschel K (2001) Interleukin-6 and C-reactive protein serum levels in sepsis-related fatalities during the early postmortem period. Forensic Sci Int 119:47-56.

this increase could be the result of an increasing post-mortem decomposition of IL-producing cells like monocytes, macrophages and lymphocytes leading to an excretion of cytokines.

Using the reference value of 1500 pg/ml all three vaccinated cases of explained UCD and 7 out of 10 vaccinated cases of unclear UCD were below this figure. The same is true for 3 out of 4 unvaccinated cases of explained UCD as well as 7 out of 10 unvaccinated cases of unclear UCD.

Table 22: IL-6 concentrations, broken down by vaccination status and UCD.
* Normal values are available for living adults only.

	Arithmetic mean (pg/ml)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=3)	525	269-856			0.7 – 6.0	100
Explained UCD, not vaccinated (N=4)	1509065	722-6030013	2762	3013965	0.7 – 6.0	100
Unexplained UCD, vaccinated (N=10)	1631	17-5496	105	2514	0.7 – 6.0	100
Unexplained UCD, not vaccinated (N=10)	5962	18-52695	267	16445	0.7 – 6.0	100

IL-10

Interleukin-10 has a number of functions as a regulator of the immune system and immune response. It is one of the most important anti-inflammatory cytokines. It is mainly produced by monocytes and TH_2 lymphocytes. Main functions are:

- IL-10 suppress the formation of TNF, IL-1, IL-2 and IL-6 in antigen presenting cells as monocytes and dendritic cells, and acts therefore as a suppressor of T-cell activation.
- IL-10 supports the proliferation of B-cells and their differentiation. On the other hand, the excretion of IgE is reduced.
- IL-10 inhibits the interferon formation by natural killer cells or can induce the same pathway if IL-12 is present.
- IL-10 facilitates phagocytises by monocytes and inhibits the antigen presentation [45].

IL-10 concentrations are in normal range except for one case (Table 23). This child had died with high fever and tracheobronchitis. Therefore, normal function of IL-10 in all other cases can be assumed independent on vaccination status.

Table 23: IL-10 concentrations, broken down by vaccination status and UCD.
* Normal values are available for living adults only.

	Arithmetic mean (pg/ml)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=3)	17.2	9.4-30.0			0 – 626	0
Explained UCD, not vaccinated (N=4)	2919	21.3-11439	108	5680	0 – 626	25
Unexplained UCD, vaccinated (N=10)	44.6	0-378	5.9	117.3	0 – 626	0
Unexplained UCD, not vaccinated (N=10)	27.5	1.3-130.2	14.6	38.3	0 – 626	0

IL-18

Interleukin-18 is related to the IL-1 family in terms of its structure, processing, receptor, signal transduction pathway and pro-inflammatory properties. It is mainly expressed by macrophages, dendritic cells, Kupffer cells, keratinocytes, epithelial cells of the intestine, and fibroblasts at sites of

[45] Grütz, G. (2005) New insights into the molecular mechanism of Interleukin-10-mediated immunosuppression. J Leukocyte Biol 77: 3-15.

chronic inflammation, in autoimmune diseases, in a variety of cancers, and in the context of numerous infectious diseases. IL-18 plays an important role in the T-cell-helper type 1 (Th1) response, primarily by its ability to induce IFNγ production in T cells and natural killer (NK) cells [46,47,48].

In all the cases investigated the IL-18 concentrations were much higher compared to “normal” values (Table 24). A post-mortem up-regulation seems to be possible, but needs further confirmation. Furthermore, the normal values were taken from Kilis-Pstrusinska et al. [49], who investigated 15 healthy children aged 3-15 years. This is a very small group. Therefore the question arises whether or not this group can be used to define normal values. In our opinion considerable doubt has to be expressed because of the small number of observations.

Table 24: IL-18 concentrations, broken down by vaccination status and UCD.
*Normal values were taken from Kilis-Pstrusinska et al., who investigated 15 healthy children aged 3-15 years [50].

	Arithmetic mean (pg/ml)	Range	Median	Standard deviation	Normal range *	Values out of normal range (%)
Explained UCD, vaccinated (N=3)	5666	4794-6979			98 – 130	100
Explained UCD, not vaccinated (N=4)	13278	2297-39448	5683	17612	98 – 130	100
Unexplained UCD, vaccinated (N=10)	7062	1883-13443	6285	3523	98 – 130	100
Unexplained UCD, not vaccinated (N=10)	5823	1923-15570	4836	4230	98 - 130	100

[46] Dinarello CA (1999) Interleukin-18. Methods 19: 121-132

[47] Gracie JA, Robertson SE, McInnes IB (2003) Interleukin-18. J Leukoc Biol 73: 213-224

[48] Lebel-Binay S, Berger A, Zinzindohoué F, Cugnenc P, Thiounn N, Fridman WH, Pagès F (2000). Interleukin-18: biological properties and clinical implications.Eur Cytokine Netw 11:15-26

[49] Kilis-Pstrusinska K, Medynska A, Zwolinska D, Wawro A (2008) Interleukin-18 in urine and serum of children with Idiopathic nephritic syndrome. Kidney Bloos Press Res 31: 122-126

[50] Kilis-Pstrusinska K, Medynska A, Zwolinska D, Wawro A (2008) Interleukin-18 in urine and serum of children with Idiopathic nephritic syndrome. Kidney Bloos Press Res 31: 122-126

5.2.4 Discussion of parameters characterising the function of the immune system

First of all it is necessary to have a critical look at the figures in the four groups. In particular, the subgroups of cases who had died due to an explained UCD, stratified by vaccination status, comprise only 2 – 4 cases. A conclusive comparison is hindered by the small sample size.
The **C1-inactivator** showed a mild decrease in eight cases, one case from the group with explained UCD and seven from unexplained cases. The significance of these results is difficult to interpret because normal values were available for adults only. Obviously, in all these cases the serum showed haemolysis influencing the results of the measurement. Nevertheless, a decreased concentration of C1-inactivator can be associated with a deficiency of C1-esterase inhibitor.

In 5 cases measurements for **C3 and C4** gave negative results. Conclusions from these low levels cannot be drawn because these results were influenced by haemolysis of the serum specimens. High C3 and C4 levels (measured in two cases) should be without pathological significance.

IFNγ could be measured in three cases and showed normal concentrations. In all other cases the concentrations were 0 mg/l. We assume that these results were influenced by a post-mortem reduction.

In 12 cases the **TNFα** concentrations were increased compared to normal values. TNFα is one of the acute phase proteins and acts as an activator of macrophages and granulocytes. Therefore increased TNFα levels can be associated with inflammatory reactions.

IL-1β is increased in 18 out of 27 cases (6 out of 7 explained UCD, 12 out of 20 unexplained UCD). This increase indicates that in both groups an activation of macrophages and lymphocytes may have happened due to inflammatory reactions. **IL-6** as well as **IL-18** concentrations were highly increased in all cases compared to normal values (available for adults only). We assume that this phenomenon may be due to an unspecific activation during death or due to post-mortem changes. In living individuals IL-6 can be used as an early marker of infection. Its concentration increases prior to CRP. IL-18 is found in high concentrations in allergic reactions. But its function is not fully understood until now.

Another major difficulty in interpreting the results is that for some of the immunoglobulins, complement factors and cytokines reference values are available only for adults [51]. For others

[51] Pascal A. Berdat1, Thomas J. Wehrle1, Angelika Küng2, François Achermann1, Martin Sutter3, Thierry P. Carrel1 and Urs E. Nydegger1 (2003) Age-Specific Analysis of Normal Cytokine Levels in Healthy Infants. Clin Chem Lab Med 2003; 41:1335–1339

the reference values are insufficiently described [52]. For some of the parameters no age-related normal values are available. In addition, the interpretation of low values is difficult. These low concentrations could be caused by haemolysis of the sera or by post-mortem changes. It could be a task for further investigations to define age-related reference values for children.

5.2.5 Cytokine polymorphisms

It is known that many cytokine genes show polymorphisms which may affect gene transcription, influencing cytokine production [53,54]. Most of these changes are single nucleotide polymorphisms, sometimes microsatellite variations; occasionally other types occur (nucleotide insertions and deletions). To investigate whether or not such polymorphisms occur in association with deaths in the first two years of life, a number of the known polymorphisms were investigated using PCR with sequence specific primers. The allele and genotype frequencies of the following genes were determined:

IL-1α	(T/C -889)		
IL-1β	(C/T -511)	(T/C +3962)	
IL-1R	(C/T pst11970)		
IL-1RA	(T/C mspa111100)		
IL-4Rα	(G/A +1902)		
IL-12	(C/A -1188)		
IFNγ	(A/T -874)		
TGFβ	(C/T codon 10)	(G/C codon 25)	
TNFα	(G/A -308)	(G/A -238)	
IL-2	(T/G -330)	(G/T -166)	
IL-4	(T/G -1098)	(T/C -590)	(T/C -33)
IL-6	(G/C – 174)	(G/A -565)	
IL-10	(G/A -1082)	(C/T -819)	(C/A -592)

[52] http://www.med4you.at/laborbefunde/referenzwerte/referenzbereiche_c3_c4_ch50.htm#C3

[53] De Capei MU, Dametto E, Fasano ME, Rendine S, Curtoni ES (2003) genotyping for cytokine polymorphisms: allele frequencies in the Italian population. J Immunogenetics 30: 5-10

[54] Mytilineos J, Laux G, Opelz G (2004) Relevance of IL10. TGFβ1, TNFα, and IL4Rα gene polymorphisms in kidney transplantation: a collaborative transplant study report. Am J Transplant 4: 1684-1690

The frequencies of the different genetic variants of the genes investigated are given below (Table 25).

Because of the low number of cases who could be investigated in this study, we decided to compare cases of infant death which occurred in their 2nd to 9th month of life (all vaccinated) to children who had died in their 10th to 24th month of life (3 vaccinated, 12 not vaccinated). Although there are some differences when comparing these groups, no substantial differences in the genotypes investigated were found. This is also true when comparing vaccinated and not vaccinated infants (results not shown).

When all dead infants and children were grouped together and genotype frequencies compared to those reported by Javor et al., there are some differences of the allele frequencies for TGF-ß (codon 25), IL-2 (T/G -330), and IL-10 (G/A -1082) (Table 25): For TGF the CG type occurs in the group investigated in 7.4% compared to 15.8% as found by Javor et al.; for IL-2, position 330, the GG genotype was not found in our cases. The frequency reported by Javor et al. was 11.6%; the IL-10 gene shows in position 1082 the homozygous AA in 18.5% of our cases compared to 35% reported by Javor et al.

Because of the small number of cases investigated, we should avoid an overvaluation of these findings. In addition there might be some genetic differences between the German population and the Czech population investigated by Javor et al. [53], as reported for other genotype frequencies [55, 56].

[55] Brdicka, R., Sieglová, Z., Loudová, M. (2000) The short history of DNA analyses used for solving paternity cases and establishing external quality assessment in the Czech Republic. Progr Forensic Genet 8: 612.

[56] Brenner, C.H. (2000) Summary of polymorphic STR allele frequencies and Y chromosome haplotype frequencies. Progr Forensic Genet 8: 109-125.

Table 25: Polymorphisms in genes encoding for various cytokines.

			2 – 9 months (all vaccinated)		10 – 24 months		2 – 24 months		Controls (Javor et al.) [57]	
Groups			1		2		1+2		3	
Cytokine	Pos.	Geno-type	N	%	N	%	N	%	N	%
IL-1 α	-889	CC	9	75.0	8	53.3	17	63.0	76	55.5
		CT	2	16.7	6	40.0	8	29.6	52	38.0
		TT	1	8.3	1	6.7	2	7.4	9	6.5
IL-1ß	-511	CC	4	33.3	7	46.7	11	56.1	69	49.3
		CF	5	41.7	7	46.7	12	36.6	57	40.7
		TT	3	25.0	1	6.6	4	7.3	14	10.0
IL-1ß	3962	CC	9	75.0	10	66.7	19	39.0	81	57.9
		CT	2	16.7	5	33.3	7	48.8	47	33.6
		TT	1	8.3	0	0	1	13.2	12	8.6
IL-1R	1970	CC	7	58.3	5	33.3	12	61.0	53	37.9
		CT	4	33.3	8	53.3	12	34.1	68	48.6
		TT	1	8.3	2	13.4	3	4.9	19	13.6
IL-1RA	11100	CC	0	0	0	0	0	43.9	21	15.0
		CT	4	33.3	6	40.0	10	48.8	55	39.3
		TT	8	66.7	9	60.0	17	7.3	64	45.7
IL-4R α	1902	AA	6	50.0	8	53.3	14	9.8	82	59.4
		AG	5	41.7	5	40.0	11	39.0	47	34.1
		GG	1	8.3	1	6.7	2	51.2	9	6.5
IL-12	-1188	AA	11	91.7	11	73.3	22	61.0	85	61.2
		AG	1	8.3	4	26.7	5	34.1	45	32.4
		GG	0	0	0	0	0	4.9	9	6.5
IFN-γ	874	AA	3	25.0	4	26.7	7	75.6	41	29.3
		AT	7	58.3	5	33.3	12	24.4	67	47.9
		TT	2	16.7	6	40.0	8	0	32	22.9
TGF-ß	10	CC	4	33.3	3	20.0	7	24.4	27	19.4
		CT	3	25.0	5	33.3	8	43.9	71	51.1
		TT	5	41.7	7	46.7	12	31.7	41	29.5

[57] Javor J, Bucova M, Ferencik S, Grosse-Wilde H, Buc M (2007) Single nucleotide polymorphisms of cytokine genes in the healthy Slovak population. Int J Immunogenet 34: 273-80.

			2 – 9 months (all vaccinated)		10 – 24 months		2 – 24 months		Controls (Javor et al.) [58]	
Groups			1		2		1+2		3	
Cytokine	Pos.	Geno-type	N	%	N	%	N	%	N	%
TGF-ß	25	CC	0	0	1	6.7	1	3.7	0	0
		CG	2	16.7	0	0	2	7.4	22	15.8
		GG	10	83.3	14	93.3	24	88.9	117	84.2
TNF α	-308	AA	0	0	0	0	0	2.4	3	2.3
		AG	0	0	5	33.3	5	4.9	21	16.2
		GG	12	100	10	66.7	22	92.7	106	81.5
TNF α	238	AA	0	0	0	0	0	0	0	0
		AG	1	8.3	0	0	1	26.8	11	7.9
		GG	11	91.7	15	100	26	73.2	129	92.1
IL-2	-330	GG	0	0	1	6.7	1	7.3	16	11.6
		GT	8	66.7	10	66.7	18	58.5	55	39.9
		TT	4	33.3	4	26.6	8	34.1	67	48.6
IL-2	166	GG	4	33.3	5	33.3	9	41.5	56	40.6
		GT	7	58.3	8	53.3	15	46.3	62	44.9
		TT	1	8.3	2	13.4	3	12.2	20	14.5
IL-4	-1098	GG	1	8.3	0	0	1	2.4	1	0.7
		GT	0	0	5	33.3	5	14.6	21	15.0
		TT	11	91.7	10	66.7	21	77.8	118	84.3
IL-4	590	CC	9	75.0	13	86.7	22	81.5	94	67.1
		CT	3	25.0	2	13.3	5	18.5	41	29.3
		TT	0	0	0	0	0	0	5	3.6
IL-4	33	CC	9	75.0	13	86.7	22	81.5	94	67.1
		CT	3	25.0	2	13.3	5	18.5	41	29.3
		TT	0	0	0	0	0	0	5	3.6
IL-6	-174	CC	1	8.3	1	6.7	2	7.4	21	15.0
		CT	6	50.0	9	60.0	15	55.6	66	47.1
		TT	5	41.7	5	33.3	10	37.0	53	37.9
Il-6	565	AA	1	8.3	1	6.7	2	7.4	18	12.9
		AG	6	50.0	8	53.3	14	51.9	67	47.9
		GG	5	41.3	6	40.0	11	40.7	55	39.2

[58] Javor J, Bucova M, Ferencik S, Grosse-Wilde H, Buc M (2007) Single nucleotide polymorphisms of cytokine genes in the healthy Slovak population. Int J Immunogenet 34: 273-80.

			2 – 9 months (all vaccinated)		10 – 24 months		2 – 24 months		Controls (Javor et al.) [59]	
Groups			1		2		1+2		3	
Cytokine	Pos.	Geno-type	N	%	N	%	N	%	N	%
Il-10	1082	AA	2	16.7	3	20:0	5	18:5	49	35:0
		AG	8	66:7	11	73:3	19	70:4	61	43:6
		GG	2	16.7	1	6.7	3	11.1	30	21.4
IL-10	819	CC	8	66.7	8	53.3	16		77	55.0
		CT	4	33.3	7	46.7	11		51	36.4
		TT	0	0	0	0	0		12	8.6
IL-10	592	AA	0	0	0	0	0		12	8.6
		AC	4	33.3	7	46.7	11		51	36.4
		CC	8	66.7	8	53.3	16		77	55.0

[59] Javor J, Bucova M, Ferencik S, Grosse-Wilde H, Buc M (2007) Single nucleotide polymorphisms of cytokine genes in the healthy Slovak population. Int J Immunogenet 34: 273-80.

6 Discussion

In this study a very sophisticated diagnostic scheme was used to investigate cases and to classify causes of death. This procedure is in accordance with international recommendations [1, 2, 6]. All decisions concerning the causes of death were made in interdisciplinary case conferences. The criteria for any decision are explained in detail in the epidemiological part of this report.

All but one infant in the age group 2-9 months had died within seven days after various types of vaccines had been administered (see App. 1, cases). In 25% of these cases, a defined natural cause of death (explained UCD) was found by autopsy, including additional investigations. Fifty percent showed typical findings of SIDS and were therefore diagnosed as SIDS (ICD-10 code R95). In the remaining 25%, some important investigations were missing and/or there were additional findings untypical for SIDS. These cases were classified as “unclear” (unexplained UCD) and coded as R98/R99. Using a very strict classification scheme for SIDS, the interdisciplinary case conferences insisted on completeness of all investigation. However, some cases were autopsied four days after death (due to outstanding decisions of the state prosecutors). After that time interval, microbiology samples are usually contaminated and, therefore, useless for diagnosis.

The investigation shows that there are a number of children who had died within the second year of life under circumstances similar to SIDS in the first year, and that autopsy findings are also very similar. This means that the phenomenon defined as “SIDS” is not observed exclusively in the first year of life. Nevertheless, the narrow age range used in the definition of the term SIDS was established by the fact that more than 90% of these deaths did occur during the first year. The frequency of explained causes of death in the second year is about twice as high as in the first year of life. This is in accordance with the general experience that the number of unexplained deaths decreases with increasing age.

Measurement of the brain weight in relation to body weight is one way to characterize brain oedema. The other way – evaluation of the brain oedema during neuropathological investigation – is more subjective. Unfortunately, at present there is no other – no better – method to evaluate brain oedema which could be done under standardised conditions. In one case of the younger age group, the ratio of brain weight to body weight was much higher than in dead controls (SIDS cases from the GeSID study). This could indicate a severe brain oedema. Looking at this case, a ratio of 28% was calculated. In this case, the brain weight of 1560 g in a 2-month-old infant is highly unlikely. All attempts to clarify the situation remained unsuccessful. Using common sense, we think that the recorded brain weight is probably faulty. In one case the ratio could not be calculated because the infant’s body weight was not recorded.

However, in 13 out of 14 infants who had died after vaccination, the brain weight was in the normal range. Nevertheless, in six cases the neuropathologist diagnosed brain oedema. One of these infants suffered from a generalised viral infection including meningoradiculitis, after having been on ICU for seven days. Another infant with a brain oedema had died due to severe cardiac malformations with chronic oxygen deprivation, which could have contributed to the brain oedema together with resuscitation attempts. In the third infant a respiratory tract infection caused by Klebsiella pneumoniae was diagnosed. In the remaining three cases a clear or obvious explanation for brain oedema was not found. We have to consider that a mild brain oedema is a frequent finding in SIDS and is unspecific with regard to its aetiology. At present we cannot fully exclude that mild brain oedema may be found occasionally in association with vaccination. From the brain weights measured in the investigated cases and from the brain-body ratios calculated in this study, however, it cannot be concluded that vaccination is associated with severe brain oedema in this age group.

Neurological disturbances followed by developmental regression in previously well infants after vaccination led to the hypothesis that the vaccine itself could be responsible for a condition called ‘vaccine encephalopathy’. This vaccine encephalopathy is inhomogeneous with regard to the type of vaccination, time lag from vaccination to onset of symptom and clinical symptoms [60].

The onset of Dravet syndrome [61] (epileptic encephalopathy) occurs in the age group when vaccination is recommended to be administered [62], and an association of the initial seizures with e.g. whole cell pertussis vaccination had been assumed [63]. Bale pointed out that since the introduction of acellular pertussis vaccine in the early 90s, the risk of severe neurological symptoms is negligible. Brown et al. [64] “noted a similarity between cases of alleged vaccine encephalopathy and Dravet syndrome” and stressed out, that it is not sufficient to have a time-related association to vaccination. They investigated systematically 14 cases suspicious for vaccine encephalopathy in which the first symptoms occurred within 72 h after vaccination. Twelve

[60] Bale JF (2004) Neurologic complications of immunization. J Child Neurol 19: 405-412.

[61] Dravet C, Bureau M, Oguni H, et al. (2005) Severe myoclonic epilepsy in infancy (Dravet syndrome). In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. Epileptic syndromes in infancy, childhood and adolescence. 4th ed.

[62] Doose H, Lunau H, Castiglione E, Waltz S (1998) Severe idiopathic generalized epilepsy of infancy with generalized tonic-clonic seizures. Neuropediatrics 29: 229–238.

[63] Nieto-Barrera M, Lillo MM, Rodriguez-Collado C, et al. (2000) Severe myoclonic epilepsy in childhood. Rev Neurol 30:620–624.

[64] Brown NJ, Berkovic SF, Scheffer IE (2007) Vaccination, seizures and 'vaccine damage'.Curr Opin Neurol 20:181-187.

cases met the criteria for severe myoclonic epilepsy of infancy (SMEI). They found mutations within the SCN1A in 11 out of 12 cases; in 9 the mutations were *de novo* [65, 66].

In the past, other complications have been discussed as potentially caused by vaccination: vaccines prepared from live-attenuated viruses (measles, mumps, rubella, and trivalent oral poliovirus) may cause symptomatic viral infection of the nervous system, as measles encephalitis, rubella neuritis, and paralytic poliomyelitis [67]. Associations between immunization and brachial plexus neuritis, acute transverse myelitis, and cranial neuropathies have been suggested, but never proven (Fenichel) [58]. An overview was given by Bale in 2004 [51].

The clinical definition of encephalopathy includes an acute generalized disturbance of the brain function, requiring hospitalization and consisting of coma or stupor that cannot be attributed to medication or postictal state. Infants show altered consciousness, delirium, obtundation and/or confusion. Symptoms and morphological findings can greatly vary. In four of our cases, increased body temperature after vaccination was observed (cases 1, 3, 4, and 10). This reaction is obviously the most frequent reaction after vaccination, and usually harmless.

Neurological symptoms were recorded in one case after vaccination (case 2). This infant had shown prolonged sleep phases after vaccination and had died suddenly and unexpectedly during sleep at day two after vaccination. Another child (case 5) had shown neurological symptoms prior to vaccination as a result of a severe malformation of the central nervous system. In all the other cases, it is unlikely from the clinical history that a vaccine encephalopathy was associated with death.

Nevertheless, from the results obtained it cannot be excluded with certainty that the vaccination may have contributed to the risk of death in some of the cases. In particular, more research is required on the question whether or not infants suffering from severe chronic diseases or malformations should be vaccinated during a short stay at hospital [68].

The extended investigations of the immune system did not show any substantial differences between cases with and without defined cause of death, vaccinated or not vaccinated, except for

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[65] 51 Berkovic SF, Harkin L, McMahon JM, et al. (2006) De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. Lancet Neurol 5:488–492.

[66] 49 Claes L, Del-Favero J, Ceulemans B, et al. (2001) De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 68:1327–1332

[67] Fenichel GM (1982) Neurological complications of immunisation. Ann Neurol 12: 119-128

[68] Gaudelus J, Lefevre-Akriche S, Roumegoux C, Bolie S, Belasco C, Letamendia-Richard E et al. (2007) Immunization of the preterm infant. Arch Pediatr 14 Suppl 1:S24-S30.

such parameters which are associated with infection. Most of the infants/children who had died due to infection showed higher levels of immune globulins and cytokines compared to infants/children without inflammatory diseases. Nevertheless, in some of the cases without an explained cause of death ("unclear cases") signs of infection were detected even though not sufficient to explain these deaths. However, any comparison of explained and unexplained cases is impeded by these minor or moderate signs of infection. In addition, as far as results could be obtained for complement factor and cytokine concentrations, it is possible that levels could have been influenced by post-mortem changes. This can be concluded as for some parameters (IL6, IL18) increased concentrations were found in all cases. Decreased concentrations for other parameters can be explained mainly by haemolysis, influencing tests results. One child who had died in the second year of life showed massively increased levels of IgG, IL-1ß, IL-6, IL-10, and IL-18. We suppose that the death occurred as a result of cytokine shock associated with septicaemia (infant with 41.2 °C fever, despite paracetamol, puerperal tracheobronchitits, tonsillitis, severe dehydration). No vaccination was given prior to death.

Unfortunately, ranges of "normal" cytokine concentrations are not available for all age groups during infancy and childhood. For some parameters, reference values were derived from laboratories where only small numbers of cases were investigated. Moreover, reference values were defined for living infants and children. Vege et al. [69] investigated the concentration of IL-6, IL-1ß and TNFα in cerebrospinal fluid of 50 Sudden Infant Death syndrome (SIDS) cases, 9 borderline SIDS cases, 18 infectious deaths, 8 violent deaths and 22 cases with heart/lung diseases. They found that the IL-6 levels in cases of infectious death, heart/lung disease and borderline SIDS were significantly higher than in the "pure" SIDS cases. They concluded that this observation is the result of an immunological stimulation. Nevertheless, in the TOKEN study, cytokine concentrations were measured in serum, that's why the measurements done by Vege et al. cannot be used as references.

In another study performed by Mimasaka [70] levels of Interleukin IL-1ß, IL-6, IL-8, IL-10 in serum obtained from adults were determined. The serum was collected within 2 days after death in 71 adults (mean age 55.5 years). The causes of death were classified as traumatic death (24 cases), unnatural deaths by other than traumatic causes (31 cases, unnatural death group), and deaths due to natural causes (16 cases, natural death group).

[69] Å Vege, TO Rognum, AO Aasen, OD Saugstad (1998) Are elevated cerebrospinal fluid levels of IL-6 in sudden unexplained deaths, infectious deaths and deaths due to heart/lung disease in infants and children due to hypoxia? Acta Paediatr 87:819-824.

[70] Mimasaka S (2002) Postmortem cytokine levels and the cause of death. Tohoku J Exp Med 197:145-150.

The authors found a significant increase of IL-6 and IL-8 levels of the “traumatic” deaths compared to those of the other unnatural death. IL-6 levels showed considerable variability even among similar cases. Unfortunately, detailed information on inflammatory changes was not available.

Only Tsokos et al. [71] investigated the time course of post-mortem IL-levels. They found increasing concentrations of IL-6 associated with an increasing post-mortem time interval. Unfortunately the measurements were done in adults (mean age 52 years). This means that any possible post-mortem change in cytokine concentrations cannot be judged with certainty in our study, particularly in cases with longer time intervals between death and autopsy. Therefore, it would be helpful to investigate cytokine concentrations dependent on age and on post-mortem time interval.

Increased levels of specific IgE were found in one child who had died at the age of 13 months (specific IgE >0.1 KU/l, CUP class 0/1). These levels may be attributed to vaccination given prior to death. Furthermore, specific IgE concentrations higher 0 were determined in some cases. These reactions can be judged as normal reaction of the immune system after contact to antigens. The positive findings in older children who had not been vaccinated within 7 days prior to death can be explained in the same way. All of these had received vaccinations – but in different time intervals before death. A treatment using such antibiotics is not known for these children.

Investigations of the genetic background show different genotypes for TGF-ß, IL-2, IL-4, and IL-10 comparing the investigated cases and results obtained by Javor et el. [72] However, this can be due to a small sample size or as a result of genetic heterogeneity of both populations.

In conclusion: Even with the extensive investigations done in the TOKEN study, not one single case showed clear signs of death due to vaccination. However, it cannot be excluded that vaccination may have played a role like a trigger in the death process of very few cases. It would be helpful to have a bigger sample size. For the immunological investigations, age-related normal values need to be investigated as suitable reference values.

[71] Tsokos M, Reichelt U, Jung R, Nierhaus A, Püschel K (2001) Interleukin-6 and C-reactive protein serum levels in sepsis-related fatalities during the early postmortem period. Forensic Sci Int 119:47-56.

[72] Javor J, Bucova M, Ferencik S, Grosse-Wilde H, Buc M (2007) Single nucleotide polymorphisms of cytokine genes in the healthy Slovak population. Int J Immunogenet 34: 273-80.

Appendix 1: Case reports

Only relevant findings are described.

Case 1

Clinical history

7-month-old boy, uncomplicated pregnancy and delivery. Vaccinated and found lifeless by mother 4 days later*. Body temperature 41 °C. Resuscitation by emergency doctor was initially successful. Admitted to hospital. Death occurred 7 days after admission.

Autopsy findings

Body weight 8030 g (weight for age 25^{th} - 50^{th} percentile), body length 71cm (length for age 10^{th} -25^{th} percentile), head circumference 47 cm (head circumference for age percentile $>97^{th}$).

Signs of intensive care. Tracheobronchitis. Meningitis. Brain weight 1050 g.

Histology/Immunohistochemistry

Purulent bronchitis, meningoradiculitis, suspicious for viral infection of the CNS. Massive oedema of the brain.

Microbiology/virology

Shiga-like-toxin positive (intestine), haemolytic B-Streptococci (trachea),

Toxicology

negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): Polymyxin B IgE 0.04 kU/l, IL-1ß 80 pg/ml, L-6 856 pg/ml, TNFα 46.0 pg/ml.

Final diagnosis: Brain death caused by meningoradiculitis (A88.8).

Epicrisis: Death after 7 days of intensive care with sign of general viral infection.

*** The event (found lifeless by the mother) was 4 days after vaccination, therefore the case conference included this cases as 'event' within 6 days after vaccination".**

Case report 2

Clinical history

2-month-old female infant. Pregnancy complicated by haemorrhages in months 2 and 3. Umbilical cord loop at delivery, mild O_2 lack after birth. Prolonged sleeping phases the day after vaccination Found lifeless in bed the second day after vaccination in the morning. No signs of illness prior to death.

Autopsy findings

X-ray examination of the skeleton without any pathological findings.

Body weight 6800 g (weight for age >97th percentile), body length 61cm (length for age 95th – 97th percentile), head circumference 40 cm (head circumference for age percentile 75th – 90th percentile)

No pathological findings. Brain oedema, brain weight 580 g (8.5%).

Histology/Immunohistochemistry

Unspecific sialadenitis of the parotid glands.

Microbiology/virology

Not done (four days between death and autopsy).

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): IgG 5540 mg/l, IgM 692 mg/l, IL-1ß 46 pg/ml, IL-6 36 pg/ml, TNFα 38.3 pg/ml

Final diagnosis: unclear (R98).

Epicrisis: SIDS-like case with no additional findings, but no microbiology done (four days between death and autopsy.

Case report 3

Clinical history

8-month-old male infant. Pregnancy uncomplicated. Delivery at 39th week. Two days later after vaccination increased body temperature (39 °C), treated with paracetamol. Found dead on the 4th day after vaccination in prone position. Sister had suffered from enteritis the week prior to death.

Autopsy findings

X-ray examination of the skeleton without any pathological findings.

Body weight 6750 g (weight for age < 3rd percentile), body length 71cm (length for age 50th – 75th percentile), head circumference 45 cm (head circumference for age percentile 50th – 75th percentile). Unreactive intussusception of the bowel. No other pathological findings. Brain weight 920 g.

Histology/Immunohistochemistry

Mild peribronchial infiltration. Generalised brain oedema and congestion.

Microbiology/virology

Klebsiella pneumonia (trachea).

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): Neomycin IgE 0.01 kU/ml, IL-1ß 201 pg/ml, IL-6 5020 pg/ml, TNFα 253 pg/ml

Final diagnosis: SIDS with mild airway infection.

Epicrisis: Classical SIDS case found in prone position with mild upper respiratory tract infection, but not sufficient to explain the death.

Case report 4

Clinical history

2-month-old male infant. Pregnancy and delivery without any complication. Vaccinated two days prior to death. Found dead in prone position. Resuscitation attempts without success. Respiratory tract infection two weeks prior to death.

Autopsy findings

No X-ray examination of the skeleton.

Body weight 6200 g (weight for age 90^{th} – 95^{th} percentile), body length 55 cm (length for age 10^{th} – 25^{th} percentile) , head circumference 39 cm (head circumference for age percentile 25^{th} – 50^{th} percentile). Putride otitis. Respiratory tract infection. No other signs of illness. Brain weight 632 g.

Histology/Immunohistochemistry

Pharyngitis, tracheitis, bronchitis, interstitial pneumonia, sialadenitis, interstitial nephritis: generalised viral infection. Brain oedema and congestion.

Microbiology/virology

Staphylococci (middle ear, trachea, lungs, leptomenix);

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): C1 inactivator 406 mg/l, C3 1990 mg/l, C4 650 mg/l, IgG 6650 mg/l, IgM 977 mg/l, IgA 605 mg/l, Polymyxin B IgE 0.07 kU/ml, IL-1ß 39 pg/ml, IL-6 269 pg/ml.

Final diagnosis: generalised viral infection (B34.9).

Epicrisis: Death due to a viral infection

Case report 5

Clinical history

13-month-old female child, born with hypoplasia of the cerebellum and clouding of the lens of the eye, tetraspastic cerebral paresis after full term pregnancy. Two days before death vaccinated. Found lifeless in bed. Resuscitation attempts without success.

Autopsy findings

Body weight 6780 g (weight for age <3rd percentile), body length 70 cm (length for age 3rd – 5th percentile), head circumference 41 cm (head circumference for age percentile <3rd percentile). Known malformation of the cerebellum (brain weight 570 g) and cataract. No signs of acute disease except of mild laryngitis. No injuries. Injection marks on the right and left hip.

Histology/Immunohistochemistry

Mild infection of the respiratory tract with lymphocytic infiltration of the trachea. Mild activation of the lymphatic tissue and organs. Agonal aspiration of stomach contents. Unspecific sialadenitis. Granularcellhypoplasia of the brain, microcephaly, mild brain oedema.

Microbiology/virology

No specific bacteria detected.

Toxicology

Paracetamol and Doxylamin in therapeutic range (e.g. Paedisup® S/-K) , alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening: normal values for all parameters. Specific IgE for Polymyxin B and Trometanol detected.

Final diagnosis: SIDS-like death with mild respiratory infect in the second year of life (R99).

Epicrisis: The malformation of the brain is a very rare disease, probably not associated with sudden death in early childhood.

Case report 6

Clinical history

3-month-old male infant. Vaccinated one day prior to death. Found dead in prone position. Resuscitation attempts not performed.

Autopsy findings

No X-ray examination of the skeleton.

Body weight 5923 g (weight for age 25th – 50th percentile), body length 64cm (length for age 75th – 90th percentile), head circumference not measured. Signs of putrefaction. Brain weight 711 g.

Histology/Immunohistochemistry

Mild leukocytic infiltration of the myocardium. IHC for inflammatory cells positive.

Microbiology/virology

Not done because of putrefaction.

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): Polymyxin B IgE 0.04 kU/ml, IL-1ß 106 pg/ml, IL-6 106 pg/ml, TNFα 22.0 pg/ml.

Final diagnosis: SIDS with findings of borderline myocarditis (R95).

Epicrisis: borderline SIDS, with findings of myocarditis, prone position.

Case report 7

Clinical history

4-month-old female infant. Pregnancy and delivery without any complication. Vaccinated 3 days prior to death. Found dead in supine position. Resuscitation attempts have not been occurred.

Autopsy findings

No X-ray examination of the skeleton.

Body weight 6300 g (weight for age 50^{th} – 75^{th} percentile), body length 64 cm (length for age 75^{th} – 90^{th} percentile) , head circumference 39 cm (head circumference for age percentile 5^{th} – 10^{th} percentile). No signs of illness. Brain weight 790 g.

Histology/Immunohistochemistry

Mild activation of lymphatic organs and tissues. Mild brain oedema.

Microbiology/virology

Staphylococcus pneumonia and aureus (middle ear, trachea).

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Final diagnosis: SIDS (R95)

Epicrisis: no additional information

Case report 8

Clinical history

4-month-old male infant. Preterm delivery (33 week). Vaccinated the day before death. At the same day increased body temperature, treated with paracetamol.

Found lifeless in side position. Resuscitation attempts without success.

Autopsy findings

X-ray examination of the skeleton without findings.

Body weight 5600 g (weight for age 5^{th} – 10^{th} percentile), body length 59 cm (length for age $<3^{rd}$ percentile), head circumference 41 cm (head circumference for age percentile 10^{th} – 25^{th} percentile). Brain weight 720 g.

Histology/Immunohistochemistry

Activated lymphatic organs. Focal emphysematic lung changes of unclear origin. Acute congestive encephalopathy (mild mononuclear cell infiltration).

Microbiology/virology

Klebsiella pneumoniae (trachea, blood).

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): IgG 4640 mg/l, IgM 859 mg/l, IL-1ß 48 pg/ml.

Final diagnosis: SIDS (R95).

Epicrisis: SIDS in a preterm infant, with upper respiratory tract infection with klebsiella.

Case report 9

Clinical history

14-month-old female child. Born after full term pregnancy. Further development without any complication. Vaccinated on the day of death. Found lifeless in bed in prone position. Resuscitation attempts not done.

Autopsy findings

Body length 78 cm.

Congestion and oedema of the brain. Brain weight 1010 g. Oedema of the lungs. No signs of acute disease. No injuries. Injection marks not detectable.

Histology/Immunohistochemistry

Mild oedema of the lungs.

Microbiology/virology

Obviously not done.

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening not done.

Final diagnosis: SIDS-like death in the second year of life, investigation incomplete (R98).

Epicrisis: A clear diagnosis cannot be made because of incomplete investigation. A cause of death was not detected.

Case report 10

Clinical history

2-month-old male infant. Pregnancy and delivery without any complication. Vaccinated two days before death. Found lifeless in prone position. Resuscitation attempts without success. Family history of Marfan Syndrome.

Autopsy findings

Body weight 5580 g (weight for age 50^{th} – 75^{th} percentile), body length 62 cm (length for age 90^{th} – 95^{th} percentile) , head circumference 40 cm (head circumference for age percentile 50^{th} - 75^{th} percentile). No signs of illness. Brain weight 1560 g.

Histology/Immunohistochemistry

Acute congestion of parenchymatous organs, brain oedema and lung oedema .

Microbiology/virology

Not done

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): not done.

Final diagnosis: unclear (R99).

Epicrisis: incomplete investigation (documented brain weight may be not correct!)

Case report 11

Clinical history

2-month-old female infant, born with atrioventricular septal defect and defect of the ventricular septum after full term pregnancy. Fed by gastric tube because of insufficient increase of body weight. Routine check-up (U4) with vaccination at the day of death, has been given paracetamol. Found lifeless in bed. Resuscitation attempts without success. Died about 10 hours after vaccination on the way to hospital.

Autopsy findings

X-ray examination of the skeleton without any pathological findings.

Body weight 4500 g (weight for age 5^{th} – 10^{th} percentile), body length 58 cm (length for age 25^{th} – 50^{th} percentile), head circumference 38 cm (head circumference for age percentile 5^{th} – 10^{th} percentile). Known malformation of the heart with massive hypertrophy of the right atrium. Heart weight 75 g. Cardiac insufficiency with congestion of the liver (210 g), the spleen (15 g), and the lungs (left 48 g, right 98 g). Effusion in body pleural and abdominal cavities (20-30 ml each). Congestion and oedema of the brain (brain weight 630 g). Hypoplasia of the thymus (12 g). Injection mark on the right hip.

Histology/Immunohistochemistry

Mild infection of the respiratory tract with lymphocytic infiltration of the larynx and focal interstitial pneumonia. Agonal aspiration of stomach contents. Congestion of the liver. Mild signs of shock in the kidneys Hypoplasia of the thymus (12 g).

Microbiology/virology

Trachea: Klebsiella pneumoniae; Streptococcus pneumoniae lungs: Klebsiella pneumoniae, Staphylococcus aureus (TSST positive); Cavum tympani: Streptococcus pneumoniae.

Toxicology

negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening not done.

Final diagnosis: acute cardiac failure due to malformation (Q21.2). Interstitial pneumonia.

Epicrisis: In this very sick child with a defect of the heart the vaccination could be a contributing factor.

Case report 12

Clinical history

3-month-old female infant. Multiple pregnancy and preterm delivery (33 week). ALTE 4 weeks after delivery. Vaccinated almost two days before death. Found lifeless next night prone position. Resuscitation attempts without success.

Autopsy findings

X-ray examination of the skeleton without pathological findings.

Body weight 4510 g (weight for age 5^{th} – 10^{th} percentile) , body length 56 cm (length for age 5^{th} – 10^{th} percentile), head circumference 38 cm (head circumference for age percentile 5^{th} – 10^{th} percentile). Brain weight 562 g. No signs of illness.

Histology/Immunohistochemistry

Not done

Microbiology/virology

No specific bacteria detected. Negative.

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): not done.

Final diagnosis: unclear (R98).

Epicrisis: incomplete investigation, otherwise classical SIDS case.

Case report 13

Clinical history

3-month-old female infant. Born after 38 weeks. Septicaemia on third day of life, was 12 days in hospital. Vaccinated almost three days before death. Found lifeless in bed in prone position. Resuscitation attempts not done. No symptoms of acute disease prior to death.

Autopsy findings

Body weight 5700 g (weight for age 25th – 50th percentile), body length 62 cm (length for age 50th-75th percentile), head circumference 40 cm (head circumference for age percentile 25th – 50th percentile). Mild congestion and oedema of the brain. Brain weight 660 g. No signs of acute disease. No injuries. Injection marks not detectable.

Histology/Immunohistochemistry

Activated lymphatic system. No other pathological findings. Generalized brain oedema and congestion.

Microbiology/virology

Intestine: Clostridium perfringens, toxin negative.

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening: C1 inactivator in creased (473 mg/l), CRP increased (32.8 mg/l), Specific IgE for Polymyxin B positive.

Final diagnosis: SIDS (R95).

Epicrisis: The infant did not show any symptom of disease prior to death. The autopsy and histology gave inconspicuous results. In particular, airway infection, enteritis, carditis, and encephalitis could not be detected. The increased CRP cannot be explained by autopsy findings, but could be a result of enteritis two weeks prior to death.

Case report 14

Clinical history

1 month - old male infant. Pregnancy, delivery and further development without complication.Vaccinated almost 3 days before death. Found prone in his bed. Resuscitation attempts unsuccessful.

Autopsy findings

X-ray examination of the skeleton not done.

Body weight 5320 g (weight for age 50 ^{h} – 75th percentile) , body length 55 cm (length for age 10th – 25th percentile), head circumference 38 cm (head circumference for age percentile 10th – 25th percentile). Mild infection of the lungs and bronchial system. Brain weight 562 g.

Histology/Immunohistochemistry

Lungs: some dyselectasis

Sialadenitis, hyperactivation of the lymphatic system, at the vaccination region: massive inflammatory infiltrates with lymphocytes and a central necrosis of the subcutaneous tissue. Brain oedema and congestion.

Microbiology/virology

Staph. aureus, in the lungs and stomach.

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening (increased parameters): not done.

Final diagnosis: SIDS (R95).

Epicrisis: complete investigation, classical SIDS case, found prone, but necrosis at the vaccination site.

Case report 15

Clinical history

11-month-old female infant. Vaccinated at the day of death. Died during feeding! Resuscitation attempts without success.

Autopsy findings

X-ray investigation of the skeleton without pathological findings.

Body weight 10700 g (weight for age 75^{th} – 90^{th} percentile) , body length 79 cm (length for age >97^{th} percentile) , head circumference 45 cm (head circumference for age percentile 50^{th} – 75^{th} percentile).

Oedema of the brain. Brain weight 985 g. Mild emphysema of the lungs. Some petechial haemorrhages subpleural. Aspiration of stomach contents. No signs of acute disease. No injuries. Injection mark on left tight.

Histology/Immunohistochemistry

Tracheitis and focal interstitial pneumonia. Aspiration of stomach contents. Acute emphysema of the lungs.

Microbiology/virology

Trachea: Klebsiella oxytoca; intestine: Clostridium difficile positive, toxin A + B positive; blood: Klebsiella oxytoca.

Toxicology

Negative, alcohol concentration 0.0 mg/l.

Screening for metabolic disturbances negative.

Immunological screening not done.

Final diagnosis: aspiration of stomach contents (W78.0).

Epicrisis: A suffocation due to aspiration of stomach contents is supposed. The emphysema of the lungs indicates the vital genesis of the aspiration. It could be due to airway infection (tracheitis, interstitial pneumoniae) and/or enteritis (detection of Clostridium difficile may occur in healthy infants too).

Appendix 2: List of references for cytokine concentrations.

TOKEN-Study/Immunologic investigation

Parameter	Methode	Normbereich (<2 J.)	Einheit	Referenz/Bemerkung	1. Normbereich Erwachsener	Referenz	Referenz
CH100	RID (Radiale Immundiffusion)		U/mL		392-1019	Teskit	
C1-INAKT.	RID (Radiale Immundiffusion)		mg/L		195-345	Teskit	
C3	RID (Radiale Imn	800-1700	mg/L	http://www.med4you.at/laborbefunde/referenzwerte/referenzbereiche_c3_c4_ch50.htm#C3	w: 1032-1495; m:	Teskit	
C4	RID (Radiale Imn	70-400	mg/L	http://www.med4you.at/laborbefunde/referenzwerte/referenzbereiche_c3_c4_ch50.htm#C3	w: 167-385; m: 1(	Teskit	
IgG	RID (Radiale Imn	ca. 139-1139	mg/L	je nach Alter sehr unterschiedlich, s. Ergebnistabelle!		Teskit	
IgM	RID (Radiale Imn	ca. 16-229	mg/L	je nach Alter sehr unterschiedlich, s. Ergebnistabelle!		Teskit	
IgD	RID (Radiale Immundiffusion)		mg/L		1,3-152,7	Teskit	
IgA	RID (Radiale Imn	ca. 3-102	mg/L	je nach Alter sehr unterschiedlich, s. Ergebnistabelle!		Teskit	
IgE (gesamt)	EUROIMMUN Mil	ca. 0-60	IE/mL	je nach Alter sehr unterschiedlich, s. Ergebnistabelle!		Teskit	
Streptomycin IgE	ImmunoCAP für IgE		kU/L		<0,1	Teskit	
Neomycin IgE	ImmunoCAP für IgE		kU/L		<0,1	Teskit	
Polymyxin B IgE	ImmunoCAP für IgE		kU/L		<0,1	Teskit	
Tromethonal IgE	ImmunoCAP für IgE		kU/L		<0,1	Teskit	
CRP	RID (Radiale Immundiffusion)		mg/L		<15	Teskit	
IL-1β	Human IL-1 beta (IL-1F2) ELISA de		pg/mL		0-34,3	BIO-Labor	Labor Eberhard
IL-6	OptEIA Human IL	ca. 1,7-9,2	pg/mL	Berdat 2003 (MW Monat 0-3: 9,0; 4-12: 3,4; 13-24: 1,8)	0-7,6	BIO-Labor	Labor Eberhard
IL-10	OptEIA Human IL	ca. 3,3-5,5	pg/mL	Berdat 2003 (MW Monat 0-3: 3,4; 4-12: 4,3; 13-24: 5,1)	0-626	BIO-Labor	
IFN-γ	OptEIA Human IFN-γ ELISA Set		pg/mL		1,6-56,2	BIO-Labor	
TNF-α	OptEIA Human T	ca. 2,2-3,5	pg/mL	Berdat 2003 (MW Monat 0-3: 2,3; 4-12: 3,6; 13-24: 3,3)	0-18,9	BIO-Labor	Labor Eberhard
IL-18	Human IL-18 ELISA		pg/mL	Datasheet Bender	55-280 (n=8)	Teskit	