Immunization and Sudden Infant Death Syndrome (SIDS): A Selected Annotated Bibliography

Vennemann MM, Hoffgen M, Bajanowski T, Hense HW, Mitchell EA.

**Do immunisations reduce the risk for SIDS? A meta-analysis.**
Vaccine. 2007 Mar 16; [E-pub ahead of print]

Background: There are claims that immunisations cause sudden infant death syndrome (SIDS), but some studies have found either no association or that they are associated with a reduced risk of SIDS. Aims: To conduct a meta-analysis examining the relationship between immunisation and SIDS. Methods: Nine case-controls studies were identified examining this association, of which four adjusted for potential confounders. Results: The summary odds ratio (OR) in the univariate analysis suggested that immunisations were protective, but the presence of heterogeneity makes it difficult to combine these studies. The summary OR for the studies reporting multivariate ORs was 0.54 (95% CI=0.39-0.76) with no evidence of heterogeneity. Conclusions: Immunisations are associated with a halving of the risk of SIDS. There are biological reasons why this association may be causal, but other factors, such as the healthy vaccinee effect, may be important. Immunisations should be part of the SIDS prevention campaigns.


**Sudden infant death syndrome: No increased risk after immunisation.**
Vaccine. 2006 Aug 4; [E-pub ahead of print]

Background: Although previous studies have shown either no association between immunisation and SIDS or even a decreased risk of SIDS, adverse effects, including death, from immunisations continue to cause concern, especially when a new vaccine is introduced. Methods: A large case control study with immunisation data on 307 SIDS cases and 971 controls. Results: SIDS cases were immunised less frequently and later than controls. Furthermore there was no increased risk of SIDS in the 14 days following immunisation. There was no evidence to suggest the recently introduced hexavalent vaccines were associated with an increased risk of SIDS. Conclusions: This study provides further support that immunisations may reduce the risk of SIDS.


Balci Y, Tok M, Kocaturk BK, Yenilmez C, Yorulmaz C.

**Simultaneous sudden infant death syndrome.**
J Clin Forensic Med. 2006 Mar 9; [E-pub ahead of print]
The simultaneous sudden deaths of twins rarely occur and therefore it has received limited attention in the medical literature. When the deaths of the twins meet the defined criteria for sudden infant death syndrome (SIDS) independently and take place within the same 24h range it can be called as simultaneous SIDS (SSIDS). The case(s): Twin girls (3.5-month-old) were found dead by their mother in their crib, both in supine position. The infants were identical twins and delivered at a hospital by cesarean section. Both infants were healthy and did not have any serious medical history. Two days prior to the incident, the twins had received the second dose of oral polio, DPT and the first dose of hepatitis B vaccines and they had fever on the first day of the vaccination and been given teaspoonful of acetaminophen. Death scene investigation, judicial investigation, parental assessment, macroscopic and microscopic autopsy findings and the toxicological analysis did not yield any specific cause of death. The case(s) were referred to a supreme board composed of multidisciplinary medical professionals at the Institute of Forensic Medicine, Ministry of Justice, in Istanbul. The Board decided that the available data was consistent with SIDS. These SIDS case(s) are presented because twin SIDS are rare and this is the first time that a simultaneous twin SIDS have been reported in Turkey. Simultaneous SIDS cases have many implications regarding definition, diagnosis and medico-legal approach.


Hepatitis B vaccines are highly effective and safe and have been incorporated into national immunization programs in over 150 countries. The major humoral immune response is to the common a determinant of the surface antigen protein of the virus. Approximately 5-10% of healthy immunocompetent subjects do not mount an antibody response (anti-HBs). Non-response is associated with different HLA-DR alleles and impaired Th cell response, among other factors such as route of injection, age, gender, body mass, and other factors. Important hepatitis B surface antigen variants have also been identified, which may have a potential impact on immunization and routine screening of blood, blood products and tissues, and organs for transplantation. Strategies for hepatitis B immunization are reviewed. Over 1,000 million doses of hepatitis B vaccine have been used with an outstanding record of safety. There is no evidence of an association between hepatitis B vaccines and the sudden infant death syndrome, chronic fatigue syndrome, and multiple sclerosis (MS). Several studies are in progress on treatment of chronic hepatitis B infection by immunization with multiple antigenic components, combination of vaccine with antiviral drugs and cytokines, T cell vaccines, DNA vaccines alone or with DNA encoded immunomodulatory cytokines, and direct genetic manipulation of antigen presenting cells.

Ottaviani G, Lavezzi AM, Matturri L.
Sudden infant death syndrome (SIDS) shortly after hexavalent vaccination: Another pathology in suspected SIDS?

Experts from panels of the European Agency for the Evaluation of Medical Products have investigated whether there might be a link between hexavalent vaccines and some cases of deaths that occurred. Participants included pathologists with experience in the field of vaccines and sudden infant death syndrome who conducted autopsies. However, to the best of our knowledge, little, if any, attention was paid to examination of the brainstem and the cardiac conduction systems on serial sections, nor was the possibility of a triggering role of the vaccine in these deaths considered. Herein we report the case of a 3-month-old female infant dying suddenly and unexpectedly shortly after being given a hexavalent vaccination. Examination of the brainstem on serial sections revealed bilateral hypoplasia of the arcuate nucleus. The cardiac conduction system presented persistent fetal dispersion and resorptive degeneration. This case offers a unique insight into the possible role of hexavalent vaccine in triggering a lethal outcome in a vulnerable baby. Any case of sudden unexpected death occurring perinatally and in infancy, especially soon after a vaccination, should always undergo a full necropsy study according to our guidelines.

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Brotherton JM, Hull BP, Hayen A, Gidding HF, Burgess MA.
Probability of coincident vaccination in the 24 or 48 hours preceding sudden infant death syndrome death in Australia.

Objective: Vaccination does not cause sudden infant death syndrome (SIDS). However, SIDS peaks at 2 months of age, when vaccination encounters are frequent. There are no published estimates using population data on age of death and immunization coverage to indicate to practitioners how often coincident vaccination may occur by chance. This study aimed to determine the probability that an Australian infant who has died of SIDS was vaccinated in the days before death. Methods: An analytical study of population death data and immunization coverage was conducted for Australian children who were born between April 1, 2002, and March 31, 2003. Also evaluated were Australian children who were registered as dying of SIDS between 1997 and 2001. The main outcomes measured were distribution of SIDS deaths by age and distribution of immunization coverage by age. Results: The probability of recent vaccination and SIDS coinciding varied by age and day of the week of death. The overall estimated probability of vaccination within the last 24 hours for a child who has died of SIDS in Australia is estimated as 1.3%. In the last 48 hours, it is 2.6%. With the average number of SIDS deaths for the period 1997-2001 equal to 130 cases per year, we estimated that a case of SIDS will occur when vaccination was given in the last 24 hours in 1.7 cases per year and within 48 hours in 3.5 cases. Conclusions: Although coincident vaccination and SIDS should not be a frequent problem, it can be expected to occur at least annually in
Australia by chance alone. The probabilities of vaccination by age estimated in this study can also be applied to estimate the probability of a vaccination encounter for children who have experienced any unusual medical condition or death, when these occurrences are known to be unrelated to vaccination.


Vaccinations are considered to be the most effective and safe method preventing infectious diseases. Although hexavalent vaccines like Hexavac((R)) and Infanrix Hexa((R)) are assumed to be well tolerated and safe regarding the rate of immunity [Liese JG, Stojanov S, Berut F, Minini P, Harzer E, Jow S, et al. Large scale safety study of a liquid hexavalent vaccine (D-T-acP-IPV-PRP-T-HBs) administered at 2, 4, 6 and 12-14 months of age. Vaccine 2002;20:448-54; Mallet E, Fabre P, Pines E, Salomon H, Staub T, Schodel F, et al. Immunogenicity and safety of a new liquid hexavalent combines vaccine compared with separate administration of reference licensed vaccines in infants. Pediatr Infect Dis J 2000;19:1119-27], it was noticed that several cases of death occurred shortly after the vaccination. We report six cases of sudden infant death that occurred within 48h after hexavalent vaccination. At post-mortal examination, those cases showed unusual findings, especially in the brain and in laboratory tests. Crude calculations of local epidemiology are compatible with an association between hexavalent vaccination and unusual cases of sudden infant death. If confirmed in systematic studies, our findings would have potentially serious clinical implications.


Deaths in temporal association with vaccination of hexavalent vaccines have been recently reported. The objective of this paper is to assess whether these temporal associations can be attributed to chance. Standardized mortality ratios (SMR) for deaths within 1 to 28 days after administration of either of the two hexavalent vaccines in the 1st and 2nd year of life were determined using the respective annual rates for sudden unexpected deaths (SUDs) from the national vital statistics. The distribution of SUD cases and the vaccination uptake by month were estimated from surveys and sales figures for the individual vaccines. Sensitivity analyses were performed to account for limitations in the data sources. For one of the vaccines, Vaccine B, all SMRs were well below one.
For the other, Vaccine A, SMRs exceeded one insignificantly on the 1st day after vaccination in the 1st year of life. In the 2nd year of life, however, the SMRs for SUD cases within 1 day of vaccination with vaccine A were 31.3 (95% CI 3.8-113.1; two cases observed; 0.06 cases expected) and 23.5 (95% CI 4.8-68.6) for within 2 days after vaccination (three cases observed; 0.13 cases expected). Extensive sensitivity analyses could not attribute these findings to limitations of the data sources. Conclusion: These findings based on spontaneous reporting do not prove a causal relationship between vaccination and sudden unexpected deaths. However, they constitute a signal for one of the two hexavalent vaccines which should prompt intensified surveillance for unexpected deaths after vaccination.

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Infant mortality in Hungary was higher than in other European countries; however, the reported incidence of sudden infant death syndrome (SIDS) has been lower than those for Western Europe and the United States. Childhood immunisation has been reported to be a protective factor for SIDS. In Britain, the change to an earlier immunisation schedule for diphtheria, pertussis, and tetanus appeared to be associated with a shift in the age distribution of SIDS. In 1999, immunisation for Haemophilus influenzae type b (Hib) was introduced for Hungarian infants at the age of 2 months. Data for total infant mortality and SIDS in Hungary were analysed between 1990 and 2002. Infection was the major cause of death among Hungarian infants followed by SIDS. Following introduction of Hib immunisation, there was a decrease in deaths due to meningitis from an average of 3.5% of all infant deaths between 1990 and 1998 to an average of 1% of all infant deaths between 1999 and 2002 (p=0.00). There was also a significant decrease in the proportion of SIDS in the age range > or =2 months from 48% in the earlier period to 39% after introduction of the vaccine (p=0.03). The decrease in SIDS might be due in part to decrease in unrecognised Hib infections or to induction of antibodies by the tetanus toxoid to which the Hib polysaccharide is conjugated that are cross reactive with bacterial toxins implicated in SIDS.


Objective: This was a prospective, controlled, multicenter study to investigate the relationship between Bordetella pertussis infections and sudden unexpected deaths among German infants. Design: Between 1995 and 1997, all infants who died at 7 to 365
days of age and for whom autopsies were performed in 1 of 8 participating institutes of legal medicine were enrolled. During a standardized autopsy, nasopharyngeal specimens (NPSs) and tracheal specimens were obtained for polymerase chain reaction (PCR) assays to detect B pertussis. The oligonucleotide primers PTp1 and PTp2, which specifically amplify a 191-base pair DNA fragment of the pertussis toxin operon of B pertussis, were used. Two control subjects (matched according to residence, age, gender, and nationality) were enrolled for each case subject, via a network of pediatricians in private practice, and NPSs were obtained from those infants. Parents of case subjects and control subjects were asked to provide specific information on respiratory illnesses of the child, contact with a known case of pertussis, or close contact with a person with a cough illness during the 4 weeks before death or enrollment, as well as the child's pertussis immunization status. The pathologists performing the autopsies were unaware of the PCR results. Results: Enrolled were 254 infants (66% male) with sudden unexpected deaths and 441 matched control subjects. Autopsies according to protocol were performed for 234 of the case subjects (92%); a diagnosis of sudden infant death syndrome (SIDS) was made for 76%. For the remaining subjects, causes of death were respiratory or other infections (14%), congenital anomalies or organ failures (4%), aspiration (2%), or accidents or traumatic events (4%). PCR results were positive for B pertussis for 12 case subjects (5.1%) (all with SIDS or respiratory infections) and 5.3% of control subjects. Of the 12 case subjects with positive PCR results, 10 (83%) were male. Questionnaires had been returned by the parents of 5 of the 12 infants. Three had experienced a respiratory illness (all with cough), beginning 7, 14, and 19 days before death. None had a known contact with a case of pertussis. Four of 15 control infants (27%) with positive PCR findings for B pertussis had a cough illness, indicating possible pertussis, and 2 of those 4 developed typical symptoms (whooping). Background information was received from 116 parents (46%) of case subjects and from parents of all control subjects. Upper respiratory tract infections within 4 weeks before death were reported for 53% of case subjects and 38% of control subjects. Also, fewer case subjects (33%) than control subjects (68%) had received age-appropriate numbers of pertussis vaccine doses. Conclusions: The concept of infection as a factor in SIDS is supported by a number of observations, including the seasonal distribution of the occurrence of SIDS; the high incidence of concurrent upper respiratory tract infections among infants dying as a result of SIDS; the peak age at 3 to 4 months; nicotine use in a child's household, which predisposes children to respiratory infections such as otitis media; and the protective role of breastfeeding. A prominent role might be suspected for B pertussis, for several reasons. 1) B pertussis infections in infancy are frequently associated with apneic spells, which are occasionally life-threatening and, if leading to death, might be reported as SIDS. 2) Epidemiologic evidence from the United Kingdom, Sweden, and Norway indicates that SIDS is associated with B pertussis infection. 3) In a previously published study, we detected B pertussis DNA in the nasopharynx of 9 of 51 consecutive infants (18%) with sudden unexpected deaths. This is the first prospective, controlled study to investigate the possible etiologic role of B pertussis in SIDS. Clinically unrecognized B pertussis infections were relatively frequent (5.3%) among control infants during the course of our study. The rate of infection was similar or perhaps greater for control subjects, compared with case subjects (1.7%), when only NPS results were compared. This may seem
surprising but is supported by other studies, in which asymptomatic infections or mild respiratory illnesses were observed among infants exposed to B pertussis. Careful autopsies, including histologic evaluations of organ specimens and use of PCR to detect B pertussis in NPSs and tracheal specimens, represented a strength of this study. Our general findings were as expected. The majority of cases were classified as SIDS. The second largest group included infants for whom respiratory infections were found. The findings of various other diagnoses, which in several instances would have been undiscovered otherwise, emphasize the need for autopsies after unexpected infant deaths. What is the significance of the identified B pertussis infections in 12 cases? Several pieces of evidence support the plausibility of a cause-and-effect relationship. Eight of the 12 case subjects died before 6 months of age, the typical age for death attributable to pertussis. In autopsies, 9 of the subjects were found to have signs of respiratory infections; for 2 infants, the autopsies suggested that death was attributable to a respiratory infection. One additional infant (data not shown) had brain edema (which could have been attributable to hypoxemia during pertussis). Lower rates of completed primary series or age-adequate numbers of pertussis vaccine doses among case subjects than among control subjects may indicate that immunization against pertussis protects children from death attributable to unrecognized B pertussis infection. Moreover, a recent study indicated that immunization with diphtheria-tetanus-pertussis vaccine induces antibodies that cross-react with pyrogenic staphylococcal toxins, which have been implicated in several cases of SIDS. Other microorganisms may be involved in the sudden death of infants, as suggested in this study by the higher rate of a history of concurrent upper respiratory tract infections among case subjects, compared with control subjects. Similarly, in a Scandinavian study, 48% of 244 SIDS case subjects, compared with 31% of 869 control subjects, exhibited symptoms of upper airway infection during the last week before death or interview, respectively. Because SIDS is a diagnosis of exclusion, every attempt should be made to identify a cause of death during autopsy. This should include the search for pathogenic microorganisms in the respiratory tract with the use of PCR and other sensitive tests. In conclusion, B pertussis infection was found for 12 of 234 infants (5.1%) with unexpected deaths, and the infections might have contributed to the deaths.

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Geier DA, Geier MR.  
An evaluation of serious neurological disorders following immunization: A comparison of whole-cell pertussis and acellular pertussis vaccines.  

Serious neurological disorders reported following whole-cell pertussis in comparison to acellular pertussis vaccines were evaluated. The Vaccine Adverse Events Reporting System (VAERS) was analyzed for Emergency Department (ED) visits, life-threatening reactions, hospitalizations, disabilities, deaths, seizures, infantile spasms, encephalitis/encephalopathy, autism, Sudden Infant Death Syndrome (SIDS) and speech
disorders reported with an initial onset of symptoms within 3 days following whole-cell pertussis and acellular pertussis vaccines among those residing in the US from 1997 to 1999. Controls were employed to evaluate potential biases in VAERS. Evaluations as to whether whole-cell and acellular vaccines were administered to populations of similar age and sex were undertaken because these factors might influence the study's results. Statistical increases were observed for all events examined following whole-cell pertussis vaccination in comparison to acellular pertussis vaccination, excepting cerebellar ataxia. Reporting biases were minimal in VAERS, and whole-cell and acellular pertussis vaccines were administered to populations of similar age and sex. Biologic mechanisms for the increased reactogenicity of whole-cell pertussis vaccines may stem from the fact that whole-cell pertussis vaccines contain 3,000 different proteins, whereas DTaP contains two to five proteins. Whole-cell pertussis vaccine contains known neurotoxins including: endotoxin, pertussis toxin and adenylate cyclase. Our results, and conclusions by the US Institute of Medicine, suggest an association between serious neurological disorders and whole-cell pertussis immunization. In light of the presence of a safer and at least equally efficacious acellular pertussis vaccine alternative, the Japanese and US switch to using acellular pertussis vaccine seems well justified. Other countries using whole-cell pertussis-containing vaccines should consider following suite in the near future.


Prenatal and postnatal exposure to cigarette smoke is associated with an increased incidence of the sudden infant death syndrome, although the cause(s) for this is unknown. Tobacco glycoprotein (TGP), a group of proteins purified from cured tobacco leaves and present in cigarette smoke, have been shown to cause anaphylaxis in excised hearts and lungs of adult rabbits that were neonatally sensitized to TGP and later rechallenged. We sought to determine whether anaphylaxis occurred in live infant rabbits who were neonatally sensitized to TGP. At the age of 1 day, 12 animals were sensitized to TGP (0.1mg in 0.25 cc alum) via intraperitoneal injection (i.p.i.) followed by a booster ipi at the age of 30 days (TGP-S). Seven animals received i.p.i. of antigen-free alum only (controls). All animals underwent an intravenous TGP challenge at age 42 +/- 2 days. Heart rate (HR) and respiratory rate (RR) were recorded for 2 min prior to and 5 min after the challenge. Baseline HR (approximately 260) and RR (approximately 120) were similar in all animals. Seven TGP-S animals developed apnea (1.9-4.7s) within 60s of the challenge while none of the controls did. The TGP-S also became bradycardic (the lowest HR over 50 consecutive beats), with the HR decreasing from 260 to 220 vs the controls, whose HR remained constant (approximately 250). We conclude that some rabbits neonatally sensitized to TGP develop apnea and bradycardia upon further intravenous TGP challenge. These studies suggest that cigarette smoke exposure may be associated with a higher rate of SIDS via an anaphylactic mechanism.
predictors of death in infants hospitalized with pertussis: A case-control study of 16 pertussis deaths in Canada.

Objectives: To describe the clinical course of fatal cases of pertussis and identify predictors of death at the time of presentation for medical care. Methods: Case-control study of 16 deaths from pertussis identified by the Immunization Monitoring Program, Active (IMPACT) surveillance network (January 1991-December 2001) matched with 32 nonfatal cases by age, date, and geography. Differences were compared by Fisher exact test and logistic regression. A multivariate model was developed using stepwise logistic regression. Results: All 16 fatal cases were < or =6 months old; 13 were <2 months old. Fatal cases were less likely to have had cough complications during pregnancy (48% vs 14%; P=.046) and more likely to have pneumonia (63% vs 16%; P=.0024) before hospital admission and more likely to have seizures, pneumonia, leukocytosis, and hypoxemia after admission (P<.001 for all comparisons). White blood cell count and pneumonia were independent predictors of fatal outcome in the multivariate model. Conclusions: Infants too young to have begun their immunizations are at highest risk of fatal pertussis infection. Leukocytosis and pneumonia are predictors of a poor outcome; however, rapid progression of the disease may make interventions difficult.

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With current recommendations calling for infants to receive multiple doses of vaccines during their first year of life and with sudden infant death syndrome (SIDS) the most frequent cause of death during the postneonatal period. It is important to respond to concerns that vaccination might play a role in sudden unexpected infant death. A death that occurs suddenly and unexpectedly in the first year of life, whether or not there is an underlying disorder that predisposes to death, has been referred to by the term Sudden unexpected death in infancy (SUDI). SUDI includes deaths that can be attributed to identifiable causes and deaths for which the causes remain uncertain. SIDS is the diagnosis most commonly given to the deaths of uncertain cause. The committee reviewed epidemiologic evidence focusing on three outcomes: SIDS, all SUDI, and neonatal death (infant death, whether sudden or not during the first 4 weeks of life). Based on this review, the committee concluded that the evidence favors rejection of a casual relationship between some vaccines and SIDS; and that the evidence is inadequate to accept or reject a causal relationship between other vaccines and SIDS, SUDI or
neonatal death. The evidence regarding biological mechanisms is essentially theoretical, reflecting in large measure the lack of knowledge concerning the pathogenesis of SIDS. Anaphylaxis related to vaccination has been discussed in detail in previous Institute of Medicine (IOM) reports and is reexamined in the report; the committee observed that anaphylaxis is known to be a rare but causally-related adverse event following the administration of some vaccines. Fatal anaphylaxis in infants is extraordinarily rare. The committee found no basis for a review of current immunization policies, but did see a clear need for continued research on adverse events following vaccination and on the biological basis for sudden unexpected infant deaths. Includes Appendices A-D and 112 references.

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Silvers LE, Varricchio FE, Ellenberg SS.
Pediatric deaths reported after vaccination: The utility of information obtained from parents.

Background: The federally administered Vaccine Adverse Event Reporting System (VAERS) is a passive reporting system that receives domestic and foreign reports of adverse events that occur following immunization. This investigation explored whether routinely interviewing parents for follow-up of VAERS pediatric deaths would provide additional information important to vaccine safety. Methods: The study was designed to follow up 100 consecutive pediatric deaths reported to VAERS by interviewing a parent and a healthcare provider (HCP) for each case. Several strategies contributed to successful follow-up. A standardized questionnaire was utilized to interview HCPs and parents. Overall and specific group frequencies (HCPs and parents) were calculated for each variable. McNemar's statistical tests of exact inference were calculated to assess whether there were statistically significant differences between HCP and parent knowledge by case for various variables. Results: The median age of the cases was 4 months. Approximately half of the deaths were attributed to sudden infant death syndrome. In many instances, the information was equivalent in quality. For certain variables, such as knowledge of the child's position when found in distress, more parents than HCPs indicated that they knew the answer. Conclusions: Conducting parental and HCP follow-up for pediatric deaths reported to VAERS was resource intensive. In some instances, parents were more likely than HCPs to provide information regarding some
important variables about the nature of the death. None of the additional information obtained from parents, however, provided a signal or confirmation of a causal link between the vaccine and death.