

Immunisation and the sudden infant death syndrome

EA Mitchell, AW Stewart, M Clements, RPK Ford, on behalf the New Zealand Cot Death Study Group

Abstract

Aims—To examine the relation between immunisation and the risk of sudden infant death syndrome (SIDS).

Methods—A large nationwide case-control study. Parental held records were used to measure immunisation status.

Results—Infants were at increased risk of SIDS if they had not received the 6 week, 3 month, and 5 month immunisations. After controlling for potential confounding variables, including those which measured health care use and infant illness, the relative risk of SIDS for infants not being immunised at 6 weeks was 2.1 (95% confidence interval=1.2, 3.5). Four per cent of cases died within four days of immunisation and 7.6% of control infants had been immunised within four days of the nominated date. There was a reduced chance of SIDS in the four days immediately following immunisation (OR=0.5; 95% CI=0.2 to 0.9).

Conclusions—Immunisation does not increase the risk of SIDS and may even lower the risk.

(Arch Dis Child 1995; 73: 498-501)

Keywords: immunisation, SIDS.

The age distribution of sudden infant death syndrome (SIDS or cot death) coincides with the timing of immunisations of infants, which has led to the suggestion that immunisations may be the cause of some deaths from SIDS.¹⁻⁵ Several studies have examined the relationship between SIDS and immunisation.⁴⁻¹¹ Some early studies supported this contention,^{4,5} but more recent studies have shown that immunisation is associated with a lower risk of SIDS.⁶⁻¹⁰

There has been considerable concern about SIDS in New Zealand because the mortality rate has been higher than in comparable countries.¹² In New Zealand the anti-immunisation lobby has continued to stress the temporal relation between SIDS and immunisation.^{13,14} Furthermore, it is claimed that these studies are not applicable to New Zealand as in New Zealand the diphtheria-tetanus-pertussis (DTP) immunisation programme begins earlier than in other countries, and hepatitis B immunisation is also given, which was not part of the immunisation programme in the other studies.

The aim of this study was to examine the relation between immunisation and SIDS in New Zealand.

Methods

The New Zealand cot death study has been described in detail previously.^{15,16} In brief it was a large nationwide case-control study that covered 78% of all live births in New Zealand over a three year study period (1 November 1987 to 31 October 1990). There were 716 postneonatal deaths, of which 485 were classified as SIDS. Necropsies were carried out in 474 of the 485 SIDS cases (97.7%).

The cases were compared with 1800 control infants, which were randomly selected from all births in the study regions except home births (less than 1%). The method of selection of controls has been described in detail.¹⁵ Control infants were randomly allocated a nominated date to ensure group matching for infant age, and to a nominated time of day so that the distribution of this time for controls was similar to the expected distribution of the time of death for cases.

Obstetric records were examined and parents (or guardians) interviewed. Parents of SIDS cases were interviewed within one month (mean 38 days, SD 46.5) of death and for controls within one week (mean 6.1 days, SD 13.3) of a nominated time and date.

The immunisation programme in New Zealand consists of: BCG at birth to those 'at risk' infants (the definition of 'at risk' being largely decided locally); DTP at 6 weeks; DTP and polio at 3 and 5 months. Hepatitis B was given according to a schedule which changed during the study period: before March 1987 only infants of mothers who were both HBsAg and HBeAg positive were included in the hepatitis B immunisation programme, which was initially four doses of a plasma derived vaccine at birth, 6 weeks, and 3 and 15 months; for infants born between March 1987 and 29 February 1988, infants of HBsAg positive mothers and all infants in selected regions were included; from 29 February 1988 all infants were included; from 1 December 1989 a recombinant vaccine replaced the plasma derived vaccine and three doses were given, at 6 weeks and 3 and 15 months.

Immunisation status of the infant was assessed from the health and development record (HDR), which is a parent held health record of the child. At the interview the parent was asked to produce the HDR. The immunisation information was extracted. A subject was considered immunised if they had received any component of the immunisation due at the specified age. Immunisation was considered to have been given at (1) birth, (2) 6 weeks, (3) 3 months, and (4) 5 months. Each immunisation component at each time was examined

University of
Auckland, Auckland,
New Zealand,
Department of
Paediatrics
E A Mitchell
M Clements

Department of
Community Health
A W Stewart

Community
Paediatrics, Health
Link South,
Christchurch, New
Zealand
R P K Ford

Correspondence to:
Dr E A Mitchell,
Department of Paediatrics,
School of Medicine,
University of Auckland,
Private Bag 92019,
Auckland, New Zealand.

Accepted 5 September 1995

Table 1 Number (percentage) and univariate and multivariate odds ratios (95% confidence intervals) of SIDS associated with not being immunised

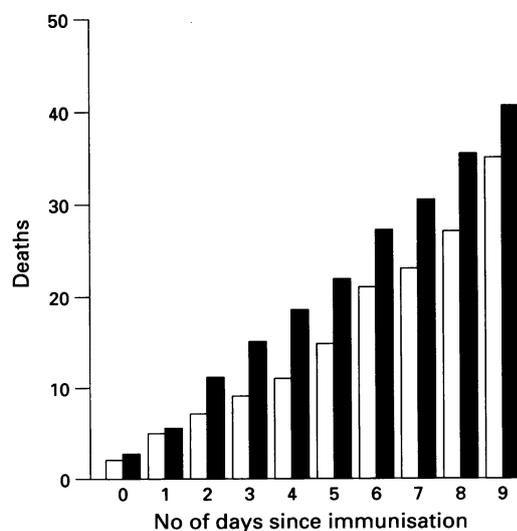
	Cases		Controls		Univariate OR (95% CI)	Multivariate OR (95% CI)
	Immunised	Not immunised	Immunised	Not immunised		
Birth	219 (69.1)	98 (30.9)	1000 (65.6)	524 (34.4)	0.9 (0.7 to 1.1)	1.1 (0.8 to 1.6)
6 Weeks	233 (83.5)	46 (16.5)	1256 (91.5)	117 (8.5)	2.1 (1.4 to 3.1)	2.1 (1.2 to 3.5)
3 Months	103 (72.0)	40 (28.0)	674 (86.7)	103 (13.3)	2.5 (1.6 to 4.0)	1.3 (0.7 to 2.5)
5 Months	31 (62.0)	19 (38.0)	259 (76.6)	79 (23.4)	2.0 (1.1 to 3.9)	2.6 (0.9 to 7.5)

OR=odds ratio; CI=confidence interval.

separately, but as most subjects receive all the individual immunisation components (in a small number of subjects the pertussis component was omitted) the results for each immunisation component at the specific time are highly correlated. Therefore, only any immunisation at the specific time is presented.

Relative risks were estimated by calculation of odds ratios (OR). The univariate ORs have confidence intervals (CI) calculated by the method of Cornfield. Logistic regression was used to control for potential confounding variables: (1) sociodemographic background: marital status, occupation, age mother left school, and age of mother; (2) pregnancy factors: parity, age at first pregnancy, late attendance at antenatal clinic, and antenatal education classes attended; (3) infant factors: ethnicity, sex, birth weight, and gestation; and (4) postnatal factors: region, season, breast-feeding, admission of special care or neonatal intensive care baby units, age of infant, infant taken to child health nurse clinic, maternal smoking, sleep position, bed sharing, and infection. These variables have been defined in detail previously.¹⁵⁻¹⁸

To assess whether immunisation increases the chance of death in the days following an immunisation, the number of cases and controls who had an immunisation in the days before death or the nominated date were compared. This comparison is stratified by age to eliminate any effect of the differences in the age of the two groups. In each stratum the expected number of immunisations within 0



Cumulative expected (black bars) and cumulative observed (white bars) number of deaths 0 to 9 days after immunisation.

to 9 days for the cases was calculated and compared with the observed number. This difference was summed over all strata to achieve a summary statistic. The variance of the observed minus expected was also calculated to give a measure of variability of the summary statistic. This was equivalent to the Mantel-Haenszel test.

Ethical approval for this study was obtained from each of the local ethics committees.

Results

Obstetric records were examined in 465 cases (95.9%) and 1762 controls (97.9%). Parental interviews were completed in 393 cases (81.0%) and 1592 controls (88.4%). Those who were not interviewed were more often Maori and smoked in pregnancy.¹⁹ Of those interviewed, the HDR was available in 317 cases (80.7%) and 1524 controls (95.7%). The cases without their HDR tended to be single, Maori, and to live in the North Island compared with cases with their HDR.

Table 1 shows the relative risk of SIDS associated with not being immunised at each immunisation time. There was no increased risk of SIDS for infants who had not been immunised at birth. At the univariate level there was an increased risk of SIDS for infants who had not been immunised at the 6 week and the 3 and 5 month immunisation times. After adjustment for potential confounding variables there was a significant increase in risk of SIDS in infants not immunised at 6 weeks of age. There was an increased risk of SIDS for infants not immunised at 3 and 5 months, but this did not reach statistical significance (p=0.3 and p=0.12 respectively).

As bias might be introduced into the analyses by there being more cases than controls with unknown immunisation status, analyses using the very extreme situations of full immunisation or no immunisation at all for all cases and controls without the HDR were undertaken. The odds ratios in table 1 changed only slightly, but only the 6 week multivariate odds ratio changed from being statistically significant (OR=2.1; 95% CI=1.2 to 3.5) to nearly statistically significant (OR=1.6; 95% CI=1.0 to 2.7; p=.07) if full immunisation is assumed for all subjects interviewed but not having the HDR.

More of the control group had immunisations within the four days before their nominated date than did the cases before their date of death (7.6% and 4.0% respectively). Whether the cut off used was the actual day or one to nine days before the death or the nominated date, a higher proportion of controls than cases had been immunised. The differences between cases and controls at four days before the death or the nominated date was significant (table 2, figure). The four day effect was the same after adjustment for potential confounding variables in a multivariate (logistic) regression.

Discussion

We have found that immunisation is associated with a lower risk of SIDS; however, potential

Table 2 Relative risk of SIDS in the days following immunisation

Days before death/nominated day	Odds ratio (95% CI)	p Value
Day of immunisation	0.7 (0.2 to 2.8)	0.6
The day plus 1	0.9 (0.3 to 2.4)	0.8
The day plus 2	0.5 (0.2 to 1.2)	0.14
The day plus 3	0.5 (0.2 to 1.0)	0.06
The day plus 4	0.5 (0.2 to 0.9)	0.03
The day plus 5	0.6 (0.3 to 1.0)	0.06
The day plus 6	0.7 (0.4 to 1.1)	0.13
The day plus 7	0.6 (0.4 to 1.0)	0.07
The day plus 8	0.6 (0.4 to 1.0)	0.06
The day plus 9	0.8 (0.5 to 1.2)	0.2

CI=confidence interval.

limitations of this study must be considered. In New Zealand, most immunisations are given by the general practitioner, with community child health nurses giving some. As there is no central record of immunisation, ascertainment of immunisation status is difficult. Although general practitioners do keep records of immunisations given, they are unsatisfactory for assessment of immunisation status of some children because of the mobility of many families between different practitioners. Community nursing records may be inaccurate as they rely on parental recall.

Evidence of immunisation in this study was based on the HDR, which relies upon the family taking the document to the general practitioner and the general practitioner completing it. However, there is good agreement between the immunisation status of the infant and that recorded in the HDR (P Stehr-Green, personal communication). The HDR could be produced for inspection by the majority of the interviewed parents of control infants (96%), but was available for significantly fewer cases. This probably reflects the loss or destruction of the HDR by the parents following the death of their baby. However, we have shown that the missing data do not affect the study's conclusions.

In this study we found that SIDS cases were less likely to have received the 6 week, 3 month, and 5 month immunisations than the control population. This observation may have been the result of confounding, as follows. (1) The sociodemographic risk factors for SIDS are similar to those for not being immunised, so we adjusted for these potential confounders.²⁰⁻²² (2) Use of health care services is also a potential confounder.²³ To adjust for this we included late attendance at antenatal clinic, non-attendance at antenatal education classes, and attendance at community child health clinics in the multivariate analysis. (3) In several previous studies,²⁴⁻²⁶ including an earlier report from this study,¹⁸ it has been found that SIDS infants are in poorer health than the control subjects. Although fever is not a contraindication to immunisation, some general practitioners are reluctant to immunise febrile children, and mothers may not bring their child to be immunised when unwell. The analysis was adjusted for an illness score, although illness was not necessarily present at the time of the immunisation. After adjusting for this wide range of potential confounding variables, including sociodemographic, health care

utilisation and illness, the 6 weeks immunisation was still associated with a significantly reduced risk of SIDS.

The earliest studies reporting an increased risk of SIDS with immunisation had no control data.¹⁻³ The first two studies with control data which suggested a temporal relationship between SIDS and immunisation has been criticised because of methodological bias.²⁷ A study from Sheffield found no association between SIDS and immunisation.⁶ More recent studies have found an increased risk of SIDS when infants are not immunised.⁷⁻⁹ Recently, the Institute of Medicine of the National Academy of Sciences has reviewed causal relations between childhood immunisations and serious health consequences, including SIDS.²⁸ Based on data from all available sources they stated that the evidence favours rejection of a causal relationship between DTP immunisation and SIDS. However, they stated that the evidence was inadequate to accept or reject a causal relationship between SIDS and oral polio, hepatitis B, and *H influenzae* type B immunisations. They concluded that, as SIDS occurs in the same age group as those who are receiving immunisations, in the past some have mistaken this temporal association for a causal association.²⁹

Our study has been able to adjust for a more extensive range of confounding variables than previous studies. For those who were immunised there was a reduced risk of SIDS in the four day period after immunisation. A biological explanation for this observation is entirely speculative. Following immunisation infants are often more irritable, restless, and have more disturbed sleep, all factors associated with a lower risk of SIDS.^{18 30} Immunisation also attenuates the fall in the infant's body temperature at night,³¹ and this might suggest that infants would be less able to cope with thermal stress, which would be expected to increase the risk of SIDS. However, in a study of 21 normal infants monitored before and after immunisation, although nearly all had a rise in rectal temperature on the night of the immunisation, this was not associated with any increase in apnoea density (R P K Ford, unpublished data).

This observation supports the finding of Griffin *et al.*¹⁰ who found a lower risk of SIDS from zero to three days, four to seven days, and eight to 14 days after DTP immunisation compared with the risk 31 days or more after immunisation. Their study was prompted by the report from a much smaller study that there was a 7.3-fold increased risk of SIDS in the period from zero to three days after DTP immunisation.⁹ However, this was based on only four SIDS cases in this period.

We cannot be certain that immunisation actually protects against SIDS, as it is possible that there is residual confounding which has not been accounted for. However, we can confidently state that immunisation is not a significant factor in the occurrence of SIDS. Furthermore, there appears to be no increased risk of SIDS with hepatitis B immunisation or with immunisation with DTP at 6 weeks of age.

Other members of the New Zealand Cot Death Study Group are Drs B J Taylor, D M O Becroft, R Scragg, E M Allen, I B Hassall, A P Roberts, Mrs S Williams, and Mr J M D Thompson. The study was funded by the Health Research Council of New Zealand (HRC) and the Hawke's Bay Medical Research Foundation (HBMRF). Mrs C Everard coordinated the study. We thank the pathologists and research interviewers in the study regions. We sincerely thank the parents who participated in this study. Mr Stewart, Mrs Williams, and Mrs Everard were funded by HRC and Mr Clements was funded by HBMRF.

- 1 Hutcheson R. DTP immunization and sudden infant death - Tennessee. *MMWR* 1979; 28: 131-2.
- 2 Hutcheson R. Follow-up on DTP immunization and sudden infant deaths - Tennessee. *MMWR* 1979; 28: 134-5.
- 3 Bernier RH, Frank JA, Dondero TA, Turner P. Diphtheria-tetanus toxoids-pertussis immunization and sudden infant deaths in Tennessee. *J Pediatr* 1982; 101: 419-21.
- 4 Torch WA. Diphtheria-pertussis-tetanus (DPT) immunization: a potential cause of sudden infant death syndrome (SIDS) [abstr]. *Neurology* 1982; 32: A169.
- 5 Baraff LT, Ablow WJ, Weiss RC. Possible temporal association between diphtheria-tetanus toxoid-pertussis immunization and sudden infant death syndrome. *Pediatr Infect Dis* 1983; 2: 7-11.
- 6 Taylor EM, Emery JL. Immunization and cot deaths. *Lancet* 1982; ii: 5-6.
- 7 Solberg LK. *DTP immunization, visits to child health center and sudden infant death syndrome (SIDS)*. Report to the Oslo Health Council, Norway, 1985; 131 pp.
- 8 Hoffman HJ, Hunter JC, Damus K, et al. Diphtheria-tetanus-pertussis immunization and sudden infant death: results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of sudden infant death risk factors. *Pediatrics* 1987; 79: 598-611.
- 9 Walker AM, Jick H, Perera DR, Thompson RS, Knauss TA. Diphtheria-tetanus-pertussis immunization and sudden infant death syndrome. *Am J Public Health* 1987; 77: 945-51.
- 10 Griffin MR, Ray WA, Livengood JR, Schaffner W. Risk of sudden infant death syndrome after immunization with the diphtheria-tetanus-pertussis vaccine. *N Engl J Med* 1988; 319: 618-23.
- 11 Bouvier-Colle MH, Flahaut A, Messiah A, Jouglu E, Hatton F. Sudden infant death and immunization: an extensive epidemiological approach to the problem in France - winter 1986. *Int J Epidemiol* 1989; 18: 121-6.
- 12 Mitchell EA, Scragg R, Stewart AW, et al. Cot death: the New Zealand study. *Contemporary Health Issues* 1989; 1: 67-72.
- 13 Kalokerinos A. Vaccinations linked to cot deaths. *Northland Times*, 26 March 1992.
- 14 The Immunisation Awareness Society Inc. Newsletter, 1992; 5(1).
- 15 Mitchell EA, Scragg R, Stewart AW, et al. Results from the first year of the New Zealand cot death study. *NZ Med J* 1991; 104: 71-6.
- 16 Mitchell EA, Taylor BJ, Ford RPK, et al. Four modifiable and other major risk factors for cot death: the New Zealand study. *J Paediatr Child Health* 1992; 28 (suppl 1): S3-8.
- 17 Ford RPK, Mitchell EA, Scragg R, Stewart AW, Taylor BJ, Allen EM. Factors adversely associated with breastfeeding in New Zealand. *J Paediatr Child Health* 1994; 30: 483-9.
- 18 Taylor BJ, Williams SM, Mitchell EA, Ford RPK. Symptoms, sweating and reactivity of infant who die of SIDS compared to community controls. *J Paediatr Child Health* (in press).
- 19 Stewart A, Mitchell EA. New Zealand cot death study and missing data [letter]. *J Paediatr Child Health* 1993; 29: 70.
- 20 Nasser K, Latifi M, Azordegan F, Shafii F, All-e-Agha R. Determinants of partial participation in the immunisation programmes in Iran. *Soc Sci Med* 1990; 30: 379-83.
- 21 Wiecha JM, Gann P. Does maternal prenatal care use predict infant immunization delay? *Fam Med* 1994; 26: 172-8.
- 22 Miller LA, Hoffman RE, Baron AE, Marine WM, Melinkovich P. Risk factors for delayed immunization against measles, mumps, and rubella in Colorado two-year-olds. *Pediatrics* 1994; 94: 213-9.
- 23 Ford RPK, Mitchell EA, Taylor BJ. Well health care and the sudden infant death syndrome. *J Paediatr Child Health* 1994; 30: 140-3.
- 24 Ray CG, Beckwith JB, Hebestreit AB, Bergman AB. Studies of the sudden infant death syndrome in King County, Washington. The role of viruses. *JAMA* 1970; 211: 619-23.
- 25 Respiratory infection and sudden infant death [editorial]. *Lancet* 1989; ii: 1191-2.
- 26 Gilbert R, Rudd P, Berry PJ, et al. Combined effect of infection and heavy wrapping on the risk of sudden unexpected infant death. *Arch Dis Child* 1992; 67: 171-7.
- 27 Mortimer EA, Jones PK, Adelson L. DTP and SIDS. *Pediatr Infect Dis* 1983; 2: 492-3.
- 28 Stratton KR, Howe CJ, Johnson RB. Adverse events associated with childhood vaccines other than pertussis and rubella. *JAMA* 1994; 271: 1602-5.
- 29 Fulginiti VA. How safe are pertussis and rubella vaccines? A commentary on the Institute of Medicine report. *Pediatrics* 1992; 89: 334-6.
- 30 Hoffman HJ, Damus K, Hillman L, Krongrad E. Risk factors for SIDS: results of the National Institute of Child Health and Human Development SIDS cooperative epidemiological study. *Ann NY Acad Sci* 1988; 533: 13-30.
- 31 Rawson D, Petersen SA, Wailoo MP. Rectal temperature of normal babies after first diphtheria, pertussis, and tetanus immunisation. *Arch Dis Child* 1990; 65: 1305-7.