The UK accelerated immunisation programme and sudden unexpected death in infancy: case-control study

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Abstract

Objectives To investigate whether the accelerated immunisation programme in the United Kingdom is associated, after adjustment for potential confounding, with the sudden infant death syndrome.

Design Population based case-control study, February 1993 to March 1996. Parental interviews were conducted for each death and for four controls matched for age, locality, and time of sleep. Immunisation status was taken from records held by the parents.

Setting Five regions in England with a combined population of over 17 million.

Subjects Immunisation details were available for 93% (305/325) of infants whose deaths were attributed to the sudden infant death syndrome (SIDS); 90% (65/72) of infants with explained sudden deaths; and 95% (15/15/588) of controls.

Results After all potential confounding factors were controlled for, immunisation uptake was strongly associated with a lower risk of SIDS (odds ratio 0.45 (95% confidence interval 0.24 to 0.85)). This difference became non-significant (0.67 (0.31 to 1.43)) after further adjustment for other factors specific to the infant's sleeping environment. Similar proportions of SIDS deaths and reference sleeps (corresponding to the time of day during which the index baby had died) among the controls occurred within 48 hours of the last vaccination (5% (7/149) vs 5% (41/822)) and within two weeks (21% (31/149) vs 27% (224/822)).

No longer term temporal association with immunisation was found (P = 0.78). Of the SIDS infants who died within two weeks of vaccination, 16% (5/31) had signs and symptoms of illness that suggested that medical contact was required, compared with 26% (16/61) of the non-immunised SIDS infants of similar age. The findings for the infants who died suddenly and unexpectedly but of explained causes mirrored those for SIDS infants.

Conclusions Immunisation does not lead to sudden unexpected death in infancy, and the direction of the relation is towards protection rather than risk.
Introduction

The age at which infants receive their primary course of immunisation corresponds to the peak age for the incidence of the sudden infant death syndrome, promoting speculation that these two events might be related. During the past 20 years sporadic reports and some methodologically weak case-control studies showed a possible association. However, a series of studies came to the opposite conclusion, and one raised the possibility that an accelerated immunisation programme directly contributed to a reduction in these deaths. All these studies share the weakness that they may be biased by residual confounding. In particular, an infant who is showing minor symptoms may have immunisation delayed, and infants from the most deprived and geographically mobile families are least likely to be immunised.

In 1990 the national immunisation programme in the United Kingdom was accelerated, with immunisation against diphtheria, tetanus and pertussis, and oral poliomyelitis given at ages 2, 3, and 4 months respectively instead of at ages 3, 5, and 9 months. Since 1992 immunisation against Haemophilus influenzae type b has also been given.

We conducted a large case-control study of sudden unexpected death in infancy as part of the Confidential Enquiry into Stillbirths and Deaths in Infancy, after the changes in the immunisation programme and the reduction in the rate of the sudden infant death syndrome in the early 1990s. We examine here one of the primary hypotheses of the study—a temporal relation between the accelerated immunisation programme and time of death.

Methods

The methods of the study are described elsewhere. Briefly, it was a large, population based, case-control study initially conducted in three former health regions (the South West, Northern, and Yorkshire regions) for two years (February 1993 to January 1995) and expanded (Wessex and Northern regions) for a third year (April 1995 to March 1996). Ethical approval was obtained in each region from the local research ethics committees. The study aimed to include all sudden unexpected deaths (both explained and unexplained) of infants aged 1 week to 1 year from a total study population of 17.7 million people. Four age matched controls for each case were selected.

An interviewer visited each control family (matched for locality) within a week of the death to collect the same data as for the index case. A period of sleep (the “reference sleep”) corresponding to the time of day during which the index baby had died was identified in the 24 hours before the interviews of the control families.

Data were collected on a questionnaire by research interviewers and from medical records, including details of immunisation from records held by parents. A multidisciplinary committee established cause of death after a full paediatric postmortem examination to a standard protocol.

A modified form of the Cambridge Baby Check was included to capture signs and symptoms of illness in the final 24 hours before death or reference sleep.

This is a check system to help to quantify illness in babies; medical contact is suggested if infants score more than 7.

An infant was considered immunised if he or she had received any component of the programme before the last or reference sleep.

Statistical methodology

Data were described by using medians and interquartile ranges. Correlation was conducted using Pearson's coefficient. The Mantel-Haenszel $\chi^2$ test was used to test individual confounders. Odds ratios, 95% confidence intervals, and $P$ values for the univariate and multivariate analyses were calculated—with the matching taken into account by using conditional logistic regression. Models were constructed with the stepwise procedure for variables significant at the 5% level in the univariate analysis.

Results

Ascertainment

Over the three years there were over 470 000 births in the study area and 456 sudden unexpected deaths in infancy, of which 363 were attributed to the sudden infant death syndrome. Interviews were conducted for 325 deaths attributed to the sudden infant death syndrome (90%), 72 of the 95 explained deaths (77%), and the controls. Immunisation details were available for 93% (303/325) of the SIDS infants (infants whose deaths were attributed to the sudden infant death syndrome), 90% (65/72) of the infants with explained deaths, and 95% (1515/1588) of controls.

The major causes of death among the 72 explained deaths were unrecognised infection (46% (33)), accidental (15% (11)), congenital anomalies (14% (10)), and non-accidental injury (13% (9)).

Proportion immunised and potential confounding

Sudden infant death syndrome

Just under half (149/303) of the SIDS infants had begun or completed the immunisation programme, compared with two thirds (822/1234) of the control for the SIDS infants (odds ratio, adjusted for matching, 0.23 (95% confidence interval 0.14 to 0.37)). The uptake of the programme, based on infants aged 3 months or older, was 93% (658/688) among the control infants and 79% (116/146) among the index infants. The table stratifies immunisation rates for confounding factors that might explain the lower uptake among SIDS infants. The difference between the SIDS infants and the control infants was consistent across the different age groups. The proportion immunised was similar across the social classes among the controls, with reduced uptake among the index families in both the highest and lowest social strata. Moving house was associated with reduced uptake of immunisation for both groups. The uptake was slightly higher among the younger index mothers but not among the younger control mothers, and lower among larger families in both index and control families. Slightly fewer of the control infants with low birth weight or short gestation had been immunised, although this was not observed among the index infants. Increased medical contact either by admission to a special care baby unit or by subsequent hospital
admission was associated with an increased uptake of immunisation for both groups; similarly, uptake was highest for the infants who had experienced a life threatening event, many of whom were seen by their doctor. Few infants had a five minute Apgar score less than 8; of those who did, a higher proportion of the controls were immunised.

After all of the above confounders were controlled for, immunisation uptake remained strongly associated with a lower risk of the sudden infant death syndrome (multivariate odds ratio 0.45 (0.24 to 0.85)). However, when we also controlled for highly significant risk factors in the infant's sleeping environment for the last or reference sleep—such as placing the infant prone or finding the infant with bedclothes over the head—the difference became non-significant (0.67 (0.31 to 1.43)).

## Explained deaths
Of the infants who died of explained causes, 54% (35/65) began or completed the immunisation programme, compared with 61% (172/281) of controls (univariate odds ratio 0.51 (0.21 to 1.26)).

## Temporal comparison
### Sudden infant death syndrome
The median age at which the first immunisation was given was 61 (interquartile range 56-71) days for SIDS infants and 59 (36-63) days for controls. The observed higher proportion of immunised controls was consistent over age.

The median time from last immunisation to death was 27 (16-68) days, similar to the 29 (13-70) days until interview for controls. Five per cent (7/149) of the immunised SIDS infants had received a vaccination in the 48 hours before death; 5% (41/822) of immunised control infants had received a vaccination in the 48 hours before the reference sleep. The longer term temporal distribution between the two groups did not differ significantly (P = 0.78).

## Signs and symptoms of illness
### Sudden infant death syndrome
Of the SIDS infants who died within two weeks of immunisation, 16% (5/31) scored > 7 on the Baby Check, compared with 26% (16/61) of the non-immunised SIDS infants who were older than 2 months (babies under this age would rarely be immunised). A plot of the interval from the last immunisation to death or reference sleep against the Baby Check score showed no correlation (Pearson's correlation coefficient 0.07, P = 0.70).

## Discussion
More than a third of the deaths attributed to the sudden infant death syndrome in this study occurred between the ages of 2 and 4 months, around the time that most infants in the United Kingdom were receiving all three primary immunisations against *Haemophilus influenza* type b, diphtheria, tetanus and pertussis, and oral poliomyelitis. For this to be more than coincidental one would expect a higher immunisation uptake among the infants who died than among age matched surviving infants, or at least some temporal pattern compatible with a reaction to immunisation. The findings from this study suggest the opposite.
The findings for the infants who died suddenly and unexpectedly but of explained causes, particularly infections, mirrored those for the infants whose deaths were attributed to the sudden infant death syndrome: lower compliance, no temporal effect, and no correlation between recent immunisation and signs or symptoms of illness. Our data suggest that even when potentially confounding factors, such as family mobility, are taken into account, immunisation does not contribute to the risk of the sudden infant death syndrome and may protect against it.

Implications
One possible source of error in previous studies would be if the effect of immunisation were to increase the risk of sudden unexpected deaths that were subsequently attributed to infection or other specific causes and thus not registered as the sudden infant death syndrome. We avoided this bias by including all infants who died suddenly of identified causes.

Shann has suggested, on the basis of observations from trials in developing countries, that measles vaccination may confer protection from death due to causes other than measles itself. Our data are consistent with the hypothesis that the standard primary course of immunisation may also have a non-specific protective effect on the risk of death in infancy, or alternatively that failure to begin the course may be a marker of the risk of the sudden infant death syndrome and may protect against it.

We therefore conclude that the accelerated immunisation programme in the United Kingdom is not associated with sudden unexpected death in infancy, whether the death is explained or unexplained. These data re-emphasise the importance of rigorous analysis of temporal associations of apparent significance.

Contributors: PJF, PSB, MWP, JT, IJS, and JG were all involved in the concepts and design from the beginning of the study. The analysis was conducted by PSB under the supervision of the others, and all authors were involved in the interpretation of the data, drafting, and revisions. PJF, PSB, JT, and IJS supervised data collection for the whole study period within their particular regions, MWP for the final year of the study.

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One hundred years ago
The doctor’s carriage and his coachman

Sir—My coachman has been called to serve as a jurymen, which may detain him three or four days. It is remarkable that though the doctor is exempt from such service his coachman should be liable. The new century might be begun with exemption for doctors’ coachmen from jury service, and abolition of the tax on the vehicle used.

In the country the doctor’s gig goes to the poor man’s door, but however cheerfully the doctor gives his services to the sick poor, he cannot pay the tax on his trap with pleasant feeling.—I am, etc., RURICUS

(BMJ 1901;i:183)