Current topic

Vaccination and cot deaths in perspective

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SUMMARY   In 1985 twin boys simultaneously succumbed to sudden unexpected deaths two to three hours after vaccination with diphtheria, tetanus, and pertussis vaccine (DTP). This occurrence again raises the question of whether an association of sudden infant death (SID) with vaccination is other than temporal. Taking the incidence of SID in conjunction with rates of infant vaccination in the United Kingdom, nine infants would be expected to die, each year by chance alone, suddenly within 24 hours of (and within each 24 hour period succeeding) vaccination with DTP. Twins are at a greater risk of SID than single born infants and occasionally are found dead together. A number of studies into DTP vaccination as a risk factor in SID have shown that SID is less common in vaccinated than in unvaccinated infants.

Sudden infant death (SID) is a term used for those unexpected sudden deaths of infants that cannot be adequately explained and is often characterised by the baby being found dead in its cot. It has a characteristic age distribution, occurring chiefly in infants less than 1 year old and peaking in those aged 2–3 months. Theories abound about the possible causes, and vaccination has been put forward as one of these, chiefly because of occasional temporal association. The simultaneous deaths of 5 month old twin boys within three hours of vaccination with adsorbed diphtheria, tetanus, and pertussis vaccine (DTP) again raises the question of association with vaccination.

Incidences of SID

Golding *et al* surveyed the epidemiological studies of SID and derived the following incidence figures.[1] Fourteen studies in North America showed an incidence of SID of 2·3 per 1000 live births. In Sweden the incidence was lower, with 1 per 1000 live births. In the United Kingdom the mean (SD) incidence across eight surveys was 3 (0·62) per 1000.[1] Variations between studies can be accounted for partly by real differences: there are certainly fewer cases of SID in Sweden where infant mortality due to all causes is very low. Artefactual variations arise from two sources. Different studies include SID from different age groups, by excluding perinatal mortality within variable periods up to 1 month of age, and by excluding children older than 1 or 2 years. A more serious source of variation is in diagnosis. Since 1972 the term 'sudden infant death' has been accepted by coroners as an explanation for infant deaths on certificates. Its use is variable, and in recent years it has taken the place of respiratory causes on death certificates. Thus in some studies SID is taken to include deaths that would not be included in other studies.

Probability of SID coincident with DTP vaccination

Fedrick's Oxford record linkage survey was a large survey of 206 cases of SID that occurred over five years at an incidence of 2·78 per 1000 live births.[2] The distribution of cases of SID in different age groups was broken down: 88% were in the first year of life and 30% between 3 and 6 months. Thus the incidence during the first year was 88% of 2·78/1000—that is, 2·45/1000—and between 3 and 6 months was 30% of 2·78/1000—that is, 0·83/1000. These figures can be used for the following observations, where:

D=Number of days in age band—for example, 365 in one year, 91 in 3–6 months.

P_o=Probability of SID in a child in a specified age band. This is equal to the incidence of SID in that age band.

Pd=Average daily probability of SID in a child in a specified age band.

  I=Total number of DTP inoculations administered to children in an age band per year. No child receives more than one per day.

  N=Expected number of children per year, in specified age band, to suffer SID within 24 hours of DTP vaccination.

So   (i) $Pd = \dfrac{Po}{D}$ and

    (ii) $N = Pd \times I$.

From (i), the average daily probability (Pd) of SID in a child during its first year=(2·45/1000)÷365=6·7×10^{-6}; also the average daily probability of SID in a child between the ages of 3 and 6 months=(0·83/1000)÷91=9·1×10^{-6}.

In the United Kingdom there are 700 000 live births a year[3] and DTP vaccination is taken up for roughly 66% of infants—that is, for 460 000. Each infant receives a course of three doses of vaccine, beginning between 3 and 6 months, with the second dose following after 6–8 weeks and the third dose given 4–6 months later. To simplify the calculations it will be assumed that all 1·4 million doses of DTP (460 000×3) are given each year to infants in their first year, with 930 000 doses (the first and second vaccinations) being given to children aged 3–6 months.

From (ii), the number per year (N) likely to die suddenly within 24 hours of vaccination with DTP=(6·7×10^{-6})×1 400 000=9·4. Similarly, the number likely to die suddenly within 24 hours of vaccination with the first or second dose of DTP=(9·1×10^{-6})×930 000=8·5.

As described, neither the risk of SID nor the probability of being vaccinated are evenly distributed throughout the first year of life. Ideally, the daily risk of either event occurring could be calculated and precise probabilities of concurrence obtained. The calculations have been kept simple to allow easy adaptation to any population. The estimates are likely to be inflated for two reasons:

(1) Some infants that die unexpectedly have symptoms for some days and therefore may not have been vaccinated.

(2) SID is associated with poor uptake of health services and hence with undervaccination.

The number of deaths reported as adverse reactions does not approach the expected level. Wellcome, who for several years have been the sole
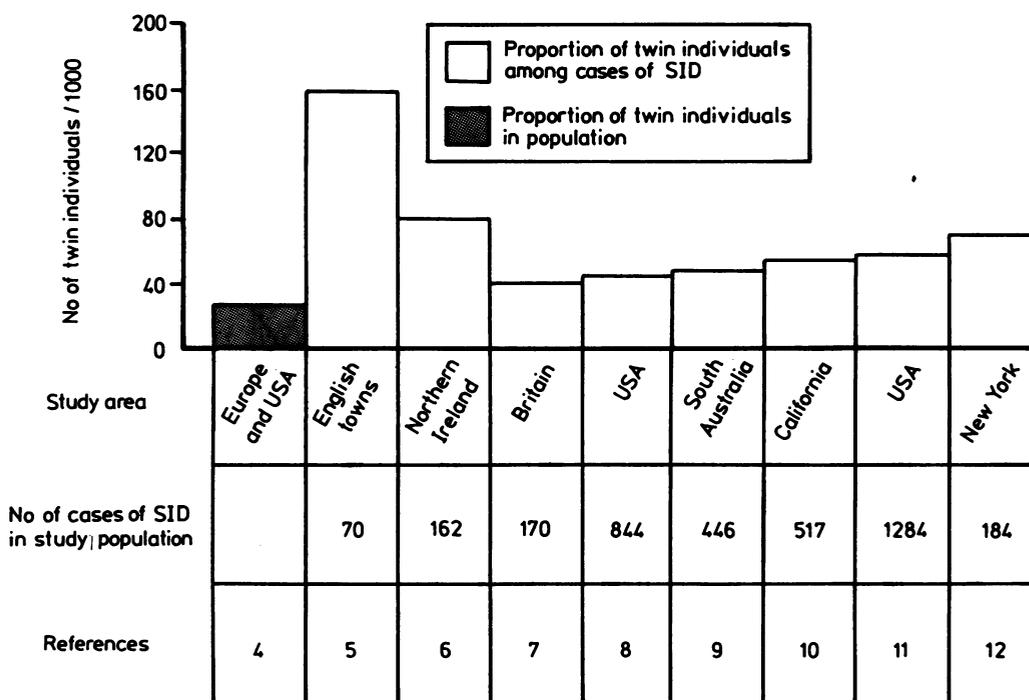

Fig. 1 *Proportion of twin born children among cases of sudden infant death (SID) from eight studies (white bars). Normal proportion of twin born individuals in live born population is shown as the black bar.*

Study area	Europe and USA	English towns	Northern Ireland	Britain	USA	South Australia	California	USA	New York
No of cases of SID in study population		70	162	170	844	446	517	1284	184
References	4	5	6	7	8	9	10	11	12

manufacturers of DTP vaccine in the United Kingdom, have received reports through the committee on the safety of medicines of six cot deaths occurring after DTP vaccination in over 20 years of reporting, but there were probably additional cases that were not reported. During the 14 months after the widely publicised case of the twins a further five cot deaths have been reported to Wellcome as occurring within 24 hours of vaccination in the United Kingdom.

Risk of SID in twins

The chance of two independent children dying simultaneously after vaccination is remote, but it is interesting to note some special features of the risk of SID to twins.

An average of 12 in every 1000 live births in Europe and North America are twins[4]—that is, 24 twin individuals. The number of twins found among SID victims is out of proportion to their representation in the population. This has been found in several studies of SID (Fig. 1), with about a threefold higher proportion of twins among cases of SID. In three of these studies, of 170, 184, and 162 cases of SID, respectively, the authors additionally compared the risk of SID in twins with that in specific control populations.[7 12 6] Knowelden *et al* selected 151 age matched controls from the population and found a fourfold higher proportion of twins among cases of SID.[7] Standfast *et al* compared death rates among single born children (singletons) with those among twins and found the risk of dying of SID for twins was 3·9 times higher than for singletons.[12] Froggatt *et al* compared SID with deaths by other causes and found an especially high risk of SID to twins, with twins constituting 8% of SIDs and 3·5% of other deaths.[6]

Concordant SID in twins

Of particular note is the greatly increased risk to the second twin if the first twin dies. This is illustrated in

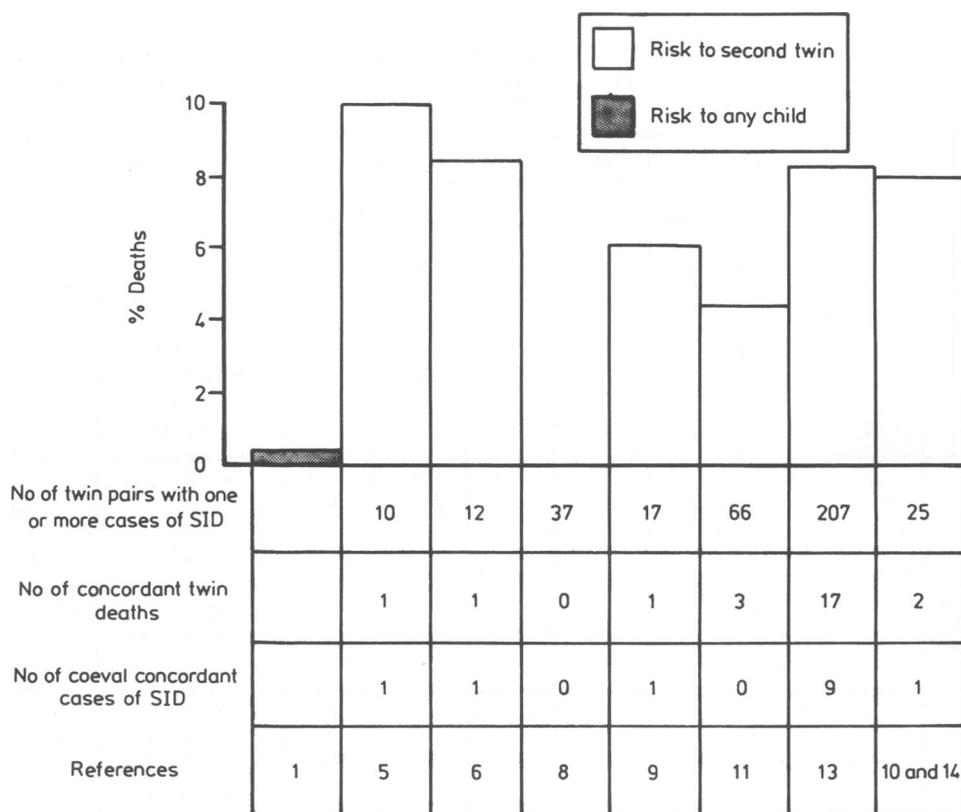|							
No of twin pairs with one or more cases of SID		10	12	37	17	66	207	25
No of concordant twin deaths		1	1	0	1	3	17	2
No of coeval concordant cases of SID		1	1	0	1	0	9	1
References	1	5	6	8	9	11	13	10 and 14

Fig. 2   *Risk of sudden infant death (SID) to a twin of a SID victim, showing the number of twins per 100 that succumb, given that their twins have died. The black control bar shows the normal risk to any child (at 2·5 per 1000).*

Figure 2. The black bar shows a normal rate of cases of SID in the population at around 0·25%.[1] The risk to the second twin in six studies was between 5 and 10%, although one study found no deaths in second twins.[8] It is not uncommon for such concordant deaths to be coeval—that is, to occur on the same day—often with the twins being found dead together. Three concordant deaths described in three separate studies were all coeval.[5 6 9] Cooke and Welch additionally described three cases of concordant, coeval SID in twins that they studied in nearby towns (not part of their study population).[5] Spiers' study was specifically of twins.[13] The number of cases of SID he describes is inflated because he excluded only deaths ascribed to traumatic causes. Only his home deaths figures are reported here, since the hospital deaths were less likely to be cases of SID. Half of the concordant deaths that he studied were coeval.

Smialek identified and presented reports on nine cases of coeval concordant twin deaths in the United States and Europe, occurring between 1966 and 1981.[15] In a study of 112 cases of SID occurring in twins over four years in England and Wales Carpenter described two coeval concordant twin deaths and estimated the rate of SID in twins to be 2·2/1000, compared with a rate of 1·4/1000 in the general population.[16]

The increased risk to the second twin does not argue a genetic explanation for SID; rather, simultaneous twin deaths seem to be because of shared environment (which could include exposure to pathogenic organisms). Thus no difference in risk has been found between identical and non-identical twins.[11 13] Data indicating that subsequent (non-twin) siblings of SID victims were at high risk of SID themselves have been refuted and updated by Peterson *et al*[17] with data from Washington that concur with the results of a Norwegian study.[18] The latter found a rate of SID of 0·48% in subsequent siblings, compared with 0·13% in the population: in Washington the rate was 0·74%, not significantly different from the 0·4% rate found in controls.

A study of 12 families with two or more cot deaths implicated psychosocial factors as the chief cause of repeated cases of SID within the family.[19] In another study investigations at the scene of death of 26 cases of SID recorded that in at least six cases accidental death was implicated and that in almost all cases the situation was exacerbated by poor judgment by the caretaker of the infant.[20] Of these 26 infants, four were members of a twin pair, and one was a triplet.

One factor that puts twins at higher risk is their low birth weights, a known predisposing factor for SID in infants.[21] In a study of 42 twin pairs in which one twin had died Kahn *et al* found both the weights and heights at birth of the SID victim to be significantly lower than those of the surviving twin and of 42 control twins.[22]

The twins who died in 1985 were not identical. This makes an idiosyncratic response to the vaccine unlikely. That they should have died together was an extraordinary event but, as shown above, not without precedent from reported cases. A case of identical twins both dying, 16 and 20 hours after vaccination with diphtheria toxoid and pertussis antigen, was reported in 1946[23] and was attributed to delayed anaphylactic shock.

DTP vaccination as a risk factor for SID

DTP vaccination is now often examined as a risk factor in epidemiological studies of SID after reports of clusters of cases of SID after vaccination in Tennessee and Oslo.[24–26] The Oslo cluster was studied in relation to a larger area of Norway and found to be non-significant.[26] The authors of this study suggested that the cluster in Tennessee was real and was an example of the 5% of occasions in which associations will be found, by chance, to be significant. Two interesting points come out of these studies of clusters: firstly, once a 'scare' has begun adverse reaction reporting multiplies through increased awareness; secondly, looking for associations in many places and at many times will certainly reveal sporadic associations that need not be causal. In the Oslo cluster deaths occurred one week and in Tennessee one day after vaccination.

DTP vaccination seemed to be further implicated by a paper that purported to show an excess of cases of SID close to the time of vaccination among 27 such deaths occurring within a month of vaccination.[27] This paper has been criticised on account of methodological flaws, such as an inadequate control group.[28] The survey was retrospective and so recall bias might be expected.[29] The dependence of the study on telephone contact of parents, for lack of which 80% of the original study population of 382 SID victims was dropped from the study, would have introduced a socioeconomic bias. The multiple testing using different periods is statistically unacceptable and Mortimer *et al*'s retesting with a 2×7 contingency table showed no significant difference in distribution of deaths between the vaccinated and 'control' populations.[29]

In other studies that have looked at vaccination and SID there have been fewer vaccinated infants among SID victims than among control infants. Thus in a study of 146 deaths in infants that died with no known predisposing organic disease, of which 47 were defined as SID, the rate of vaccina-

tion of any kind was 18%, compared with an approximate 60% uptake in the population at large.[30] A study of 26 unexpected infant deaths, each with two age matched controls, found the rate of immunisation of any kind to be greater in the control group.[31] (This study was continued to incorporate 47 index cases,[32] of whom 55% were vaccinated, usually with DTP, compared with 75% of controls.) In another study of 151 cases of SID 10 of the controls, matched for age and geographical area, had received vaccinations of any kind within 28 days of death of the index case compared with eight of the index cases themselves.[7] In a study of 400 cases of SID controls were matched for age, geographical area, birth weight, and race.[8] Disparities in vaccine uptake between different racial groups were thus controlled for, and it was found that of 378 index cases with known vaccination histories, 39% had received DTP vaccination compared with 57% of the 399 controls.

In a prospective study of 6004 infants who started primary immunisation with DTP, and 4024 who started with diphtheria tetanus (DT), seven died suddenly within six weeks of vaccination.[33] This was no more than was expected by chance. Three of the deaths were in the DTP group (at 4, 20, and 37 days) and four in the DT group (at 2, 5, 37, and 40 days).

Hypoxaemia as a cause of SID

Hypoxaemia has often been studied, with equivocal results, as a potential cause of SID.[34] In a recent study of 10 infants who suffered severe episodes of hypoxaemia the episodes were caused by prolonged expiratory apnoeas.[35] One of the subjects, with clinically unnoticed and yet frequent episodes of hypoxaemia, was the twin of a SID victim. In contrast to whooping cough itself, in which hypoxaemia is caused by prolonged expiratory paroxysmal coughing, DTP immunisation was not found to increase abnormalities in ventilatory patterns for 30 control infants, 46 infants with unexplained apnoeas, and 33 subsequent siblings of SID victims.[34] This study was unable to quantify obstructive apnoeas, which have been implicated as a further mechanism for SID.[36]

Conclusion

In conclusion, it is not surprising that a routine procedure in infants such as vaccination has been implicated in SID. Unexpected deaths require explanation and vaccinations are administered to infants at an age of high risk of SID. By chance alone, however, around nine infants a year would be expected to die suddenly in the United Kingdom within 24 hours of DTP vaccination (and, equally, another nine to die during each 24 hours succeeding vaccination). The simultaneous death of twin boys after vaccination was, rightly, regarded as an extraordinary and distressing event, yet it is true that twins are particularly susceptible to SID. Although it is natural to link an unexpected event with its precursor events, coincidences do occur and should be seen in perspective.

References

1 Golding J, Limerick S, MacFarlane A. *Sudden infant death: patterns, puzzles and problems.* Somerset: Open Books, 1985:264.
2 Fedrick J. Sudden unexpected deaths in infants in the Oxford record linkage area: an analysis with respect to time and place. *British Journal of Preventative and Social Medicine* 1973;**27:** 217–24.
3 Central Statistical Office. *Central Statistical Office annual abstracts of statistics—1984 edition.* London: HMSO, 1984: 120–30.
4 Hrubec Z, Robinette CD. The study of human twins in medical research. *N Engl J Med* 1984;**310:**435–41.
5 Cooke RT, Welch RG. A study in cot death. *Br Med J* 1964;**ii:**1549–54.
6 Froggatt P, Lynas MA, Mackenzie G. Epidemiology of sudden unexplained death in infants ('cot death') in Northern Ireland. *British Journal of Preventative and Social Medicine* 1971;**25:** 119–34.
7 Knowelden J, Keeling J, Nicholl JP. *Post neonatal mortality. A multicentre study undertaken by the Medical Care Research Unit, University of Sheffield.* London: HMSO, 1985.
8 Hoffman HJ, Hunter JC, Hasselmeyer EG. SIDS and DTP. In: Centers for Disease Control. *17th immunisation conference proceedings, Atlanta, Georgia, May 1982.* Atlanta: Centers for Disease Control, 1982:79–88.
9 Beal S. Some epidemiological factors about sudden infant death syndrome (SIDS) in South Australia. In: Tildon JT, Roeder LM, Steinschneider A, eds. *Sudden infant death syndrome.* New York: Academic Press, 1983:15–29.
10 Kraus JF. Methodologic considerations in the search for risk factors unique to sudden infant death syndrome. In: Tildon JT, Roeder LM, Steinschneider A, eds. *Sudden infant death syndrome.* New York: Academic Press, 1983:43–58.
11 Peterson DR, Chinn NM, Fisher LD. The SIDS repetition in families. *J Pediatr* 1980;**97:**265–7.
12 Standfast SJ, Jereb S, Janerich DT. The epidemiology of sudden infant death in upstate New York: II: birth characteristics. *Am J Public Health* 1980;**70:**1061–7.
13 Spiers PS. Estimated rates of concordance for the sudden infant death syndrome in twins. *Am J Epidemiol* 1974;**100:**1–7.
14 Kraus JF, Borhani NO. Post-neonatal sudden unexplained death in California: a cohort study. *Am J Epidemiol* 1972;**95:**497–510.
15 Smialek JE. Simultaneous sudden infant death syndrome in twins. *Pediatrics* 1986;**77:**816–21.
16 Carpenter RG. *Sudden death in twins. Appendix 9 of enquiry into sudden death in infancy.* London: HMSO, 1965:51–2. (Ministry of Health reports on public health and medical subjects No 113.)

17 Peterson DR, Sabotta EE, Daling JR. Infant mortality among subsequent siblings of infants who died of sudden infant death syndrome. *J Pediatr* 1986;**108**:911–4.

18 Irgens LM, Skjaerven R, Peterson DR. Prospective assessment of recurrence risk in sudden infant death syndrome siblings. *J Pediatr* 1984;**104**:349–51.

19 Emery JL. Families in which two or more cot deaths have occurred. *Lancet* 1986;i:313–5.

20 Bass M, Kraveth RE, Glass L. Death-scene investigation in sudden infant death. *N Engl J Med* 1986;**315**:100–5.

21 Black L, David RJ, Brouillette RT, Hunt CE. Effects of birth weight and ethnicity on incidence of sudden infant death syndrome. *J Pediatr* 1986;**108**:209–14.

22 Kahn A, Blum D, Muller MF, *et al.* Sudden infant death syndrome in a twin: a comparison of sibling histories. *Pediatrics* 1986;**78**:146–50.

23 Werne J, Garrow I. Fatal anaphylactic shock. Occurrence in identical twins following second injection of diphtheria toxoid and pertussis antigen. *JAMA* 1946;**131**:730–5.

24 Centre for Disease Control. DTP vaccination and sudden infant deaths – Tennessee. *MMWR* 1979;**28**:131–2.

25 Centre for Disease Control. Follow-up on DTP vaccination and sudden infant deaths – Tennessee. *MMWR* 1979;**29**:134–5.

26 Solberg LK. *DTP vaccination, visit to child health centre and sudden infant death syndrome (SIDS); evaluation of DPT vaccination.* Oslo: Health Council, 1985:1–19.

27 Baraff LJ, Ablon WJ, Weiss RC. Possible temporal association between diphtheria-tetanus toxoid-pertussis vaccination and sudden infant death syndrome. *Pediatr Infect Dis* 1983;**2**:7–11.

28 Fulginiti VA. Sudden infant death syndrome, diphtheria-tetanus toxoid-pertussis vaccination and visits to the doctor: chance association or cause and effect? *Pediatr Infect Dis* 1983;**2**:5–6.

29 Mortimer EA, Jones PK, Adelson L. DTP and SIDS. *Pediatr Infect Dis* 1983;**2**:492.

30 Richards IDG, McIntosh HT. Confidential inquiry into 226 consecutive infant deaths. *Arch Dis Child* 1972;**47**:697–706.

31 Taylor CM, Emery JL. Immunisation and cot deaths. *Lancet* 1982;ii:721.

32 Anonymous. Immunisation and sudden infant death syndrome [Editorial]. In: *Cot death research and support.* Newsletter 29. London: Foundation for the Study of Infant Deaths, 1986:3.

33 Pollock TM, Miller E, Mortimer JY, Smith G. Symptoms after primary immunisation with DTP and with DT vaccine. *Lancet* 1984;ii:146–9.

34 Keens TG, Davidson Ward SL, Gates EP, Andree DI, Hart LD. Ventilatory pattern following diphtheria-tetanus-pertussis immunization in infants at risk for sudden infant death syndrome. *Am J Dis Child* 1985;**139**:991–4.

35 Southall DP, Talbert DG, Johnson P, Morley CJ, Salmons S, Miller J. Prolonged expiratory apnoea: a disorder resulting in episodes of severe arterial hypoxaemia in infants and young children. *Lancet* 1985;ii:571–7.

36 Guilleminault C, Heldt G, Powell N, Riley R. Small upper airway in near-miss sudden infant death syndrome infants and their families. *Lancet* 1986;i:402–7.

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