

# Possible temporal association between diphtheria-tetanus toxoid-pertussis vaccination and sudden infant death syndrome

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Because diphtheria and tetanus toxoids pertussis (DTP) vaccine is routinely given during the period of highest incidence of sudden infant death syndrome (SIDS), this study was undertaken to determine if there is a temporal association between DTP immunization and SIDS. Parents of 145 SIDS victims who died in Los Angeles County between January 1, 1979, and August 23, 1980, were contacted and interviewed regarding their child's recent immunization history. Fifty-three had received a DTP immunization. Of these 53, 27 had received a DTP immunization within 28 days of death. Six SIDS deaths occurred within 24 hours and 17 occurred within 1 week of DTP immunization. These SIDS deaths were significantly more than expected were there no association between DTP immunization and SIDS. An additional 46 infants had a physician/clinic visit without DTP immunization prior to death. Forty of these infants died within 28 days of this visit, seven on the third day and 22 within the first week following the visit. These deaths were also significantly more than expected. These data suggest a temporal association between DTP immunization, physician visits without DTP immunization and SIDS.

## INTRODUCTION

Sudden infant death syndrome (SIDS) is a clinicopathological entity defined as the sudden death of any infant which is unexpected by history and in which a thorough postmortem examination fails to demonstrate an adequate cause for death.<sup>1</sup> Of the many hypotheses which have been enumerated, strong evidence now suggests a primary respiratory etiology, including upper airway obstruction and/or a defective ventilatory control mechanism with or without respi-

ratory infection.<sup>2-7</sup> In March 1979 it was suggested that there might be an association between immunization with Diphtheria and Tetanus Toxoids and Pertussis Vaccine absorbed® (DTP), Wyeth Lot 64201, and the sudden infant death syndrome in Tennessee. An extensive investigation following report of this possibility neither established nor refuted a causal relationship.<sup>8,9</sup>

The majority of studies on SIDS have not specifically addressed the question of the association of childhood immunizations and SIDS. Because DTP and attenuated live trivalent oral poliovirus vaccine (TOPV) are routinely administered between 2 and 6 months of age, the period of highest incidence of SIDS, it is important to determine whether or not receipt of these vaccines is a risk factor in the development of SIDS. Immunization with a reactogenic vaccine might, in selective instances with underlying predisposing factors such as abnormal ventilatory control, be a component in the multifactorial causation of this syndrome. Pertussis vaccine is such a reactogenic vaccine which has been associated with neurologic reactions including convulsions, hypotonic-hyporesponsive episodes, hypersarrhythmias and encephalopathy.<sup>10-14</sup> If DTP immunization were temporarily linked to SIDS, then this vaccination could be rescheduled so that it would not coincide with the period of highest SIDS risk.

## METHODS

The Division of Maternal and Child Health of the Los Angeles County Department of Health Services, in conjunction with the Los Angeles Coroner's Office, maintains a list of all SIDS cases reported by the Deputy Coroners. This list includes the parents' names, address and phone number; date of birth; and date of death. The postmortem diagnosis of SIDS is made after a routine gross and microscopic postmortem examination fails to reveal any apparent cause of death. No viral cultures, toxicologic studies or special pathologic studies are routinely conducted. Los Angeles County statute requires that in all instances, when there is not sufficient past medical history to be

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able to certify cause of death, the case be referred to the Coroner. Therefore, all SIDS cases are referred to the Coroner.

With the permission of the Los Angeles County SIDS Foundation, an attempt was made to contact the parents of all SIDS victims who died in Los Angeles County between January 1, 1979, and August 23, 1980. Telephone interviews of the parent(s) were conducted utilizing the telephone numbers when available from the records of the Division of Maternal and Child Health. When parents could be contacted and were willing to cooperate, they were asked the following questions:

1. What was the baby's sex?
2. What was the age at death?
3. When did the baby last see a doctor or nurse prior to death?
4. When was the baby's last immunization?
5. What was the name of the doctor who gave it and his phone number?
6. What type of immunization was this?

Beginning in March 1980 the Division of Maternal and Child Health began conducting home visits to families of SIDS victims in conjunction with a County and State program designed to gather epidemiologic data of SIDS and to provide psychosocial counseling for these families. These home visits are conducted by either a registered nurse or a licensed social worker. The history of immunizations, including DTP, in the month prior to death, is obtained as part of this interview process. Families are not asked when the baby last saw a doctor or nurse prior to death or the name of the physician or clinic who provided the immunization. These data were also reviewed. When infants were reported to have died within 48 hours of immunization, an attempt was made to contact the physician or clinic to verify the date of immunization.

The age of SIDS victims was calculated from the date of birth and date of death. The interval from the last DTP immunization to death, obtained by either home or telephone interview, was utilized to prepare a frequency distribution of SIDS victims by interval. The interval from the last physician/clinic visit to death, obtained by telephone interview, was used to prepare a similar frequency distribution when a DTP immunization was not given at the time of the visit or thereafter. To test for association between DTP immunization and SIDS, a chi square value was calculated for each interval between immunization and SIDS. This was done using frequencies obtained by classifying SIDS subjects into groups by interval from DTP immunization to death and comparing them with the expected distribution of deaths, assuming there was no relationship between immunization and the occurrence of SIDS. A similar analysis was conducted for the frequency distribution of intervals from last physician/clinic visit when no DTP was given and

when there was no intervening DTP to the occurrence of SIDS.

#### RESULTS

From January 1, 1979, to August 23, 1980, there were 382 cases of SIDS reported by the Los Angeles County Coroner's Office. In 1979 there were 131,698 live births recorded in the County.<sup>15</sup> Assuming the birth rate to be the same in 1980, there would be 216,849 live births during the period of the study. Therefore the rate of SIDS was approximately 1.76 per 1,000 live births.

Only 74 parents of these 382 SIDS victims could be contacted who were willing to cooperate with the telephone interview. The small proportion of cooperating parents was due to a high number of families with no phone (187) or for whom phone numbers were given at which the parents could not be reached (118). Only three families were unwilling to cooperate. An additional 71 parents were interviewed at home. Therefore parents of 145 SIDS victims were contacted by home visit and/or telephone.

Table 1 presents the age of death in months of the SIDS cases whose parents we were able to contact and interview. Cases have been divided into those who did and did not receive a DTP immunization prior to death. The DTP recipients had an older mean and mode age at death which probably reflects the fact that routine immunization is usually begun at 2 months of age.

Table 2 presents the temporal relationship of DTP immunization to SIDS, the expected number of deaths per interval for the first 28 days assuming that all 27 deaths were equally distributed in this period and the *P* value obtained using chi square calculations.

Fifty-three of the 145 SIDS victims whose families were interviewed had received a DTP immunization. Twenty-seven of the 53 had received a DTP within 28

**TABLE 1**

*Interviewed SIDS families in Los Angeles County from January 1, 1979, to August 23, 1980*

Age at Death (mos.)	DTP Immunization Status		
	No DTP	DTP	Total
<1	21	0	21
1	30	6	36
2	25	14	39
3	6	12	18
4	3	7	10
5	3	6	9
6	1	3	4
7	1	2	3
8	1	1	2
9	1	0	1
10	0	0	0
11	0	0	0
12	0	0	0
>12	0	2	2
Total	92	53	145

TABLE 2

*Temporal relationship of DTP immunization to SIDS*

Interval (days) from DTP to SIDS	Observed No.	Expected No. (0-28 days)	<i>P</i> <sup>a</sup>
<1	6	0.96	<0.0005
2	2	0.96	NS <sup>b</sup>
3	1	0.96	NS
4-7	8	3.86	<0.05
8-14	6	6.75	NS
15-21	4	6.75	NS
22-28	0	6.75	<0.01
0-7	17	6.75	<0.0005
0-28	27	27.00	
>28	26		

<sup>a</sup> Calculated using Pearson chi square.<sup>b</sup> NS, not significant (*P* > 0.05).

days of death. Six of these 27 deaths occurred within 24 hours of DTP immunization and 17 occurred within 1 week of immunization. No deaths occurred in the fourth week following immunization. The accuracy of the immunization history of the eight infants who died within 48 hours of DTP immunization was verified by telephone calls to the physician or clinic. If the 27 deaths which occurred within 28 days of immunization were randomly distributed throughout this interval, one would expect 0.96 death per day, or 6.75 deaths per week. The excess of deaths in the 24 hours and first week following immunization and the absence of deaths in the fourth week following immunization were all statistically significant.

Table 3 presents the temporal relationship of the last physician visit when no DTP was given at the time of visit or thereafter to SIDS. Also presented, as in Table 3, are the expected number of deaths per interval for the first 28 days after the visit and the *P* value obtained using the chi square calculations. Of the 46 infants who had a physician visit without DTP immunization and who had no subsequent DTP immunization, 40 died within 28 days. Therefore if there were no associations between the physician visit and subsequent SIDS, 1.43 deaths would be expected per day and 10 deaths would be expected per week. There was a statistically significant excessive number of deaths in the first week following immunization, notably on the third day, and significantly fewer than expected deaths during the third and fourth week following the visit.

#### DISCUSSION

In March 1979 the Tennessee State Department of Health reported four deaths in infants 2 to 3 months of age who had received, within 24 hours of their deaths, a dose of DTP vaccine from a single lot, Lot 64201, manufactured by Wyeth Laboratories, Inc.<sup>8,9</sup> Autopsies were performed on two children, and all four deaths were listed as unexplained sudden infant death. Approximately 96,105 doses of DTP from this

TABLE 3

*Temporal relationship of last physician visit, no DTP given, to SIDS*

Interval (days) from DTP to SIDS	Observed No.	Expected No. (0-28 days)	<i>P</i> <sup>a</sup>
<1	4	1.43	NS <sup>b</sup>
2	3	1.43	NS
3	7	1.43	<0.0005
4-7	8	5.71	NS
8-14	14	10.00	NS
15-21	1	10.00	<0.005
22-28	3	10.00	<0.05
0-7	22	10.00	<0.0005
0-28	40	40.00	
>28	6		

<sup>a</sup> Calculated using Pearson chi square.<sup>b</sup> NS, not significant (*P* > 0.05).

lot were administered in Tennessee. Additional investigations were conducted in association with the Center for Disease Control (CDC) in Tennessee during the periods of August 1977 through March 1978 and August 1978 through March 1979. Vaccines from the suspect lot were available in Tennessee during the latter interval. The numbers of cases of sudden infant death in infants who received DTP vaccination in the two periods were 16 and 33, respectively. The numbers of cases of sudden infant death within 24 hours of DTP immunization were 0 and 5, respectively, during the two intervals, with four of the five cases which occurred in the latter period having been vaccinated with Wyeth vaccine, Lot 64201. The manufacturer voluntarily withdrew this lot of vaccine. The CDC concluded that the available data indicated no association between DTP vaccination and SIDS.

Subsequently analysis of data collected by the Immunization Division of the CDC regarding vaccine reactions within 28 days of immunization revealed 23 reports of death within 28 days of DTP immunization.<sup>16</sup> In 16 of the 23 deaths autopsy findings were consistent with SIDS. Twelve of the 23 deaths occurred within 24 hours of DTP immunization, and 18 occurred within 1 week. Of the 16 SIDS deaths, 6 occurred within 24 hours and 12 occurred within 1 week.

This study further substantiates the possible association between DTP immunization and SIDS. Of the 145 cases of SIDS which occurred in Los Angeles County in the 20-month interval studied whose parents could be contacted regarding immunization history, 53 were immunized with DTP vaccine prior to death. Fifty-one percent were immunized within 4 weeks, 32% within 1 week and 11% within 1 day of death. This distribution is skewed towards the time of immunization with significantly more than the expected number of deaths occurring within 1 day and 1 week of vaccination, suggesting a temporal association between DTP immunization and SIDS.

There was also significant temporal association be-

tween SDS and physician/clinic visits when no DTP was given. This distribution was also skewed toward the time of the visit, with a greater than expected number of deaths occurring during the first week and fewer than expected deaths occurring during the third and fourth week following visit. However, unlike the association with DTP immunization, there was not an excessive number of deaths during the first 24 hours. Since the reasons for these physician visits were not asked at the time of the interview, interpretation of these data is difficult. If these visits were for an illness, it suggests that these illnesses might also predispose to SIDS.

We have previously investigated the nature and rates of adverse reactions associated with DTP and Diphtheria and Tetanus Toxoids adsorbed (DT) immunization.<sup>10</sup> In the prior study we demonstrated that local reactions occurred following 40% of DTP immunizations and that systemic reactions were also frequent. Fever greater than 38°C occurred in approximately 50% of infants and children, drowsiness in 34%, fretfulness in 56% and persistent crying in 3.6%. All reactions were significantly more frequent than in the control group who received DT vaccine. Furthermore nine convulsions and nine hypotonic-hyporesponsive episodes were observed following 15,752 DTP immunizations. All these reactions occurred within 24 hours of immunization. TOPV was given with equal frequency (97%) to both DTP and DT recipients. Therefore, it is unlikely that the difference in reaction rates was associated with TOPV.

If an infant is predisposed to SIDS due to abnormal ventilatory regulation secondary to brain stem immaturity or other transient neurologic impairment, then a reactogenic vaccine which frequently is associated with fever, drowsiness and fretfulness in a significant proportion of vaccine recipients, and rarely with more serious reactions, might be one of many factors which adversely affect such a subgroup of infants. The fact that physician visits when no DTP was given were also temporally associated with DTP immunization suggests that these visits were for other illnesses such as respiratory infection or were routine visits for immunization when this immunization was withheld because of minor illness. Unfortunately, we did not ascertain the reason for physician visits as part of this study.

We wish to point out that this study is a preliminary effort with only provisional findings. These findings may not be substantiated in more carefully controlled studies. The fact that only 38% of the total 382 infants who died of SIDS during the study period are included is considered a significant difficulty. Because of the retrospective nature of this study, there were many occasions of significant time lapse between the SIDS event and parental interview by telephone or home

visit. During this time many families moved and therefore could not be contacted. When the interval between SIDS and the interview was shorter the rate of patient inclusion was higher. Therefore we have no reason to believe that the group which was not interviewed was significantly different from the group which was interviewed with respect to intervals between SIDS and DTP immunization.

No control group was included in this study. Rather we have made the assumption that there should be no temporal association between DTP immunization and SIDS were there no causal relationship between these two events. A preferable method of analyzing for an association would be to include a matched control group of infants dying of other causes or a control group of infants who did not die, but who are assigned a date of death identical to that to their age-matched case. The former type of study is impossible because SIDS is the leading cause of death in this age group and infants dying of other causes except accidents usually are not in normal health and have preexisting illnesses which may alter the timing of routine immunizations. The latter method is preferential and should be undertaken to either substantiate or refute the findings in this preliminary study. Interestingly we did examine the distribution of dates of the infants who did not receive a DTP and did not visit a physician by date of the month. There was no significant difference between the actual grouping by date of death and one which would be predicted were an equal number to die on any given day.

#### CONCLUSION

Both the efficacy and safety of pertussis vaccine have been questioned recently, particularly in the United Kingdom.<sup>17, 18</sup> The decreasing incidence of pertussis and concern regarding vaccine-associated complications have led some to consider curtailment of vaccination programs. Recent experience in both Japan and Great Britain, where public acceptance of pertussis vaccination has declined in the past 5 years, has demonstrated that with decreasing immunization levels there is a significant rise in pertussis case reporting.<sup>19, 20</sup> A formal risk-benefit analysis performed by Koplan et al.<sup>21</sup> has demonstrated that the benefits of vaccination outweigh the risks.

However, pertussis vaccine has been noted to be reactogenic, with minor reactions occurring in 50 to 60% of vaccine recipients and convulsions and hypotonic-hyporesponsive episodes occurring in approximately 1:1,750 immunizations.<sup>10</sup> Encephalopathy has been variously estimated to occur in from 1:6,500 to 1:510,000 vaccines.<sup>11-13</sup> If the temporal association reported here is substantiated, it is most probably secondary to reactions which occur in the subpopulation of infants who are predisposed to SIDS by abnormal-

ities in central ventilatory control mechanisms and the upper airway.

Currently the temporal distribution of SIDS coincides with the recommended times for DTP immunization. If further studies substantiate our findings it seems prudent to consider rescheduling DTP immunization until after the period of highest risk of SIDS, i.e. the latter half of the first year of life.

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