Diphtheria-Tetanus-Pertussis Immunization and Sudden Infant Death Syndrome

ALEXANDER M. WALKER, MD, DRPH, HERSHEL JICK, MD, DAVID R. PERERA, MD, MPH, ROBERT S. THOMPSON, MD, AND THOMAS A. KNAUSS, MD, PHD

Abstract: We compared the recency of diphtheria-tetanus-pertussis (DTP) immunization in healthy children with birthweights greater than 2500 gms who died of sudden infant death syndrome (SIDS) to that of age-matched reference children, using a modified case-control analysis. Focusing on very narrow time intervals following immunization, we found the SIDS mortality rate in the period zero to three days following DTP to be 7.3 times that in the period beginning 30 days after immunization (95 per cent confidence interval, 1.7 to 31). The mortality rate of non-immunized infants was 6.5 times that of immunized infants of the same age (95 per cent CI, 2.2 to 19). The latter result and to some extent the former appear to be ascribable to known risk factors for SIDS. Although the mortality ratios for SIDS following DTP, as estimated from this study, are high the period of apparently elevated risk was very short, so that only a small proportion of SIDS cases in infants with birthweights greater than 2500 gms could be associated with DTP. (*Am J Public Health* 1987; 77:945–951.)

Introduction

Sudden infant death syndrome (SIDS) has been reported as a possible complication of pertussis immunization on a number of occasions and despite studies which have been interpreted as unsupportive of the idea, a causal relation has not been ruled out.[1–7] There is some *a priori* credibility to the hypothesis that pertussis vaccination might induce a fatal disorganization of respiratory control in susceptible infants. Minor systemic reactions are common,[8] and pertussis vaccine is thought to have rare but serious neurologic sequellae.[9] Neither vital statistics on infant death nor case reports are very helpful for the elucidation of a link between SIDS and pertussis vaccine, since the period of highest risk for SIDS coincides in the United States with the recommended dates for first two diphtheria-tetanus-pertussis (DTP) immunizations. Formal analyses must moreover contend with the potential distortive effect of risk factors for SIDS that in themselves influence pertussis immunization schedules: poverty and low birthweight[10] are prominent in this category.

The present study was designed to re-examine the hypothesis that DTP vaccine might be associated with an increased risk of SIDS in the first year of life. We have been fortunate in having access to complete medical records and notifications of death in a well-defined population. In order to clarify the examination of an outcome thought to have many possibly independent causes,[10] we further focused attention on children possessing no obvious medical risk factors for SIDS.

Methods

Group Health Cooperative of Puget Sound (GHC) is a consumer-owned health maintenance organization founded in 1945 which provides its members with full coverage for virtually all aspects of outpatient and inpatient medical care. According to internal surveys, the GHC population is 90 per cent non-Hispanic White; 92 per cent of members over the age of 18 have completed high school, and two-thirds have had *more* than 12 years of education. Unemployment among GHC members was 4 per cent in 1985. GHC maintains its own clinics, hospitals, and a centralized pharmacy to serve its membership, which now exceeds 309,000 persons. Since 1972, all hospital discharges have been recorded in a machine-readable format and can be linked with GHC's membership file and with computerized death records from the State of Washington. All pharmacy prescriptions and refills have been recorded since July 1976 and can be similarly linked to the other GHC data bases. Coded abstracts of GHC's computerized files, including archival records, are maintained by the Boston Collaborative Drug Surveillance Program to facilitate joint research.

The study population for the present report consists of all apparently healthy infants of birthweight greater than 2500 grams born in GHC hospitals from 1972 to 1983, who were subsequent users of GHC services, and for whom all medical records were retrievable in 1985 and 1986, the period during which this investigation was carried out. There were 35,581 deliveries at GHC hospitals during the period of study. An analysis of a random sample of records (see below) indicates that 75 per cent of these deliveries were of infants eligible for the present investigation. The surveyed population experience thus comprises the immunization and mortality of approximately 26,500 infants. These infants remained under surveillance, and therefore in the study population, for the duration of their families' membership in GHC.

All deaths occurring from 1972 through 1983 among GHC members from 30 to 365 days of age were identified by linkage of GHC membership files to State records. These deaths were reviewed in a two-step process. First, all deaths which on the basis of death certificate diagnosis, hospital discharge data, and pharmacy use taken together could be clearly ascribed to causes not related to immunization were excluded. All remaining records were then abstracted in order to determine cause of death in cases in which computerized data left room for doubt. Copies of death certificates and autopsy results were sought whenever cause of death was not evident from attending physicians' notes.

SIDS was defined as any death for which no cause could be discerned among infants of normal birthweight and without predisposing medical conditions born at GHC hospitals in the years 1972 through 1983. The case series consisted of all 29 SIDS deaths, so defined. Although an autopsy compatible with SIDS was not required for eligibility for this study, all but one of the eligible cases had been autopsied, and the

Address reprint requests to Alexander M. Walker, MD, DrPH, Boston Collaborative Drug Surveillance Program, Boston University Medical Center, 400-1 Totten Pond Road, Waltham, MA 02154. He is also with the Department of Epidemiology, Harvard School of Public Health, Boston. Dr. Jick is also with the Boston Collaborative Drug Surveillance Program; Drs. Perera, Thompson, and Knauss are with Group Health Cooperative of Puget Sound, Seattle, WA. This paper, submitted to the Journal December 16, 1986, was revised and accepted for publication March 1, 1987.
Editor's Note: See also related editorial p 925 this issue.

autopsy diagnosis was in every case SIDS. An additional 14 deaths certified as SIDS occurred among GHC members over the age of 30 days. These have been retained for some of the descriptive material, as described below, and are presented in some detail in the Appendix, but they did not enter into formal analyses.

The overall incidence of SIDS was estimated by dividing the number of deaths (including low birthweight and medically predisposed cases) by the number of infant years at risk in the age range 30 to 365 days.

The timing of DTP administration was determined for the case group by abstracting each infant's lifetime outpatient record. The timing of immunization in the population giving rise to the cases was estimated by examining 262 records of infants with birthweight >2500 grams, without medical conditions placing them at high risk for SIDS, and receiving their primary medical care at GHC during the period under review. These reference records were the complete set of eligible records identified out of 350 randomly selected records of children born at GHC hospitals. (The list of 350 records reviewed comprised 50 records identified at random from computerized files of children born in each of the years 1972, 1974, 1976, 1978, 1980, 1982 and 1984.) The sampled target population may be estimated to constitute about 75 per cent (262/350) of all births at GHC. Most of the first two DTP immunizations were accompanied by oral polio vaccine (OPV) through 1979. From 1980 the first OPV appears to have been given often in conjunction with the second DTP. All DTP and OPV administrations took place in a GHC clinic.

Each case was compared to all the reference children born in the calendar year closest to the case's date of birth, and immunization status was evaluated from the primary medical record for the case and all of the corresponding reference children as of the case's age in days at death. Immunization status was categorized as "No pertussis vaccine to date," "Last immunization within the past three days," "Last immunization within four to seven days," "Last immunization within eight to 29 days," and "Last immunization 30 or more days earlier." Split vaccine doses were counted as separate immunizations.

Variation in mortality from SIDS in relation to DTP immunization status was calculated by means of a matched case-control analysis[11] performed in GLIM,[12] using Whitehead's[13] algorithm. All analyses were carried out both with and without matching on calendar period, with essentially identical results. Analyses presented in what follows retain the period matching. Since no SIDS victim studied was born after June 30, 1983, the 1984 reference group was not invoked for the period-matched analyses, and the reference series used in the period-matched analyses numbered 225 infants. All reference series children were counted for the graphical displays.

Confidence intervals for the relative mortalities in the crude analyses of Tables 2 through 4 were derived by considering pairs of case counts to be distributed as binomial variables and obtaining the binomial counterpart of Cornfield's[14] limits, without continuity correction. A product-limit estimate[15] was used to calculate the cumulative probability of immunization in children excluded from the study.

Results

Case Characteristics

Some details of the 29 case histories are listed in Table 1. Corresponding data for 14 deaths ascribed to SIDS in GHCmembers who were not part of the study population are listed in Appendix Table A1. Thirty-nine of the total 43 cases identified on their death certificates as SIDS occurred in children born at GHC hospitals, during a period that encompassed 27,940.8 infant years of observation, giving an overall mortality of 1.4 cases per 1,000 infant years at risk.

Never Immunized Infants

Six of the 29 infants had not received pertussis vaccine at the time of their death (Table 1). This proportion is compared to that expected (1.56 out of 29) and further analyzed in Table 2. The relative mortality can be approximated by the cross product of Table 2, giving $(6 \times 27.44)/(23 \times 1.56) = 4.6$. The formal matched analysis yields an estimate of 6.5 fold increase in mortality of never-immunized over ever-immunized infants (95 per cent CI 2.2 and 19).

At the time of their deaths, all but one of the non-immunized had passed the 95th percentile of the population distribution of age at first DTP (Figure 1). In order to determine whether any common circumstances related to risk of SIDS affected their immunization schedules, we reabstracted the charts of the non-immunized SIDS victims for data on social characteristics and utilization of medical care. Four out of six mothers were single parents, three of whom were unemployed, and two of whom were receiving public assistance. Physical abuse, at least of the mother, appears to have characterized one other family.

Although at least five of these infants who died before recorded DTP immunization (and/or their mothers) appeared to be using GHC services in the interval between delivery and the infant's death, it is conceivable that the mother might have sought infant immunizations elsewhere. We identified and contacted all well child clinics operating near the homes of these children or near the homes of other possible caretakers listed in the chart, such as grandparents. None of these clinics had any record of visits of any kind by any of the children in question.

Immunized Children

We analyzed SIDS mortality among immunized children by a procedure analogous to that above, except that non-immunized cases were deleted and non-immunized reference group members were omitted from every matched set. There was an important decline in SIDS mortality rates over the days following immunization (Table 3). Four infants died within three days of DTP (three following the first immunization, one following the second) yielding an estimated age- and period-adjusted relative mortality rate of 7.3 (95 per cent CI 1.7 to 31) by comparison to children immunized at least 30 days earlier. Age-adjusted mortality declined gradually over the four weeks following immunization. It should be noted that the confidence intervals for relative mortality in the fourth through 29th days following immunization extend well below one and therefore into the range of a mortality deficit. The overall mortality in the period 0 to 29 days following DTP was 2.9 times that in the period 30 or more days after immunization; the 95 per cent CI was 0.93 to 9.1. The data therefore do not rule out the possibility of a compensatory decline in SIDS mortality after a brief post-immunization rise.

Reabstraction of the medical records of the four children dying soon after immunization for indications of non-medical risk factors for SIDS was not productive of the kinds of indicators of risk found with the non-immunized cases. However, an indirect indicator of postnatal care, the date of first DTP immunization, was somewhat delayed in three of

TABLE 1—SIDS Deaths in Children without Predisposing Medical Conditions Born at Group Health Cooperative of Puget Sound

Patient #	Sex	Race[a]	Birth Weight	Month/Year of Death	Age at Death (days)	Days Since Last DTP	No. of DTPs Preceding Death	Autopsy Diagnosis	Observations
1	F	W	2982	8/72	160	—	0	(SIDS)[b]	post mature
2	M	W	3863	10/72	167	6	3	SIDS[c]	
3	F	W	3579	12/72	102	3	2	(SIDS)	
4	F	W	3124	1/74	117	25	2	(SIDS)	
5	F	A	3323	1/74	60	14	1	SIDS	
6	M	W	3295	10/74	78	25	1	(SIDS)	twin
7	M	W	3380	11/74	133	20	2	(SIDS)	history of fracture of right humerus, ?child abuse
8	M	W	3240	12/75	52	5	2	SIDS	
9	F	B	3039	12/76	87	—	0	SIDS	
10	M	W	3721	4/77	80	14	1	SIDS	
11	M	W	4346	7/77	77	49	1	SIDS	
12	F	W	2897	11/77	87	42	1	SIDS	
13	M	W	3607	12/77	115	44	1	SIDS	
14	M	W	3493	2/78	175	28	1	SIDS	
15	F	W	2812	7/78	56	13	1	SIDS	
16	F	W	3636	8/78	277	137	2	SIDS	
17	F	W	3437	12/79	60	31	1	SIDS	
18	F	AI	3266	2/80	78	—	0	SIDS	fever, vomiting, 2 days before death
19	M	W	4090	4/80	84	—	0	SIDS	
20	M	W	3238	6/80	114	72	1	SIDS	
21	M	W	3266	7/80	81	37	1	Refused	
22	F	W	3550	8/80	134	—	0	(SIDS)	
23	M	W	3777	8/81	58	2	1	SIDS	
24	M	W	3181	11/81	59	—	0	SIDS	
25	M	W	4573	1/82	103	2	1	SIDS	
26	M	W	3181	7/82	134	95	1	SIDS	
27	M	W	3493	8/82	46	0	1	SIDS	family disruption
28	F	A	2925	9/82	53	9	1	SIDS	
29	M	W	4402	1/83	178	45	2	SIDS	

[a]Race: A—Asian, AI—American Indian, B—Black, W—White
[b](SIDS) autopsy performed and recorded on Death Certificate as supportive of diagnosis of SIDS, but original documentation no longer available.
[c]SIDS full autopsy results available and supportive of diagnosis.

TABLE 2—SIDS Mortality in Relation to DTP

	DTP Immunization Status		
	Never	Ever	Total
Observed Case Distribution	6	23	29
Age- and Period-Matched Expected Case Distribution[a]	1.56	27.44	29
Relative Mortality			
Crude Analysis[b]	4.6	1.0	
95% Confidence Limits	(1.9,11)		
Matched Analysis[c]	6.5	1.0	
95% Confidence Limits	(2.2,19)		

[a]Based on immunization histories in a random sample of children born at Group Health hospitals.
[b]Calculated as: (6/1.56)/(23/27.44) = 4.6.
[c]Age- and period-matching accounted for in analysis (see text).

these children (including Case 3, whose death followed the second DTP administration). Figure 1 plots these ages at first DTP and those of the remaining SIDS infants.

Three of the cases dying shortly after immunization did so during a 13-month span beginning in August 1981. For these children, it was possible to identify the lot numbers of the vaccines used. The infants had each received vaccine from a different lot; the lots came from two different manufacturers. Of the four children dying shortly after DTP, only Case 3 had had a concurrent OPV.

Discussion

The major finding of the present study is an apparent 7.3 fold elevation in the risk for SIDS in the first four days following immunization with DTP in the first year of life. In addition, children without any DTP immunization had a SIDS mortality more than six times higher than those who had been immunized. All of the children who died without immunization had already passed the normal ages of first DTP immunization at Group Health, as had a majority of those children who died within a few days of immunization.

Delay in immunization of high-risk infants might lead both to an elevated risk in the never-immunized and to a foreshortening of the interval between immunization and SIDS in the immunized. Both phenomena could operate in the absence of any causal connection between immunization and risk of SIDS death, and could account at least in part for the results obtained here. Review of the individual non-immunized cases suggested a high prevalence of factors that might well lead to a delay in immunization and which are known to predispose to SIDS. Although these elements are not in themselves entirely sufficient to explain the observed risk elevation, both the pattern itself (high risk of SIDS associated with absence of immunization) and probable confounding by socioeconomic factors have been observed previously.[4,6] Data reported from a prospective study of SIDS in Sheffield, United Kingdon,[4] yield a crude SIDS

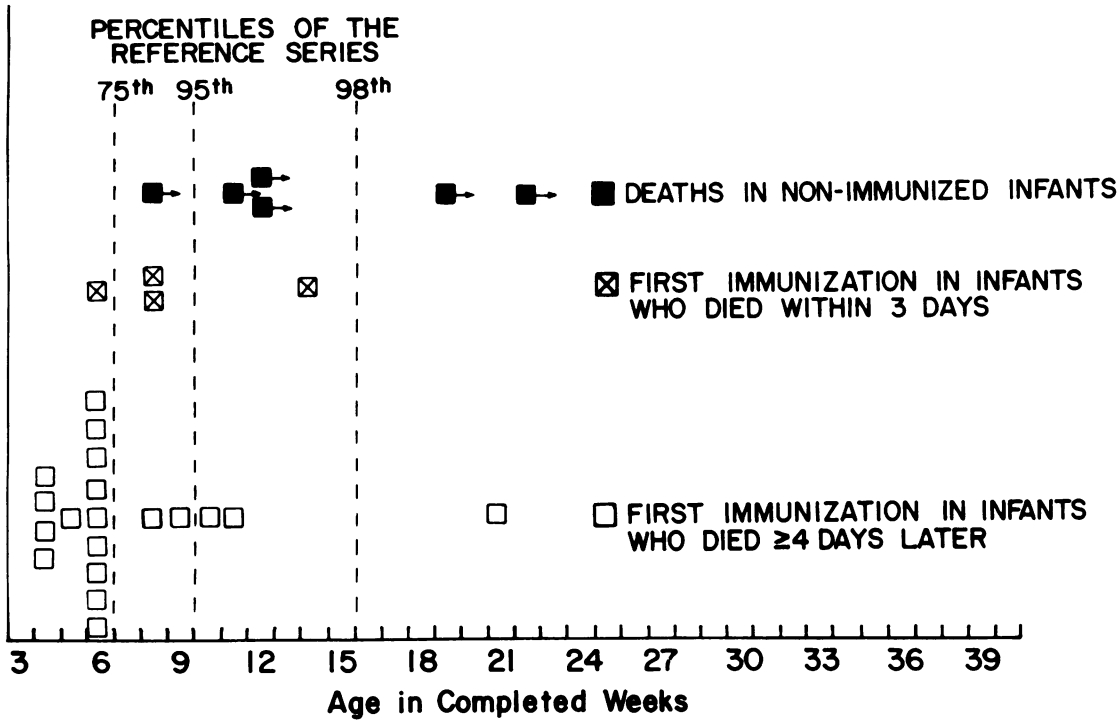

FIGURE 1—Timing of first DTP in immunized SIDS cases, and of death in the non-immunized. Arrows are on the non-immunized to emphasize that date of first DTP would have been later than the date indicated for death. Vertical lines give the percentiles of the cumulative distribution of age at first DTP in the reference series. Time of first DTP serves here as an index of timeliness of postnatal care. The proportions of cases beyond the 75th percentile of the reference distribution are: non-immunized, 100%; recently immunized, 75%; others, 26%. The first two categories of infants experienced delays in their postnatal care.

TABLE 3—SIDS Mortality among the Immunized in Relation to Post-Immunization Interval

	Days Since Last DTP				
	0–3	4–7	8–29	30+	Total
Observed Case Distribution	4	2	8	9	23
Age- and Period-Matched Expected Case Distribution[a]	1.36	1.56	8.23	11.85	23
Relative Mortality					
Crude Analysis[a]	3.9	1.7	1.3	1.0	
95% Confidence Limits	(1.3,12)	(0.41,6.9)	(0.51,3.2)		
Matched Analysis[a]	7.3	3.1	1.9	1.0	
95% Confidence Limits	(1.7,31)	(0.52,19)	(0.53,6.9)		
		2.9			
		(0.93,9.1)			

[a]Non-immunized excluded from reference series.

relative risk of 2.4 for never immunized as compared to age-matched immunized children. The NICHD Cooperative Epidemiological Study of Sudden Infant Death Syndrome[6] found crude relative risks of about two for SIDS in unimmunized infants compared to those who had received DTP in both Whites and Blacks.

All candidate explanations for the observation of increased risk of SIDS in nonimmunized infants hinge on an artifact of some sort. SIDS rates in the UK did not rise and fall with the mass abandonment of pertussis vaccination, nor with the ensuing epidemics of pertussis.[17] It seems therefore unlikely that pertussis immunization protects against SIDS, as for example by aborting an idiosyncratic, fatal reaction to *Bordetella pertussis*.

Several factors mitigate also against acceptance of the data on immunized children (Table 3) as evidence for a simple causal association. A delay in the immunization schedule among high-risk infants could produce an increase in the number of short intervals between immunizations and death, if immunizations were postponed from an age of lower risk (six weeks) to one of higher risk (eight to 16 weeks). The relatively small number of SIDS cases in the present study also admits the possibility of substantial random error.

Preceding investigations of the relation between SIDS and DTP have been subject to a variety of interpretations, partly because of differences in methodology. Table 4 presents an attempt to abstract elements common to this earlier work. For various time intervals following immunization, Table 4 gives the number of SIDS cases reported and the durations of the intervals. A crude relative mortality has been calculated in Table 4 as the ratio of two ratios: (deaths in interval/duration of interval) divided by (deaths in last reported interval/duration of last reported interval). The rationale for this comparison is that the number of child days at risk in the populations giving rise to the SIDS cases in various time intervals must be, to a very close approximation, proportional to the length of the interval. Thus, for example, Baraff, *et al*,[6] reported five cases in the 3.5-day period 0–3 days following DTP and nine cases in the 22-day period 8–29 days following DTP. If the number of children at risk is N, then the ratio of SIDS daily mortality rates in the two periods is $[5/(3.5 \times N)]/[9/(22 \times N)] = (5/3.5)/(9/22) = 5.4$. To the extent that immunizations occur in periods of declining risk for SIDS, the comparisons in Table 4 are somewhat biased toward higher relative mortality in the earlier intervals. Two of the studies tabulated were undertaken in response to reported deaths; the index deaths and the mortality ratios obtained by the inclusion of the deaths that

TABLE 4—Case Series of SIDS Preceded by Pertussis Vaccine Relative Mortality Inferred from Ratios of Cases to Days-at-Risk

Source	Period I			Period II			Period III		
	Definition	Duration[a]	Cases	Definition	Duration	Cases	Definition	Duration	Cases
Bernier, et al. (ref 2)									
Data	0–3 days	3.5	3(+4)[c]	4–7 days	4	5	8–29 days	22	11
Relative Mortality[b]		1.7 (4.0)			2.5			1.0	
95% CI		0.52–5.7 (1.6–10)			0.91–6.9				
Torch[c] (ref 3)									
Data	0–3 days	3.5	9(+3)	4–7 days	4	5	8–21 days	14	16
Relative Mortality		2.3 (3.0)			1.0			1.0	
95% CI		1.0–5.0 (1.4–6.2)			0.37–2.5				
Hoffman et al. (ref 4)									
Data	24 hours	1	2	1–14 days	14	33			
Relative Mortality		0.85			1.0				
95% CI		0.23–3.2							
Taylor and Emery (ref 5)									
Data	0–2 days	2.5	1	3–7 days	5	0	8–28 days	21	3
Relative Mortality		2.8			0			1.0	
95% CI		0.41–20			0–5.4				
Baraff et al. (ref 6)									
Data	0–3 days	3.5	9	4–7 days	4	8	8–28 days	21	10
Relative Mortality		5.4			4.2			1.0	
95% CI		2.3–13			1.7–10				
Solberg[e] (ref 7)									
Data	0–3 days	3.5	4	4–7 days	4	11	8–28 days	21	38
Relative Mortality		0.63			1.5			1.0	
95% CI		0.24–1.7			0.79–2.9				
Current Study									
Data	0–3 days	3.5	5	4–7 days	4	2	8–29 days	22	9
Relative Mortality		3.5			1.4			1.0	
95% CI		1.2–9.9			0.33–5.7				

[a]Day 0 counted as 0.5 days unless authors state to contrary.
[b]Relative mortality [(deaths in interval)/(days in interval)]/[(deaths in last interval)/(days in last interval)]
[c]Numbers in parentheses are based on inclusion of additional cases that prompted the investigation in question.
[d]Table entries derived from percentages reported in the original.
[e]Table entries derived from graphical presentation in the original.

prompted the studies are given in parentheses. In the line corresponding to the present study, the otherwise eligible cases who were excluded for not having been born at a GHC hospital are reintroduced.

The studies presented in Table 4 vary enormously in the detail of data acquisition and in the thoroughness of analysis, a variation which is not reflected in the table. Although, unfortunately, the full text of Solberg's[7] report has had only limited distribution in English (in the form of an NIH Library Translation), its negative result should be given especially serious consideration. Of all the investigations listed, only that one is comparable to the present study in that: 1) analysis of the DTP-SIDS relation was a primary initial objective of the research; 2) case identification and exposure ascertainment were based on medical and vital statistics data of a relatively standard format and accessibility for all the population covered; and 3) the data have been fully reported (i.e., not only in an abstract or letter form).

While the results of the present study are worrisome, they do not constitute an appropriate basis for any specific action other than a thorough examination of data from other sources. First, the study is confined to children at a low baseline risk for SIDS. There were not enough births at GHC to permit an approach to the question of vaccine risks in low birthweight or ill children, but the sparse data available do not indicate an elevated risk in that group (see the Appendix). Even if all the SIDS occurring within three days after immunization were due to DTP, immunization practice would not have accounted for more than about 10 per cent of SIDS cases at GHC. The possibility of compensatory decline in mortality after an initial rise cannot be ruled out.

In the absence of infant immunization programs there would have been a substantial risk of pertussis itself,[18] a serious illness requiring hospitalization for the great majority of infected children under six months of age and resulting in death for about one infant in a hundred.[19] Even a six-month postponement in the currently recommended US schedule for DTP immunizations is thought to entail serious potential consequences.[20]

The present study was one whose logistics were not complex, given the health maintenance organization (HMO) in which it was carried out. It should be replicable in any population with a defined infant membership, clear immunization records, linked death files, and reasonably complete autopsy data on children. Since many HMOs and governmental programs meet these minimal criteria, it should be possible to organize routine administrative data into vaccine surveillance systems capable of addressing the questions raised here.

Reevaluation of the immunization status of a single reference group at different ages for different cases produces a variant of case-control studies which has been termed a "case-cohort" design, since the evolving exposure status of the reference series mirrors that of the underlying cohort.[11] When the cases are few by comparison to the size of the reference series or when the exposure status at one time is a weak predictor of exposure status at another time, the appropriate analysis is just that of a matched case-control

TABLE A1—Sudden Unexplained Death in GHC Infants Who Were Not Members of the Study Population

Patients	Sex	Race[a]	Birth Weight	Month/Year of Death	Age at Death (days)	Days Since Last DTP	No. of DTPs Preceding Death	Death Certificate Diagnosis	Autopsy Diagnosis	Reason for Ineligibility
x1	F	AI	1647	10/73	161	—	0	SIDS	SIDS[b]	Low birthweight
x2	M	W	1619	8/74	93	—	0	SIDS	(SIDS)[c]	Low birthweight
x3	M	W	2727	5/77	76	—	0	SIDS	SIDS	Failure to thrive, PDA, hospitalized for pneumonitis × 22 days, discharged 2 days before death
x4	M	B	2101	10/78	47	18	1	SIDS	SIDS	Low birthweight
x5	F	W	n/a	12/78	182	3	3	SIDS	Refused	Not born GHC
x6	M	W	1220	10/80	52	—	0	SIDS	Not performed	Low birthweight
x7	F	W	2100	12/80	228	78	1	SIDS	SIDS	Low birthweight
x8	F	W	n/a	1/81	217	148	2	SIDS	Not available	Not born GHC
x9	M	W	n/a	10/81	124	71	1	SIDS	Not available	Not born GHC
x10	M	W	n/a	11/81	64	17	1	SIDS	SIDS	Not born GHC
x11	M	W	2868	12/81	88	45	1	SIDS	SIDS	Severe birth asphyxia, Neonatal Group B strep sepsis
x12	F	B	2073	3/82	76	34	1	SIDS	SIDS	Low birthweight
x13	M	W	1350	5/82	77	49	1	SIDS	Not performed	Low birthweight
x14	F	W	2329	9/83	91	43	1	SIDS	SIDS	Low birthweight

[a]Race: AI = American Indian, B = Black, W = White
[b]SIDS full autopsy results available and supportive of diagnosis.
[c](SIDS) autopsy performed and recorded on Death Certificate as supportive of diagnosis of SIDS, but original documentation no longer available.

study (R. L. Prentice, personal communication). The variance of estimates arising from a case-cohort study tend to be smaller than those of more traditional designs. In the present instance, however, all error estimates were determined principally by the relatively small numbers of cases, and so the advantage was small.

APPENDIX

SIDS Deaths in Children Not Members of the Study Population

Fourteen GHC members who were not from the study population were certified as having died of SIDS at age 30 days or older during the years 1972–83. Eight had birthweights below 2500 grams, two had life-threatening medical conditions, and four were not born at GHC hospitals. Although these children could not be entered into the formal comparisons, some of their case data are presented in Table A1 in order to provide a complete portrait of SIDS at GHC.

The prevalence of immunization among the SIDS cases excluded for medical reasons exceeded 50 per cent only at 150 days of life. This observation tends to confirm the anticipated relation between medical risk factors for SIDS and delay in immunization. As a group, very high-risk infants may therefore not be exposed to pertussis vaccine at an age comparable to that of lower risk children. None of the 10 high-risk children who died of SIDS at GHC had had a DTP in the two weeks preceding death.

The four cases ineligible because of not having been born at a GHC hospital (cases x5, x8, x9 and x10) had unremarkable DTP immunization histories. The intervals between DTP and death in these children (3, 17, 71, and 148 days) were similar to those of the eligible cases, and addition of these deaths to the case series would have strengthened the associations documented in Table 3.

ACKNOWLEDGMENTS

The authors benefited from advice and criticism provided by an advisory committee consisting of James D. Cherry, MD, UCLA School of Medicine; Harriet Kiltie, MD, Lederle Laboratories; John A. Livengood, MD, and Harrison C. Stetler, MD, Centers for Disease Control; Edward A. Mortimer, Jr., MD, Case Western Reserve University School of Medicine; Karin B. Nelson, MD, National Institute of Neurological Disease and Stroke; Donald R. Peterson, MD, MPH, University of Washington School of Public Health. This acknowledgment should not be construed as an endorsement of the study or its results by the advisory committee members or the institutions to which they belong. The findings and conclusions of this study do not necessarily represent the views of Group Health Cooperative of Puget Sound.

The Boston Collaborative Drug Surveillance Program is supported by the Food and Drug Administration (Cooperative Agreement FD-U-000071-04) and by grants from: Burroughs Wellcome Co., Ciba-Geigy, Glaxo Inc., Hoffmann-La Roche Inc., Lederle Laboratories, Lilly Research Laboratories, McNeil Pharmaceuticals, Merck Sharpe and Dohme Research Laboratories, Pfizer Inc., Winthrop-Breon Laboratories.

Dr. Walker is supported by awards from the Burroughs Wellcome Foundation and from the Mellon Foundation.

REFERENCES

1. Stewart GT: Infection and immunization. Scot Med J 1979; 24:47–52.
2. Bernier RH, Frank JA, Dondero TJ, Turner P: Diphtheria-tetanus toxoids-pertussis vaccination and sudden infant deaths in Tennessee. J Pediatr 1982; 101:419–421.
3. Torch WC: Diphtheria-pertussis-tetanus (DPT) immunization: A potential cause of the sudden infant death syndrome (SIDS). Abstract. Neurology 1982; 32:A169–170.
4. Hoffman HJ, Hunter JC, Hasselmeyer EG: SIDS and DTP. *In:* Proceedings of the 17th Immunization Conference, Atlanta, GA, May 1982.
5. Taylor EM, Emery JL: Immunization and cot deaths (letter). Lancet 1982; 2:721.
6. 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.
7. Solberg LK: DPT vaccination, visit to child health center and sudden infant death syndrome (SIDS); Evaluation of DPT vaccination. Oslo Health Council 1985. NIH Library Translation NIH-85-152. Distributed by CR Manclark, Laboratory of Pertussis, Food and Drug Administration, Bethesda, MD.
8. Cody CL, Baraff LJ, Cherry JD, March SM, Manclark CR: Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. Pediatrics 1981; 68:650–660.
9. Miller DL, Ross EM, Aldershade R, Bellman MH, Rawson NSB: Pertussis immunization and serious acute neurological illness in children. Br Med J 1981; 282:1595–1599.
10. Peterson DR: Evolution of the epidemiology of sudden infant death syndrome. Epidemiol Rev 1980; 2:97–112.
11. Prentice RL: A case-cohort design for epidemiologic cohort and disease prevention trials. Biometrika 1986; 73:1–11.
12. GLIM Working Party: The generalized linear interactive modeling system, Release 3.77. Numerical Algorithms Group Ltd., Oxford.
13. Whitehead J: Fitting Cox's regression model to survival data using GLIM. Appl Stat 1980; 29:268–275.
14. Cornfield J: A statistical problem arising in retrospective studies. *In:*

Neyman J (ed): Proceedings of the Third Berkeley Symposium, IV, Berkeley, University of California Press, 133–148.
15. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457–481.
16. Pharoah POD, Morris JN: Postneonatal mortality. Epidemiol Rev 1979; 1:170–183.
17. Swansea Research Unit of the RCGP: Effect of a low pertussis vaccination uptake on a large community. Br Med J 1981; 282:23–26.
18. Hinman AR, Koplan JP: Pertussis and pertussis vaccine; reanalysis of benefits, risks and costs. JAMA 1984; 251:3109–3113.
19. Miller CL, Fletcher WB: Severity of notified whooping cough. Br Med J 1976; 1:117–119.
20. Funkhouser AW, Wassilak SGF, Orenstein WA, Hinman AR, Mortimer EA: Estimated effects of a delay in the recommended vaccination schedule for diphtheria and tetanus toxoids and pertussis vaccine. JAMA 1987; 257:1341–1346.

Unique AIDS Library Available on Colleague

Since this Journal went "on-line" with the electronic publishing activity called Colleague in July 1985—one of the first journals to be included in the BRS/Saunders Colleague Program—the program has expanded greatly and now includes over 60 professional journals and health-related periodicals.

To assist those who are trying to keep up with the literature and latest information on AIDS (acquired immunodeficiency syndrome), Colleague is developing a comprehensive library of databases devoted exclusively to AIDS. The AIDS Library includes:

LIBRARY DATABASES	LABEL
AIDS Abstracts from the Bureau of Hygiene and Tropical Diseases	AIDD
AIDS Articles from Colleague's Complete Text Library	AACC
Medical and Psychological Previews	PREV
MEDLINE References on AIDS	MRAI
PDQ Cancer Information	PDQC
PDQ Protocols	PDQP

BRS has *created* two of these files, AACC and MRAI, and is the only place you can find these unique collections:

- *AIDS Articles from Colleague's Complete Text Library (AACC)* is a collection of full text articles on AIDS taken from the Colleague Journal Collection—JOUR. AACC is exclusively devoted to the subject of AIDS.
- *MEDLINE References on AIDS (MRAI)* consists of citations and abstracts from MESH which deal with all aspects of AIDS.
- *AIDS Abstracts from the Bureau of Hygiene and Tropical Diseases (AIDD)* is produced by the Bureau of Hygiene and Tropical Diseases in the United Kingdom. The Bureau scans the published literature on AIDS and then creates the records for AIDD. Only articles that represent good work and that are new, important and relevant are fully abstracted.

The *AIDS KNOWLEDGE BASE,* a unique, new database on AIDS from San Francisco General Hospital, to be available this summer online on BRS, is designed for use by clinicians, researchers, nurses, public health personnel, hospital administrators, educators, and others working to combat AIDS. The *AIDS KNOWLEDGE BASE* will evolve through continuous updating as new developments and practices emerge in this rapidly changing area, allowing users to keep current with all aspects of clinical practice and research.

For further information about this or other Colleague Program activities, contact BRS Colleague, BRS Information Technologies, 555 East Lancaster Avenue, St. Davids, PA 19087, or check the newsletter *On Call,* published bimonthly at BRS/Colleague, 1350 Avenue of the Americas, New York, NY 10019.