Adverse Events Following DTP Immunization in Maryland, 1987

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Between January 1, 1987 and December 31, 1987, a total of 184 adverse events were reported to have occurred within 28 days following diphtheria, tetanus, pertussis (DTP) immunization in Maryland. More than half the reports (54 percent) were of serious or major vaccine reactions. Screaming episodes were the most frequently reported serious reaction, having occurred in 64 (35 percent) of the reports.

The objective of immunization is to enhance an individual's immunity against an organism or an endotoxin while incurring minimal side effects. The DTP vaccine is a combination of diphtheria toxoid, tetanus toxoid, and whole cell inactivated *Bordetella pertussis*.[1] The pertussis component of the DTP vaccine may contain whole bacteria, bacterial antigen, or bacterial endotoxin.[2] Administration of any of these components can enhance the immunological response in an individual.

The Immunization Practice Advisory Committee (ACIP) recommends 0.5 ml intramuscular DTP vaccination of children at 2, 4, and 6 months of age, and a fourth dose at approximately 15 months of age.[3] A booster dose before a child enters school or before the seventh birthday is recommended. It has been estimated that the efficacy of DTP vaccine is about 80 percent for pertussis in recipients who have had at least three doses.[1]

Minor and febrile reactions associated with pertussis vaccine are common. Pertussis vaccine has been infrequently associated with serious or major adverse events such as temperature of 105°F and greater, anaphylaxis, arthritis/arthralgia, seizures, encephalitis/encephalopathy, Guillian-Barré syndrome, Reye's syndrome, paralysis, screaming episodes, hypotonic hyporesponsive episodes, other neurological symptoms, and death.

As early as 1979, the Centers for Disease Control (CDC) recommended reporting of all vaccine reactions occurring within 28 days after immunization with vaccine purchased with public funds, if the reaction was more severe than a local reaction and if the patient was seen by a physician. Reactions were to be reported to the local health department or to the Maryland Department of Health and Mental Hygiene Monitoring System for Adverse Events Following Immunization (MSAEFI) Program. In May 1986 an additional state regulation on pertussis disease and pertussis vaccine became effective in Maryland.[4] This regulation required public and private health care providers to report major vaccine reactions occurring within seven days following pertussis immunization.

Although not required, some clinicians have reported minor vaccine reactions to the Maryland MSAEFI program.

We present the analysis of vaccine adverse event reports received by the Maryland MSAEFI program following administration of DTP vaccine between January 1, 1987 and December 31, 1987.

Methods

Within 24 hours of receiving an adverse event report, the local health department initiates an investigation and completes information on a Centers for Disease Control vaccine adverse event report form (CDC 71.19). The CDC report form contains information about the source of vaccine (public or private), type of vaccine given, vaccine manufacturer, vaccine lot number; a description of the clinical symptoms (including personal or family history of seizures), and any occurrence of reaction to the previous immunization. The information is obtained from either the reporting physician by telephone or from the parent/guardian by telephone or a home visit. Permission is obtained from the attending physician before contacting the parent. When the investigation is completed, the report is submitted to the MSAEFI program for review and analysis. If information is missing on the report form, the MSAEFI program coordinator contacts the local health department or the reporting physician to obtain complete information.

Reactions were defined by the occurrence of one or more symptoms occurring within 28 days of immunization, whether or not the child was seen by a doctor. A screaming episode was defined as high-pitched abnormal crying or unconsolable crying lasting at least 3 hours as reported by the physician or the parent. A hypotonic hyporesponsive episode (HHE) was defined as an unusual reaction characterized by paleness, hypotonia, and unresponsiveness occurring within 10 hours of vaccination and lasting 10 minutes to 36 hours.

Reaction rates were calculated for the public sector by using the total number of DTP vaccine doses administered at public clinics. Rates for private reports were calculated using the estimated number of doses administered by the private providers. The number of DTP immunizations given by private physicians was estimated by subtracting the number of doses of DTP vaccine administered by public clinics from the estimated total number of DTP doses given during 1987. The total number of DTP doses given in 1987 was approximated by using the number of children born in Maryland, the average number of DTP doses per child, and the estimated percentage of children immunized.

All MSAEFI reports were entered into a computerized data base for analysis. Probability values for two-by-two tables were calculated by the chi square test.

Results

A total of 184 children with adverse events following administration of DTP vaccine were reported among infants and children (ages 0 to 7 years) between January 1, 1987 and December 31, 1987. This was a 104 percent increase over the preceding four-year mean of 90 reports per year. Private providers reported 72 adverse events (as compared to 24 reports in 1986) and public providers reported 112 (Table 1). These adverse events occurred following administration of approximately 259,000 doses of DTP vaccine (41,000 doses administered by public health care providers and an estimated 218,000 doses administered by the private health care providers).

The rate of reporting by public provider was over eight times greater than by private providers (approximately 273.2/100,000 vs 33.02/100,000, respectively). The MSAEFI program received reports from 17 of the 23 Maryland counties and from Baltimore City. Reaction rates by county ranged from zero to 2206.6/100,000 doses, with a median rate of 120/100,000 doses administered in the public sector. The public clinic in county A with the highest rate reported 27.7 percent of all reactions reported in 1987. Privately administered vaccine reaction rates ranged from zero to 196.3/100,000 doses administered with a median rate of 4.1/100,000 doses. Although the overall rate of reported adverse events was higher for publicly administered vaccine, there was no difference between public and private reports in the percentage of reported events classified as serious events ($p = 0.25$) or in the percentage who saw a physician following the vaccine reaction ($p = 0.33$).

Table 1. Reported Reaction Rates and Percent of Children Examined by Physician Categorized by Source of Vaccine and Type of Reaction Maryland, January 1, 1987 - December 31, 1987

Reaction Type	Source of Vaccine							Total			
	Private				Public						
	Number	Seen by MD n	(%)	Rate*	Number	Seen by MD n	(%)	Rate**	Number	Seen by MD n	(%)	Rate*
Serious	43	12	(28)	19.7	56	20	(36)	136.5	99	32	(32)	38.2
Minor	29	11	(38)	13.3	56	25	(45)	136.5	85	36	(42)	32.8
Total	72	23	(32)	33.0	112	45	(40)	273.2	184	68	(37)	71.0

* rate per 100,000 doses DTP estimated to have been administered by private providers
** rate per 100,000 doses DTP administered in public clinics

Most children with adverse events had received DTP vaccine and other vaccines simultaneously. Of the 184 reports, 60 (33 percent) vaccine recipients received DTP vaccine alone; 109 (59 percent) had DTP and OPV; 12 (6 percent) had DTP, OPV and other vaccines (for example, Hib, MMR, etc.); and the remaining 3 (2 percent) cases had been given DTP and other vaccines.

Table 2 presents the frequency of adverse events following DTP vaccination. Reactions are categorized by the most severe reaction reported. Minor reactions were reported to have occurred in 85 (46 percent) children. Ninety-nine (54 percent) of the reports were classified as serious or major adverse events, with a rate of approximately 38.2 reports for every 100,000 doses of DTP vaccine administered. Screaming episodes were the most frequently occurring serious adverse event, occurring in 64 (65 percent) of the reported serious events. Ten (10 percent) seizures, 9 (9 percent) hypotonic hyporesponsive episodes (HHE), 7 (7 percent) other neurological symptoms, 8 (8 percent) fever cases of 105°F or greater, and one case of arthralgia/arthritis were reported as the most severe event.

Table 3 provides details of the three most severe reactions: screaming episodes, seizures, and hypotonic hyporesponsive episodes. Screaming episodes occurred in 64 children for a rate of approximately 24.7 cases/100,000 doses of DTP vaccine. The median age of a case was 4 months (range 1 month to 43 months). Most of the screaming episodes occurred within one day of vaccination. Only 15 (23 percent) saw a physician because of the reaction. Of the 64 screaming episodes, 20 (31.3 percent) were reported by one public clinic, county A, which administered 4.9 percent of the total publicly administered DTP vaccine.

Ten children had seizures following DTP vaccination, with a rate of approximately 3.9 cases/100,000 doses administered. These children ranged from 1 month to 28 months old, with a median age of 11.5 months. Seven cases had elevated temperature. None had a prior history of seizures or neurological illness. One case had a family history of seizures. Three cases had history of reactions to prior vaccination (one had a serious reaction, and two were minor reactions). In 8 of the 10 cases, onset of seizures took place within 24 hours of immunization, and two cases had onset seven days following immunization. Three cases had been given MMR vaccine simultaneously with DTP vaccine: two had seizures within 24 hours of immunization and one had seizures seven days following immunization. Nine of the ten children with seizures were seen by a physician. One child who developed seizures seven days after receiving DTP and OPV was later diagnosed as having cerebral infarcts and cerebral palsy; the seizures were temporally but probably not causally related to DTP immunization.

Nine cases of hypotonic hyporesponsive episodes (HHE) following DTP vaccination were reported, with a rate of approximately 3.5 cases/100,000 doses administered. These cases ranged in age from 1 month to 42 months, with a median age of 4 months. None of these children had any history of seizure activity or neurological illness prior to immunization. One child had a local reaction to a previous vaccination, and another had a family history of seizures. Seven of the 9 cases experienced elevated temperature (average temperature was 102.1°F). Hypotonic hyporesponsive episodes frequently occurred following the first dose of DTP vaccination. Two of the nine were seen by a physician because of the reaction.

We determined the outcome of the adverse events at 30 days following immunization for 180 (98 percent) of the reported events. Four cases could not be located for follow-up. One-hundred seventy-six children (98 percent) were fully recovered. The remaining four were partially recovered; one had cerebral palsy determined by the physician to be unrelated to immunization, one had a residual abscess, one had asthma, and one was described to have irritability.

The MSAEFI system identified no lots of vaccine that had to be recalled because of elevated reaction rates.

Table 2. Adverse Events Reported following DTP Immunization Categorized by Most Severe Event January 1, 1987 - December 31, 1987, Maryland

Type of Reaction	# of Reports	% of Total
Serious adverse events (N=99)		
Convulsions	10	4
HHE*	9	5
Screaming episodes	64	35
Other neurologic symptoms	7	4
Arthritis/arthralgia	1	1
Fever (=105°F)	8	4
Minor adverse events (N=85)		
Rash	6	3
Adenopathy	2	1
Allergy	3	2
Fever (100°F - 104.9°F)	45	24
Other minor events	21	12
Local reactions	8	4
Total	184	100

* HHE Hypotonic hyporesponsive episode

Discussion

In the first year following a Maryland law requiring reporting of major vaccine reactions following pertussis immunization, public and private sector health care providers reported 184 adverse events following DTP immunization. Although the 104 percent increase over the preceding four-year average was largely due to increased reporting by the private sector, private health care providers are still underreporting, compared to public providers. Marked variation also was seen among counties, with the public clinic in one county reporting 27.7 percent of all vaccine reactions in the state, a rate 18 times the public sector median.

The county that reported a significantly higher number of adverse events following immunization was investigated. The high rate of reactions was not due to different vaccine lots being administered in that county, and staff were found to be using standard vaccine administration techniques. The high rate of reactions may have been due to increased surveillance for vaccine adverse events or more active parent education about pertussis side effects and, thus, better reporting of adverse events by parents.

The Maryland law did not specifically define the reactions to be reported. Many reactions require subjective interpretations on the part of the parent or health care provider. Additionally, some providers may still be unaware of the requirement to report. Our data illustrate that parents, clinicians, and counties have different definitions for various vaccine reactions, and set different thresholds for reporting. These differences are reflected in the reported vaccine reaction rates. It must be emphasized that the occurrence of an adverse event within 28 days after administration of vaccine is not necessarily confirmation of a causative relationship and may, in fact, be only temporally associated.

Rates of screaming episodes, seizures, and HHE that are reported here were approximately ten times lower than those reported in prospective DTP vaccine studies,[5-9] but higher than the rate of 1:800,000 reported to one vaccine manufacturer.[10]

The Maryland reporting system is a passive surveillance system and, as such, all vaccine reactions are not reported. The calculated rates of reported reactions lack precision since the denominator is, by necessity, only an estimate of the total number of doses administered. However, passive reporting plays an important role in identifying types and relative frequencies of reactions, in monitoring trends, and possibly in identifying lots of vaccine associated with high rates of reactions. Our experience is particularly timely in light of the National Vaccine Injury Act passed in 1988.[11] The act makes major reactions following certain vaccines reportable. Other states can expect more than a doubling of reports, if our experience with DTP is repeated.

Diphtheria, tetanus, and pertussis vaccine continues to be a safe and effective vaccine. No cases of encephalitis or death due to DTP were reported in Maryland in 1987. Research on an acellular vaccine of greater efficacy and fewer side effects is under way.[12]

Table 3.
Characteristics of Total Adverse Event Reports and Selected Serious Adverse Event Reports January 1, 1987 - December 31, 1987, Maryland

	Total Adverse Events	Screaming Episodes	Convulsions	HHE*
Number	184	64	10	9
Rates(100,000 Doses)	71	24.7	3.9	3.5
Median Age (Months)	5	4	11.5 +	4
Age Range (Months)	1 - 82	1 - 43	1 - 28	1 - 42
Day of Onset				
Day Of Immunization	150	57	7	8
1 Day Following	30	7	1	1
2 Days Following	1	0	0	0
≥ 3 Days Following	3	0	2	0
DTP Dose				
First	65	28	2	5
Second	46	20	1	3
Third	31	11	4	0
Fourth	29	5	3	1
Fifth	12	0	0	0
Unknown	1	--	--	--
Accompanying Fever				
No	57	25	3	2
Yes	127	39	7	7
(100°F - 103°F)	73	26	2	5
(103.1°F -104.9°F)	41	11	4	2
(≥105°F)	13	2	1	0
Seen by MD (%)	68 (37%)	15 (23%)	9 (90%)	2 (22%)
Pub/priv reports	112/72	37/27	4/6	6/3
# Reptd by county A	51(27.7)	20(31.3)	1(10.0)	3(33.3)

* HHE = Hypotonic Hyporesponsive Episode
+ 3 cases (age 15, 21, and 28 months) received DTP and MMR; Median age is 7 months if these three cases are excluded.

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