

# Infant Immunization With Acellular Pertussis Vaccines in the United States: Assessment of the First Two Years' Data From the Vaccine Adverse Event Reporting System (VAERS)

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**ABSTRACT.** *Objective.* To evaluate the safety of infant immunization with acellular pertussis vaccines in the United States.

*Background.* The US Food and Drug Administration approved the first acellular pertussis vaccine for use in infants in the United States on July 31, 1996.

*Outcome Measures.* Adverse events in the United States after infant immunization with pertussis-containing vaccines, representing temporal (but not necessarily causal) associations between vaccinations and adverse events.

*Data Source.* Reports to the Vaccine Adverse Event Reporting System (VAERS), a passive national surveillance system.

*Design.* Reports concerning infant immunization against pertussis between January 1, 1995 (when whole-cell vaccine was in exclusive use) and June 30, 1998 (when acellular vaccine was in predominant use) were analyzed, if the reports were entered into the VAERS database by November 30, 1998.

*Results.* During the study, there were 285 reports involving death, 971 nonfatal serious reports, and 4514 less serious reports after immunization with any pertussis-containing vaccine. For 1995 there were 2071 reports; in 1996 there were 1894 reports; in 1997 there were 1314 reports, and in the first half of 1998 there were 491 reports. Diphtheria-tetanus-pertussis vaccine (DTP) was cited in 1939 reports, diphtheria-tetanus-whole-cell pertussis-*Haemophilus influenzae* type b vaccine (DTPH) in 2918 reports, and diphtheria-tetanus-acellular pertussis vaccine (DTaP) in 913 reports. The annual number of deaths during the study was 85 in 1995, 82 in 1996, 77 in 1997, and 41 in the first half of 1998. The annual number of reported events categorized as nonfatal serious (defined as events involving initial hospitalization, prolongation of hospitalization, life-threatening illness, or permanent disability) to VAERS for all pertussis-containing vaccines declined: 334 in 1995, 311 in 1996, 233 in 1997, and 93 in the first half of 1998. Similarly, the annual number of less serious reports to VAERS for pertussis-containing vaccines declined: 1652 in 1995, 1501 in 1996, 1004 in 1997, and 357 in the first half of 1998. A comparison of the adverse event profiles (proportional distributions) for DTaP, DTP, and DTPH, as well as an analysis

of specific adverse events considered in a 1991 Institute of Medicine report on the safety of diphtheria-tetanus-pertussis vaccine, did not identify any new, clear safety concerns.

*Conclusions.* These findings reflect the administration of millions of doses of acellular pertussis vaccine and are reassuring with regard to the safety of marketed acellular pertussis vaccines. VAERS data, although subject to the limitations of passive surveillance, support the precicensure data with regard to the safety of the US-licensed acellular pertussis vaccines that we evaluated. *Pediatrics* 2000;106(4). URL: <http://www.pediatrics.org/cgi/content/full/106/4/e51>; vaccine, pertussis vaccine, acellular pertussis vaccine, vaccine safety, adverse effects.

ABBREVIATIONS. IOM, Institute of Medicine; DTP, diphtheria-tetanus-whole-cell pertussis vaccine; VAERS, Vaccine Adverse Event Reporting System; DTaP, diphtheria-tetanus-acellular pertussis vaccine; FDA, Food and Drug Administration; CDC, Centers for Disease Control and Prevention; DTPH, diphtheria-tetanus-whole-cell pertussis-*Haemophilus influenzae* type b vaccine; SIDS, sudden infant death syndrome.

Development of acellular pertussis vaccines resulted from concerns about the safety of less purified whole-cell pertussis vaccines.<sup>1</sup> These concerns led to popular antivaccination movements in several countries abroad, with decreased acceptance of the whole-cell vaccine, decreased pertussis vaccine coverage in these populations, and consequently increased rates of pertussis.<sup>2</sup> A 1991 report prepared under the auspices of the Institute of Medicine (IOM) found that the evidence was consistent with a causal relationship between diphtheria-tetanus-whole-cell pertussis vaccine (DTP) immunization and acute encephalopathy, and based on postlicensure studies, estimated the range in excess risk of acute encephalopathy after DTP to be 0 to 10.5 per million immunizations.<sup>3,4</sup> A subsequent IOM report published in 1994 found that the balance of evidence was consistent with a causal relationship between DTP and the forms of chronic nervous system dysfunction described in the National Childhood Encephalopathy Study in those children who experience a serious acute neurologic illness within 7 days after receiving DTP vaccine.<sup>5,6</sup> (Acute and chronic encephalopathy are not the primary focus of our study, but rather provide examples of rare, serious adverse event concerns arising postlicensure.)

In clinical trials, acellular pertussis vaccines have

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been clearly shown to be less reactogenic than whole-cell vaccines with regard to common, relatively benign adverse effects such as fever, injection site reactions, and fussiness.<sup>7-9</sup> Because clinical trials of acellular pertussis vaccines generally have included no more than ~20 000 participants per study arm, ability to detect very rare adverse events is severely limited. During the postlicensure period, when millions of doses of vaccine are administered, there is a possibility that rare adverse events after immunization may be detected.

The Vaccine Adverse Event Reporting System (VAERS) is a national passive surveillance system; as such, it is subject to certain limitations.<sup>10,11</sup> Adverse events reported to VAERS follow vaccination but may not be causally related to the vaccine. Conversely, underreporting of adverse events related to vaccination also can occur.<sup>12,13</sup> Despite these limitations (and others, detailed below), VAERS can be useful for detecting previously unrecognized adverse events after immunization, such as alopecia<sup>14</sup>; for gaining new and clinically useful insights into recognized adverse events, such as thrombocytopenia<sup>15</sup> and syncope<sup>16</sup>; and for assessing the safety of newly licensed vaccines.<sup>17-19</sup> VAERS data also provided an important early safety signal concerning intussusception among recipients of the recently licensed and now withdrawn rotavirus vaccine.<sup>20</sup>

DTaP was initially licensed in the United States in 1991 for use as the fourth and fifth dose in the pertussis vaccination schedule for children from 15 months of age to the seventh birthday.<sup>21</sup> Review of postlicensure safety data after 5 million doses of DTap had been distributed showed reporting rates to VAERS for all adverse events, seizures, and hospitalizations for DTap that were approximately one third of those for whole-cell pertussis-containing vaccines.<sup>17</sup> DTap was licensed for use in infants in the United States in 1996,<sup>22</sup> and our study now reviews the safety experience of the first 2 years from VAERS.

## METHODS

VAERS, described in detail elsewhere,<sup>10,11</sup> was established in 1990. The VAERS reporting form requests demographic information, information on the vaccination(s) administered, as well as a description of the adverse event, treatment, and severity. The reporting form is reprinted in the American Academy of Pediatrics' *Red Book*<sup>23</sup> and at the back of the *Physicians Desk Reference*<sup>24</sup>; in addition the form may be obtained by telephoning 1-800-822-7967. The US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) administer VAERS with the aid of a contractor. The National Childhood Vaccine Injury Act mandates reporting to VAERS of specific adverse events occurring within specified time intervals after listed vaccines.<sup>10</sup> Reporters to VAERS include physicians, nurses, pharmacists, parents, vaccinees, and others.

On July 31, 1996, the first acellular pertussis vaccine (Tripedia, Aventis Pasteur, Swiftwater, PA) was approved by FDA for use in infants. The second such vaccine was approved on Dec 30, 1996 (Acel-Imune, Lederle, Pearl River, NY); the third on Jan 29, 1997 (Infanrix, SmithKline Beecham Pharmaceuticals, Philadelphia, PA); and the fourth on July 29, 1998 (Certiva, North American Vaccine, Columbia, MD). The data reported herein, however, do not reflect the adverse event experience of Certiva because of its relatively recent approval.

Reports to VAERS represent temporal (but not necessarily causal) relationships between vaccinations and adverse events.

The analyses presented in this report are restricted to infants <1 year of age at the time of vaccination. To make this age determination for an individual report, either the infant's age or dates of both birth and vaccination had to be reported. Foreign reports were excluded. Some of the analyses were stratified according to seriousness: reports of death, reports of nonfatal serious events, and reports of less serious events. Nonfatal serious event reports, as defined in the Code of Federal Regulations (21CFR600.80), involved initial hospitalization, prolongation of hospitalization, life-threatening illness, or permanent disability; this information is available from check-off boxes on the VAERS form. Analyses of specific adverse events utilized computerized coding terms associated with each report that represent the signs, symptoms, and diagnoses mentioned by the reporter. When multiple VAERS reports were detected for the same event, only the first report and information available from follow-up of that report were used in our analyses.

Time trends (using date of vaccination) in number of VAERS reports according to severity of adverse event and type of pertussis vaccine are presented rather than adverse event reporting rates (defined as the number of adverse events reported divided by the number of doses administered) for the following reasons. First, vaccination coverage rates for all pertussis-containing vaccines as a group were stable during the relatively brief period (January 1995 through June 1998) of the time trends analysis.<sup>25,26</sup> It is also worth noting that the annual numbers of US infant births and deaths during the study were relatively stable (see Table 1). Therefore, other factors being equal, it is acceptable to compare the numbers of reports for all pertussis-containing vaccines as a group in the period before the licensure of acellular pertussis vaccines with the corresponding numbers in later time periods, when acellular pertussis vaccines were increasingly utilized and became the most widely used type of pertussis vaccine. Second, using manufacturers' reports of the number of vaccine doses distributed to estimate the number of doses administered during a period when manufacture of whole-cell pertussis vaccines was being curtailed and manufacture of acellular pertussis vaccines was being increased in anticipation of rising demand could lead to overestimation of the whole-cell pertussis adverse event reporting rates and underestimation of the rates for acellular pertussis vaccines. For example, CDC Biologics Surveillance data show that the net number of doses of DTap sold or distributed increased from 4.9 million in 1995 (when DTap was recommended only for the fourth and fifth doses) to 14.8 million in 1997 (the first full year that DTap was licensed for use in infants). The corresponding annual totals for DTP are 5.2 million and .5 million, and for diphtheria-tetanus-whole-cell pertussis *Haemophilus influenzae* type b vaccine (DTaP), 12.7 million and 5.5 million. Moreover, the proportions of these dose totals that were administered to infants are not known.

The 1991 report of the Committee to Review the Adverse Consequences of [whole-cell] Pertussis and Rubella Vaccines under the auspices of the IOM evaluated possible associations between selected adverse events and DTP vaccination.<sup>3</sup> Using the computerized adverse event coding terms in the VAERS database as of September 15, 1998, we counted the number of reports after DTap immunization in infants <1 year of age that cited adverse events selected by the IOM for review for a possible association with DTP. Selected reports were individually reviewed to verify that the reported diagnoses were correctly reflected in the computerized coding terms, and to determine whether possible explanations other than vaccination for the adverse event were noted in the report. Several adverse events considered by the IOM committee in their report are not considered here; learning disabilities, attention-deficit disorder, and autism are detected and diagnosed after infancy, beyond the chronological scope of this study. A separate report describes in greater detail events consistent with hypotonic-hyporesponsive episode.

**TABLE 1.** Annual Numbers of Births and Deaths in Infants Less Than One Year of Age: United States, 1995-1998\*

	1995	1996	1997	1998
Live births	3 899 589	3 891 494	3 880 894	3 941 553
Infant deaths	29 505	28 419	27 968	28 486†

\* Data from National Center for Health Statistics' National Vital Statistics Reports.

† Preliminary data.

**TABLE 2.** Reports to VAERS, by Year and Level of Seriousness, for Pertussis-Containing Vaccines Administered to Infants Ages Younger Than One Year of Age in the United States\*

Year	Level of Seriousness and Vaccine											
	Less Serious				Serious				Death			
	DTaP	DTP	DTPH	Total	DTaP	DTP	DTPH	Total	DTaP	DTP	DTPH	Total
1995	7	818	827	1652	2	185	147	334	0	35	50	85
1996	39	453	1009	1501	17	122	172	311	4	27	51	82
1997	344	186	474	1004	99	57	77	233	32	17	28	77
1998†	269	25	63	357	63	12	18	93	37	2	2	41

\* Reports to VAERS represent temporal, but not necessarily causal, associations between vaccinations and adverse events.

† Data from first half of 1998 only.

## RESULTS

A total of 5770 domestic reports filed with VAERS as of November 30, 1998 mentioned pertussis vaccination in infants during the period from January 1, 1995 through June 30, 1998. Of these reports, 285 involved death, 971 involved nonfatal serious reports, and 4514 involved less serious reports. For 1995 there were 2071 reports; in 1996, 1894 reports; in 1997, 1314 reports; and in the first half of 1998, 491 reports. DTP vaccine was cited in 1939 reports, DTPH in 2918 reports, and DTaP vaccine in 913 reports. Nearly all the reports described below involved administration of other vaccines along with acellular pertussis vaccine; the proportion of VAERS reports mentioning administration of a pertussis-containing vaccine alone was only 6.6% for DTaP (60/913), 2.9% for DTP (57/1939), and 8.2% for DTPH (238/2918).

Trends in reports of less serious events, serious events, and death after immunization with pertussis-containing vaccines reported to VAERS since 1995 are shown in Table 2. During the transition from nearly exclusive use of whole-cell pertussis vaccine in 1995 to predominant use of acellular pertussis vaccine in infants in 1998, the annual number of less serious reports to VAERS for pertussis-containing vaccines declined sharply from 1652 in 1995 to 357 in the first half of 1998. A similar, but somewhat less pronounced, decrease was observed for nonfatal serious reports, from 334 in 1995 to 93 in the first half of 1998. Such a clear-cut trend was not observed for deaths.

Adverse event profiles are a preliminary screening tool for detecting potential differences among vaccines in the types of adverse events reported. A comparison of the adverse event profiles (proportional distributions) for DTaP, DTP, and DTPH is shown in Table 3. Fever was the most commonly reported event for both DTP and DTPH (43.9% and 38.8%, respectively, of the infant reports for each of the vaccines); for DTaP, however, fever was the second most commonly reported event (25.0%), with agitation the most common (25.7%). "Agitation," "screaming syndrome," and "abnormal cry" are coding terms that correspond to crying of different character and duration, with "abnormal cry" representing unusual or high pitched crying, "screaming syndrome" representing crying  $\geq 3$  hours, and "agitation" constituting a nonspecific term used when crying, fussiness, agitation, or crankiness of  $< 3$  hours

(or unknown) duration is reported. The coding term in Table 3 for which the percentage reported for DTaP most exceeded, proportionally, that for DTP and DTPH was urticaria: the percentages of reports in infants for the individual vaccines were 7.7%, 2.9%, and 3.2%, respectively; for DTaP, the number of urticaria reports was nearly equal for the first, second, and third doses. For the other coding terms, with the exception of crying-related coding terms, the percentages did not differ substantially among the vaccines. In addition to the commonly reported coding terms shown in Table 3, we also listed (not shown) every other adverse event coding term reported after DTaP immunization and compared the frequency of each term with the frequency for DTP and DTPH. This analysis did not detect any adverse event term that showed a substantial and clinically meaningful higher frequency for DTaP than DTP or DTPH.

Reports in the VAERS database for DTaP as of September 15, 1998 were further reviewed for selected adverse events that had been evaluated for a possible association with whole-cell pertussis vaccination in the 1991 report of the IOM Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines.<sup>3</sup> There were no reports in VAERS of DTaP-vaccinated infants who developed any of the following conditions: Stevens-Johnson syndrome, toxic epidermal necrolysis, Guillain-Barré syndrome, hemolytic anemia, diabetes mellitus, and anaphylaxis. Of reports that mentioned urticaria (but not anaphylaxis), 2 reports also mentioned respiratory symptoms and might have represented mild anaphylaxis; however, neither hospitalization nor an emergency department visit was reported for either of these infants.

Thrombocytopenia was cited in 1 report. A 4-month-old infant was diagnosed with thrombocytopenic purpura, with a platelet count of 11 000 per cubic mm 1 week after his second set of vaccinations with DTaP, *Haemophilus influenzae* type b vaccine, and inactivated poliovirus vaccine; the infant subsequently recovered. Three reports were coded for neuritis or neuropathy; however, on review 2 of these reports were noted to involve infantile spasms or hypsarrhythmia. The other report involved brachial neuritis.

Encephalitis or encephalopathy was cited in 8 reports. One report on further follow-up was found not to involve encephalitis, and possible nonvaccine

**TABLE 3.** Coding Terms for Adverse Events Reported to VAERS for Pertussis-Containing Vaccines Administered to Infants Younger Than One Year of Age in the United States, January 1995 Through June 1998\*

Coding Term	DTaP (%) n = 913	DTP (%) n = 1939	DTPH (%) n = 2918
Agitation	235 (25.7)	608 (31.4)	890 (30.5)
Fever	228 (25.0)	851 (43.9)	1132 (38.8)
Screaming syndrome	129 (14.1)	506 (26.1)	678 (23.2)
Convulsion	96 (10.5)	203 (10.5)	254 (8.7)
Abnormal cry	89 (9.7)	386 (19.9)	588 (20.2)
Stupor	80 (8.8)	174 (9.0)	243 (8.3)
Somnolence	77 (8.4)	146 (7.5)	215 (7.4)
Vomit	73 (8.0)	126 (6.5)	179 (6.1)
Rash	72 (7.9)	93 (4.8)	145 (5.0)
Urticaria	70 (7.7)	56 (2.9)	92 (3.2)
Hypotonia	69 (7.6)	163 (8.4)	214 (7.3)

\* More than 1 term may be coded for each adverse event report. Percentages represent the proportion of adverse event reports that named the specific coding term, not the percentage of vaccinees who had a specific adverse event. Reports to VAERS represent temporal, but not necessarily causal, associations between vaccinations and adverse events.

causes were prominent in several other reports: infant botulism; severe pneumonitis with mucus plugging; sudden infant death syndrome (SIDS) in a child with macrocephaly; severe hydrocephalus with Arnold-Chiari deformity; and hypsarrhythmia. One report involved an infant who had disease onset 4 days after vaccination and was treated for herpes encephalitis. Another report cited an infant 5 months old with a history of birth at 35 weeks' gestation and a previous hospitalization for respiratory syncytial virus bronchiolitis and bacteremia at or before 1 month old, who presented 9 days after vaccination with a fever of 103°F and status epilepticus; the electroencephalogram was consistent with encephalitis, but no further positive information or follow-up was provided.

Meningitis was cited in 11 reports. Seven involved diagnoses of viral or aseptic meningitis or meningitis of unknown cause, and 1 report noted that meningitis was being considered as a diagnosis (rule-out). The intervals from vaccination to meningitis for these reports ranged from 1 to 61 days; only 2 reports noted intervals of 3 days or less (they were both 1 day). One report involved a death with meningitis on the day of vaccination; cause of death was "complications of meningitis," and pathologic diagnoses included lymphocytic meningitis, basilar artery thrombosis, basilar subarachnoid hemorrhage, intraventricular hemorrhage, subdural hemorrhage, and cerebral edema. No infectious cause was reported, but fever, vomiting, and diarrhea occurred 3 days before death and resulted in presentation to hospital at that time. Two reports involved pneumococcal meningitis.

There were 82 evaluable reports citing convulsions. Several of these reports have already been discussed because they involved meningitis (2 reports) or encephalopathy or encephalitis (4 reports). After exclusion of convulsions 1 week or more after vaccination, febrile seizures, convulsions with reported likely nonvaccine cause, and possible (or rule-out) convulsions, 34 reports remained for analysis.

The infants' median age was 3 months, and 79% were male. Of the 33 infants with known interval from vaccination to seizure, 11 (33%) had seizures the same day as vaccination, and 20 (61%) had seizure 1 to 3 days after vaccination. Twenty of the 34 were hospitalized, with a median hospital stay of 3 days. Of the 34 with convulsions, 27 were reported to have recovered, for 7 the recovery status was unknown, and none were reported to have not recovered; none of the 34 were reported to have developed a seizure disorder or epilepsy. The number of febrile seizures reported for any pertussis-containing vaccine was 39 in 1995, 30 in 1996, 21 in 1997, and 20 for the first half of 1998. The proportion of infant DTaP reports citing convulsions was 10.2%; for DTP and DTPH the corresponding proportions were 10.4% and 8.7% (Table 3). Prolonged crying of  $\geq 3$  hours (coded as "screaming syndrome," see Table 3) was reported for 13.8% of infant DTaP reports; the corresponding proportions for DTP and DTPH were 25.8% and 23.1%, respectively. Erythema multiforme was noted in 9 adverse event reports—none serious.

## DISCUSSION

Concerns about the safety of whole-cell pertussis vaccine throughout the 1970s and 1980s<sup>1</sup> led to the development and licensure of acellular pertussis vaccines, initially for older children<sup>21</sup> and more recently for infants.<sup>22</sup> Inherent limitations in sample size of prelicensure trials highlight the importance of postlicensure surveillance systems such as VAERS, especially once millions of doses of vaccine have been administered.<sup>10,11</sup> Our assessment of the first 2 years of experience with acellular pertussis vaccines in infants in the United States extends earlier postlicensure data in older children.<sup>17</sup> Both studies are reassuring with regard to the safety of marketed acellular pertussis vaccines.

Data from both VAERS and CDC Biologics Surveillance suggest that from July 31, 1996, the date of licensure of the first acellular pertussis vaccine for infants through the end of our study, June 30, 1998, acellular pertussis vaccines replaced whole-cell pertussis vaccines as the predominant vaccines against pertussis. The decreases in the number of serious and less serious VAERS reports after acellular pertussis immunization in infants (Table 2) are, therefore, interesting. The following analysis suggests that the decrease in VAERS reports is not an artifact of reporting lag. The VAERS dataset used for our study includes reports citing vaccinations on or before June 30, 1998 that were entered into the VAERS database by November 30, 1998. For the period of January 1, 1995 to June 30, 1995, 89.4% of reports were entered into the VAERS database by November 30, 1995, and similar proportions were observed for the other study years. Therefore, we believe it likely that VAERS reporting is nearly complete for our study.

The decrease in the number of less serious reports after vaccination with pertussis-containing vaccines, while utilization of DTaP was increasing, is consistent with findings from clinical trials showing that acellular pertussis vaccines are associated with lower rates than whole-cell vaccines of such common ad-

verse events as high fever, prolonged crying, and injection site reactions.<sup>7-9</sup> Whether the greater safety of acellular pertussis vaccines also explains the decrease in the number of serious reports is less obvious. The IOM found that: 1) the evidence was consistent with a causal relation between DTP vaccine and acute encephalopathy, chronic encephalopathy (as a sequela of acute encephalopathy), and hypotonic-hyporesponsive episode; and 2) the evidence indicated a causal relation for anaphylaxis and protracted inconsolable crying.<sup>5</sup> However, decreasing numbers of these specific events reviewed by the IOM do not explain the bulk of the decreases in the numbers of serious reports, because the proportions of specific serious events reported for acellular and whole-cell pertussis vaccines were broadly similar (data not shown). The FDA definition of "serious" includes events considered by the reporter to be life-threatening, to involve permanent disability, or to require hospitalization or prolongation of hospitalization.<sup>24</sup> It is possible that the reputation of acellular pertussis vaccines for enhanced safety compared with whole-cell vaccines could result in reporting bias by affecting perceptions of health care providers and by affecting reports as to whether a particular event was life-threatening or merited hospitalization. Similarly, it is possible that in some cases, coincidental illnesses occurring in temporal association with vaccination might be more likely to be reported for whole-cell than for acellular pertussis vaccines, or that the constitutional symptoms associated with whole-cell vaccines might, in the setting of a concomitant illness, cause that illness to be considered more serious than it otherwise would. It is also possible that adverse events that in the setting of a clinical trial would be considered less serious (such as fever with prolonged crying) might in a nonclinical trial setting result in hospitalization. Because these adverse events are more common for the whole-cell than for the acellular vaccine, serious reports to VAERS would be more likely for the whole-cell vaccine.

Recommendations for routine infant immunization result in simultaneous administration of vaccines against diphtheria, tetanus, pertussis; *Haemophilus influenzae* type b; polio; and hepatitis B. In our study, solo vaccination against pertussis was therefore rare. During the study period, there was one major change in the routine infant immunization schedule. In September 1996, two doses of inactivated polio vaccine, rather than live oral polio vaccine, were recommended for the first two polio immunizations usually given at 2 and 4 months of age.<sup>27</sup> As a result of these recommendations that took effect in the latter part of the study when acellular pertussis vaccines were increasingly used, the frequencies of the types of polio vaccine differed with respect to the type of pertussis vaccine that was simultaneously administered. VAERS reports citing acellular pertussis vaccine also cited inactivated polio vaccine in 46% of reports and oral polio vaccine in 31% (the rest did not mention polio vaccination), whereas the corresponding proportions for DTP were 5% and 80% and for DTPH, 5% and 82%. Based

on available data, the higher utilization of inactivated polio vaccine with acellular than with whole-cell pertussis vaccine cannot fully explain the decreasing trends in adverse event reports in Table 2. The reason is that oral polio vaccine has not been commonly associated with the fever, crying, and fussiness in the immediate postvaccination period that, along with injection site reactions (that oral vaccines do not cause), constitute the bulk of adverse reactions for whole-cell pertussis-containing vaccines. In addition, the serious adverse events that have been associated with oral polio vaccine, vaccine-associated paralytic poliomyelitis and Guillain-Barré syndrome, are far too rare to have affected the trends in serious reports that we observed.<sup>27,28</sup>

A previous study showed that SIDS represented the assigned cause of death for the majority of deaths reported to VAERS<sup>29</sup>; however, SIDS has been shown not to be associated with pertussis-containing vaccines.<sup>3</sup> In our study, the peak age of death in all years remained in the second and third month of life, consistent with the peak age for SIDS.<sup>30</sup> From 1995 to 1996 in the United States, the incidence of death (irrespective of vaccination) among infants 28 days of age or greater decreased 4.7%, and for SIDS the decrease was 10.6%<sup>31</sup>; for later years, published data are not yet available. Our study found a modest decrease in the annual number of deaths through 1997, with the totals for 1998 incomplete. Differences between the trends in deaths we observed and the US rates may reflect reporting variation, random variation (because the number of deaths in our study was, statistically speaking, small), or other factors. Continued monitoring of death trends is indicated.

The broadly similar proportional distributions of adverse event coding terms for acellular and whole-cell pertussis vaccine (Table 3) should be interpreted in the context of the decreasing numbers of adverse event reports for all pertussis-containing vaccines taken together during a time of increasing utilization of acellular pertussis vaccines. Thus, lower reporting rates (defined as the number of adverse events reported divided by the number of doses administered) for acellular pertussis vaccines than for whole-cell vaccines can be inferred. In addition, it should be recalled that the lower proportions of fever and crying-related coding terms for acellular compared with whole-cell vaccine will, in a proportional distribution, be compensated by higher proportions of other events. When examining proportional distributions for the purpose of evaluating the safety of acellular pertussis vaccines, it is particularly important to determine whether any specific adverse events appear at substantially higher proportions for acellular than for whole-cell vaccines; this was not observed. Urticaria was noted in 7.7% of the acellular pertussis vaccine reports compared with only ~3% for whole-cell vaccine; however, urticaria after acellular pertussis vaccination was not associated with life-threatening anaphylactic reactions or recurrence with readministration of vaccine. A recent study of anaphylaxis after exposure to gelatin-containing measles, mumps, and rubella vaccines in Japanese children suggested that they were previously sensitized

to gelatin contained in some acellular pertussis vaccines, highlighting the importance of closely monitoring this issue.<sup>32</sup>

Several of the adverse events reviewed by IOM for a possible association with whole-cell diphtheria-tetanus-pertussis vaccine were absent for diphtheria-tetanus-acellular pertussis vaccines in our study.<sup>3</sup> Regarding other adverse events, brachial neuritis was reported in 1 case, but that illness has already been associated with the tetanus component of the vaccine.<sup>3</sup> Another report mentioned infantile spasms, but that condition was found by the IOM not to be associated with diphtheria-tetanus-pertussis immunization. With respect to convulsions, the fact that the proportions of reports for DTaP, DTP, and DTPH were approximately similar while reporting rates for DTaP are nearly certainly lower reassures us as to the safety of DTaP, although reporting bias (as described above) may play a role in these findings. Although the lower pyrogenicity of acellular compared with whole-cell pertussis vaccines suggests that febrile seizures (particularly for third doses administered at 6 months to 1 year of age, when febrile seizures are more likely to occur) might be less frequent after acellular pertussis vaccines, our data do not permit us to make inferences on this issue. Concerning the handful of other conditions for which there were reports, the small numbers, the lack of consistent clinical descriptions, and the frequent occurrence of plausible nonvaccine explanations provide reassurance; such a picture is often seen in temporal, but not demonstrably causal, vaccine adverse event associations reported in VAERS.

Because VAERS is a passive surveillance system, there are important caveats for making inferences from its data.<sup>11</sup> Reports to VAERS represent temporal, but not necessarily causal, relationships between vaccination and adverse events. Conversely, underreporting is also a potential problem.<sup>12,13</sup> In addition, VAERS has somewhat limited ability to detect adverse events with long latency after vaccination or those that have not been previously recognized to be associated with vaccination<sup>33</sup>; a necessary prerequisite for making a report to VAERS is that someone links (at least temporally, if not causally) vaccination with an adverse event. Most of these drawbacks of VAERS are largely absent in another database, the Vaccine Safety Datalink,<sup>34</sup> which uses prospectively collected patient care data from 4 health maintenance organizations on the west coast of the United States. Ongoing studies in the Vaccine Safety Datalink will further assess the safety of DTaP in a rigorous fashion in infants. Because of their smaller size and narrower geographic focus, however, the Vaccine Safety Datalink and similar databases may have less ability than VAERS to detect very rare or geographically localized adverse events.

### CONCLUSION

This study summarizes the first 2 years of safety experience of immunization with acellular pertussis vaccines in US infants. VAERS data support the prelicensure data with regard to the safety of the US-licensed acellular pertussis vaccines that we evalu-

ated. Phase IV (postapproval) studies undertaken by the manufacturers of 3 of the 4 licensed acellular pertussis vaccines are underway. Continued post-marketing adverse event monitoring in these and other studies<sup>34</sup> should provide additional useful safety data.

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