参考文献

ORIGINAL CONTRIBUTION

Postlicensure Safety Surveillance for 7-Valent Pneumococcal Conjugate Vaccine

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Context Clinical trials evaluate a vaccine's safety before approval, but some risks may escape detection or adequate characterization until larger population exposures occur after licensure.

Objective To summarize reports of events occurring after vaccination with 7-valent pneumococcal conjugate vaccine (PCV), including those that may warrant further investigation to assess possible causation by PCV.

Design Descriptive epidemiology of reports submitted to the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance database.

Setting and Patients United States during first 2 years after licensure of PCV (February 2000 through February 2002). Reports studied were for children younger than 18 years and vaccinated with PCV.

Main Outcome Measures Numbers and proportional distributions of reports.

Results A total of 4154 reports of events following PCV were submitted to VAERS, for a rate of 13.2 reports per 100 000 doses distributed. Multiple vaccines were given in 74.3% of reports. The most frequently reported symptoms and signs included fever, injection site reactions, fussiness, rashes, and urticaria. Serious events were described in 14.6% of reports. There were 117 deaths, 23 reports of positive rechallenges, and 34 cases of invasive pneumococcal infections possibly representing vaccine failure. Immune-mediated events occurred in 31.3% of reports. All 14 patients with anaphylactic or anaphylactoid reactions survived. Thrombocytopenia developed in 14 patients and serum sickness in 6 others. Neurologic symptoms occurred in 38% of reports. Seizures described in 393 reports included 94 febrile seizures.

Conclusions The majority of reports to VAERS in the first 2 years after licensure of PCV described generally minor adverse events previously identified in clinical trials. The proportion of reports portraying serious events was similar to that for other vaccines. Although there are important limitations in passive surveillance data, and caution in their interpretation is necessary, symptoms experienced by a few children more than once after successive PCV doses, including allergic reactions, prolonged or abnormal crying, fussiness, dyspnea, and gastrointestinal distress, warrant continued surveillance, as do reports of rare but potentially serious events, such as seizures, anaphylactic or anaphylactoid reactions, serum sickness, and thrombocytopenia.

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THE FOOD AND DRUG ADMINISTRATION (FDA) licensed the 7-valent pneumococcal conjugate vaccine (PCV, trade name Prevnar, Wyeth Pharmaceuticals, Philadelphia, Pa) on February 17, 2000. The recommended vaccination series includes doses at ages 2, 4, 6, and 12 to 15 months, with catch-up doses through 9 years of age.[1] Pneumococcal conjugate vaccine has been rapidly adopted into routine pediatric practice, reflecting concern for the gravity of serious pneumococcal infections and confidence in the efficacy and safety of PCV.

Prior to licensure, almost 19 000 infants and children received PCV in randomized clinical trials that demonstrated good efficacy against invasive infections and a favorable safety profile. Common adverse events in the first days after vaccination included injection site reactions, fever, irritability, drowsiness, restless sleep, decreased appetite, vomiting, and diarrhea.[1] However, rare vaccine complications may not emerge before licensure for a variety of reasons, particularly the relatively limited sample sizes of trials.[2] In addition, the control group in the main study received another experimental vaccine, rather than a placebo.[3] If both vaccines provoked similar adverse effects, little or no difference between the 2 groups might have been evident. Therefore, postmarketing safety surveillance remains essential. This report summarizes data from the Vaccine Adverse Event Reporting System (VAERS) in the first 2 years after PCV licensure.

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METHODS

We studied case reports to VAERS of events occurring after PCV vaccinations through February 2002, allowing at least 3 months for potential follow-up of each case. We excluded 86 foreign reports and 19 reports detailing patients older than 17 years but applied no other criteria, such as minimum or maximum intervals after vaccination.

Jointly operated by the FDA and the Centers for Disease Control and Prevention (CDC) since 1990, VAERS accepts voluntarily submitted reports of events from manufacturers, health care workers, and patients.[4-6] (Manufacturer reporting to VAERS is required but mainly comprises transmission of information that had been voluntarily supplied by physicians, patients, or other primary reporters.) Although experiences reported to VAERS are generally voluntary, unsolicited, and reflect concern or suspicion of a possible relationship to 1 or more vaccine products, VAERS received a few reports for events detected through a systematic safety surveillance study in a health maintenance organization. Because of important limitations in passive surveillance, data from VAERS require cautious interpretation.[3] Reported events may be a small fraction of all that occur, and they frequently defy facile assessment of whether vaccinations played a causal role. Nonetheless, the potential to detect important clues from patterns among collected reports warrants careful surveillance.

We used information from the VAERS report form on the vaccinee (name, date of birth, age, sex, address); the event(s) (date of onset, therapy, and clinical course); and vaccine(s) administered (date, lot identifier, and dose sequence). The VAERS database indexes reported events with standardized coding terms[7] that trained nurses assign after reviewing each submitted report. The date of onset refers to the earliest symptom in each report. Although most reports received multiple codes, we obtained intervals from vaccination to onset of pertinent events for selected subsets during individual case reviews. We also queried free text fields from the report form and follow-up notes. For example, we sought potential anaphylaxis cases by looking for the anaphylaxis code as well as "anaphyl," "epineph," or "laryngismus."

To select subsets of reported cases for analysis, we weighed their frequencies and medical severity as indicators of potential population impact, as well as practical preventability and plausibility for relationship with vaccination.[8] Regulatory criteria were used to classify VAERS reports as serious and mainly involved death, life-threatening illness, hospitalization, or persistent disability.[5,9] Positive rechallenge reports, events that followed PCV and recurred after a subsequent dose, were analyzed in detail, as such reports suggest (but cannot confirm) causal association with vaccination. Neurologic and immune-mediated events were also highlighted. Because of the suggestion of more seizures in the PCV group than in the comparator group in the primary clinical trial,[2] we planned to study the first 100 seizure reports with supplementary follow-up to clarify previous medical history and subsequent clinical course. The final data set excluded 2 duplicates, leaving 98 cases for analysis. For injection site reactions, we reviewed reports in the first year after PCV licensure to identify the pertinent vaccine in cases with multiple immunizations. Many physicians understand that no vaccine is 100% effective and, therefore, do not consider vaccine failure to be an adverse event. However, we included reports of pneumococcal infections subsequent to administration of PCV as potential vaccine failures.

Unless otherwise specified, we excluded missing data when calculating proportions. Reporting rates are calculated by dividing numbers of reports by estimated PCV doses distributed, extrapolated from CDC biologics surveillance data.[10]

Table 1. Pneumococcal Conjugate Vaccine Reports by Age Group and Seriousness, United States, March 2000-February 2002

Age Group	Deaths, No.	Nonfatal Serious, No.*	Nonserious, No.	Total, No.	Age Group Percentage†
0-5 mo	80	211	780	1071	27.3
6-11 mo	19	98	659	776	19.8
1 y	15	135	1272	1422	36.2
2-4 y	3	28	521	552	14.1
5-9 y	0	9	85	94	2.4
10-17 y	0	0	11	11	0.3
Unknown	0	10	218	228	...
Total	117	491	3546	4154	...
Reporting rate‡	0.4	1.6	11.3	13.2	...

*By Food and Drug Administration regulations, serious reports describe deaths, life-threatening events, hospitalizations, persistent or significant disabilities, congenital anomalies, and other events of medical importance.[5]
†Percentages by age calculated on basis of reports with ages, excluding 228 without age information.
‡Reporting rates describe numbers of Vaccine Adverse Event Reporting System reports received per 100000 doses distributed.

RESULTS

Among 4154 reports of events after immunization with PCV, 608 (14.6%) described serious events, including 117 deaths (TABLE 1). The number of reports received increased over the first year after licensure and then declined. Infants younger than 6 months accounted for 27.3% of reports. Females accounted for slightly less than half of all cases (47.5%). Based on an estimated distribution of 31.5 million doses within the United States during the first 2 years after licensure of PCV, the overall reporting rate was 13.2 per 100000 vaccinations and 1.9 per 100000 for serious reports. Three fourths (74.3%) of reports described multiple vaccines administered together (TABLE 2). Reported symptoms began within 1 week after vaccination in 86.6% of cases. The most frequently reported symptoms and signs included fever, injection site reactions, fussiness, rashes, urticaria, and vasodilation.

Table 2. Events Reported After Pneumococcal Conjugate Vaccine (PCV), United States, March 2000-February 2002*

Event	No. of Cases			PCV Alone, %			Comments
	Serious	Nonserious	Total	Serious	Nonserious	Total	
All reports	608	3546	4154	14.8	27.6	25.7	
Fever	228	1225	1453	13.6	25.6	23.7	90% Included rash or other symptoms
Injection site reactions	30	1125	1155	23.3	32.1	31.9	54% Involved PCV site; 8 serious reports described abscess or cellulitis
Rash	42	754	796	21.4	23.1	23.0	12 Cases with petechiae; 10% of rash reports included urticaria
Vasodilation	61	496	557	13.1	24.6	23.3	420 Cutaneous (hot flashes, flushing, hyperemia, erythema, or warm feeling); 144 venous (pallor, syncope, or dizziness) cases
Neurologic	366	1209	1575	11.2	19.2	17.3	52.4% Had symptoms within 24 h
Neuroexcitation	109	672	781	9.2	19.6	18.2	Fussiness (599), twitch (87), tremor (74), insomnia (73), nervousness (59), hyperkinesia (5)
Convulsions	159	234	393	9.4	17.9	14.5	33% Had symptoms within 24 h: 24% febrile seizures, 130 others also had fever; 1 positive rechallenge for febrile seizure confounded by URI and otitis media 1 d after PCV dose 2, MMR, and VV, and pneumonia 2 d after PCV dose 3
Prolonged or abnormal crying	22	235	257	4.5	7.2	7.0	
Ataxia or gait disturbance	10	44	54	10.0	31.8	27.8	
HHE or hypotonia or hyporesponsiveness	24	25	49	12.5	20.0	16.3	Fever in 18.4%; emesis in 14.3%; 3 seizures; 3 others with ocular deviation; 1 botulism (by stool culture); 1 possible allergic reaction (laryngeal edema)
Meningitis	34	2	36	23.5	100.0	27.8	
Encephalopathy	4	0	4	50.0		50.0	1 Acute disseminated encephelomyelitis 12 h after vaccination; differential diagnosis included viral encephalitis, but multiple viral cultures negative, and patient recovered with steroids; 1 acute demyelinating cerebellar encephalitis 2 d after vaccination with subsequent recovery
Immunologic	121	1178	1299	19.0	31.3	30.2	33.7% of immunologic cases aged <1y vs 49.4% for other reports
Allergic reactions	93	1105	1198	18.3	31.5	30.5	
Urticaria	19	373	392	5.3	34.3	32.9	1 Positive rechallenge; 20% of urticaria cases describe rash
Pruritus	3	85	88	33.3	37.6	37.5	
Allergy, unspecified	21	67	88	9.5	26.9	22.7	
Facial edema	7	68	75	14.3	27.9	26.7	2 Patients with anaphylaxis; 35 others had symptoms during first day after vaccination but not anaphylaxis (intervals >4 h before first symptoms and/or lacked multiple body system manifestations)
Asthma	15	36	51	26.7	33.3	31.4	
Anaphylaxis or anaphylactoid	8	6	14	25.0	16.7	21.4	
Angioedema	0	13	13		61.5	61.5	1 Positive rechallenge
Other possibly immune-mediated	69	152	221	23.2	28.3	26.7	51% Also had definite or possible allergic reactions
Thrombocytopenia	9	5	14	11.1	0.0	7.1	
Erythema multiforme	3	36	39	33.3	22.2	23.1	No case of Stevens-Johnson syndrome or toxic epidermal necrolysis
Arthritis or arthralgias	4	22	26	0.0	45.5	38.5	

(continued)

Table 2. Events Reported After Pneumococcal Conjugate Vaccine (PCV), United States, March 2000-February 2002* (cont)

Event	No. of Cases			PCV Alone, %			Comments
	Serious	Nonserious	Total	Serious	Nonserious	Total	
Immunologic (cont)							
Other possibly immune-mediated (cont)							
Vasculitis	6	9	15	33.3	55.6	46.7	Diagnoses or suspicions but none with biopsy evidence; 10 of 11 cases with dose data followed first PCV; 6 final diagnoses of HSP and 4 "rule out" diagnoses; most intervals to first symptoms in first week
Serum sickness	2	4	6	50.0	100.0	83.3	Ages 4 mo-4 y; 3 cases after first PCV doses and without other vaccines; symptoms within 1 d after vaccination in 3 patients; 1 confounded by antibiotic before symptoms began
Diabetes mellitus (DM), type 1	6	0	6	66.7		66.7	5 Males, 1 female; 2 family histories of DM (juvenile or adult onset); 5 received only first PCV dose; ages 11-22 mo; symptoms followed PCV by 2-10 wk; 8 others had incidental, transient, and often mild hyperglycemia without evident clinical significance
Alopecia	0	2	2		0.0	0.0	1 Positive rechallenge
Gastrointestinal	121	410	531	13.2	29.3	33.2	49.2% of reports with dates described symptoms within 1 d after vaccination and 74.0% within 2 d
Diarrhea and/or vomiting	67	289	356	19.4	31.8	29.5	3 Positive rechallenges
Anorexia	43	124	167	7.0	23.4	19.2	
Dysphagia	5	10	15	0.0	10.0	6.7	
Hepatic disorders	7	1	8	28.6	0.0	25.0	
Intussusception	5	0	5	20.0		20.0	1 Fatality (after months of frequent diarrhea); no rotavirus or oral polio vaccine; symptoms within 2 d in 4 boys and after 2 wk in 1 girl
Infections	147	298	445	20.4	27.5	25.2	
URI and viral infections	51	165	216	21.6	24.8	24.1	
Cellulitis	15	62	77	20.0	30.6	28.6	
Bacterial infections	51	24	75	29.4	54.2	37.3	
Pulmonary	191	184	375	15.7	28.3	21.9	40.3% <6 mo old vs 24.3% in other reports
Respiratory distress	152	134	286	11.8	23.1	17.1	
Pneumonia, bronchiolitis	45	35	80	31.1	42.9	36.3	
Bronchoconstriction	18	37	55	27.8	32.4	30.9	Asthma, wheezing, or stridor; 3 positive rechallenges (a fourth positive rechallenge report described dyspnea)

Abbreviations: HHE, hypotonic hyporesponsive episode; HSP, Henoch-Schönlein purpura; MMR, measles, mumps, rubella; URI, upper respiratory tract infection; VV, varicella vaccine.

*Percentages indicate fractions of reports in each adverse event group that describe administration of PCV alone, without other vaccinations. Numbers reflect Vaccine Adverse Event Reporting System reports for PCV administered after licensure in February 2000 through February 2002. Serious cases include 117 deaths: Event categories are not mutually exclusive. Addition of row frequencies would fallaciously double-count numerous case reports that describe multiple symptoms, eg, a rash that accompanies fever and arthralgias. Febrile seizures contribute to both fever and seizures. Encephalopathy includes encephalitis and acute brain syndrome but omits 4 cases with disease prior to vaccination. Another 5 excluded reports have different or more specific diagnoses (1 each for Sydenham chorea, HHE, streptococcal sepsis, ataxia, and seizures). See text for additional information about case reports with seizures, ataxia or gait disturbance, anaphylaxis, thrombocytopenia, and gastrointestinal problems.

Table 2 provides a detailed account of reported events. Data are summarized below for reports of death, positive rechallenges, neurologic events, potentially immune-mediated events, and reports of pneumococcal infection.

Deaths

Reports to VAERS described 117 deaths after vaccination with PCV (TABLE 3). A cause was identified in 37.6%. Median intervals from vaccination to death were 51 days in the 12 cases reported from the health maintenance organization active surveillance and 3 days for the other 105.

Three patients who died had seizures without evident etiologies. A 9-month-old female developed status epi-

lepticus 2 days after her second dose of PCV, given with hepatitis B vaccine and a tuberculin skin test. She had a recent diagnosis of "gross motor delay"; no autopsy was performed. A pair of fraternal twins had seizure disorders that began after immunizations. One died at 12 months of age with no cause identified at autopsy. Her sister died 4 months later; postmortem histology indicated she had bronchopneumonia, and the pathologist attributed death to a seizure disorder.

Three deaths involved incidental liver pathology. One patient had liver enzyme elevations with septic shock and meningitis due to *Streptococcus pneumoniae* (serotype 14). The conclusion after postmortem examination of the second patient was probable sudden infant death syndrome (SIDS) with mild nonspecific hepatic and pulmonary congestion. The autopsy for the third also disclosed hepatic congestion, but the cause of death remained unexplained.

Autopsies on 2 patients identified acute encephalopathy after multiple immunizations. A previously healthy 10-week-old female died 11 days after vaccinations. Her postmortem examination disclosed anoxic encephalopathy, "resuscitated SIDS," and multisystem ischemia. A 12-month-old male with a history of premature birth had vomiting, diarrhea, and fever 1 day before multiple vaccinations and then died with acute cerebral edema less than 1 day afterward.

A patient with frequent diarrheal episodes over the previous few months was waiting for surgery when he died 3 days after multiple vaccinations. A barium enema had disclosed intussusception.

Table 3. Fatalities Reported After Pneumococcal Conjugate Vaccine (PCV), United States, March 2000-February 2002

	No. of Cases (%)	Comments
Vaccinations	117 (100.0)	
PCV with other vaccines	105 (89.7)	
PCV alone	12 (10.3)	
Sex		
Male	69 (59.0)	
Female	48 (41.0)	
Age, mo		
<6	80 (68.4)	
6-11	19 (16.2)	
12-23	15 (12.8)	
>23	3 (2.6)	
Surveillance mode		
Passive	105 (89.7)	Spontaneous case reports to VAERS; median interval from vaccination to death, 3 d (range, 0-315 d)
Active (postlicensure study)	12 (10.3)	Prospective HMO-based monitoring; median interval from vaccination to death, 51 d (range, 12-157 d)
No cause identified	73 (62.4)	
After autopsy	68 (58.1)	
Without autopsy	5 (4.3)	
Classifications		
SIDS	51 (43.6)	Includes 3 deaths at age >12 mo
Possible SIDS	8 (6.8)	Without clear distinction from suffocation, eg, when infant had been sleeping with parent
Unknown cause	14 (12.0)	No cause identified but not designated SIDS
Cause identified	44 (37.6)	
Antenatal or perinatal conditions	13 (11.1)	Congenital anomalies, congenital cytomegalovirus infection, or bronchopulmonary dysplasia
Infections	22 (18.8)	Pneumococcal infections in 7 cases
Pneumonia or bronchitis	11 (9.4)	
Meningitis	7 (6.0)	
Other infections	4 (3.4)	
Seizures	8 (6.8)	
Congenital or perinatal disorders	2 (1.7)	
Meningitis	3 (2.6)	
Pathophysiology unclear	3 (2.6)	See text
Hepatic pathology	3 (2.6)	See text
Acute encephalopathy	2 (1.7)	See text
Thymoma	1 (0.9)	
Myocarditis	1 (0.9)	
Probable asphyxia	1 (0.9)	
Intussusception	1 (0.9)	See text

Abbreviations: HMO, health maintenance organization; SIDS, sudden infant death syndrome; VAERS, Vaccine Adverse Event Reporting System.

Positive Rechallenges

In 23 reports, patients experienced the same event after PCV (often with additional vaccines) more than once. These positive rechallenges involved fever, irritability, or other nonspecific symptoms (7 cases); respiratory symptoms (4 cases); prolonged or abnormal crying (4 cases); gastrointestinal (GI) disturbance (3 cases); possible allergic reactions (2 cases); seizures (2 cases); and hair loss (1 case).

Neurologic Events

Of all PCV reports, 37.9% included at least 1 potential neurologic symptom or diagnosis. Among the first 98 patients with reported seizures, supplementary follow-up disclosed that 79 (80.6%) had a prior history of seizure or a fever at the time of the seizure; the other 19 (19.4%) had no fever reported with the seizure and did not appear to have a medical history that might account for the seizure. By 2 months after the initial postvaccinal sei-

zure, 12 of the 19 patients had no further seizures and were not receiving anticonvulsant therapy. Two others experienced at least 1 additional seizure associated with high fever or epilepsy diagnosed after vaccination but were not treated with anticonvulsants. The remaining 5 patients did receive anticonvulsant medications. Three of these 5 continued receiving therapy, 2 for epilepsy and 1 for atypical Aicardi syndrome (a congenital neurologic seizure disorder); the other 2 children discontinued anticonvulsants 1 month and 5 months after their initial seizures and remained free of seizure activity.

The 54 patients with ataxia (11 cases), abnormal gait (39 cases), or both (4 cases) developed symptoms from hours to weeks after vaccination, except for 1 patient who developed ataxia more than 2 months after receiving PCV and varicella vaccine. In 19 cases, patients had received live virus vaccines for varicella (12 cases) and/or measles, mumps, and rubella vaccine (15 cases). One patient who received only PCV and hepatitis B vaccine began to vomit repeatedly and manifested truncal ataxia (inability to stand despite having begun to walk 2 weeks earlier) and nystagmus about 13 hours after vaccination, interpreted as acute cerebellar ataxia. Three reports described ataxia, and 12 described gait disturbance after PCV alone. One patient's ataxia began before his vaccination. The second developed ataxia and slurred speech 3 weeks after vaccination and was later diagnosed as having Sydenham chorea. The third had persistent otitis media, already treated with 2 antibiotics before vaccination, when his physician added cefpodoxime (possible adverse effects include dizziness, vertigo, shakiness), followed 6 to 12 hours later by onset of ataxia.

Table 4. Pneumococcal Meningitis in 23 Reports*

	Pneumococcal Conjugate Vaccine, No. of Doses			
	1	2	3	4
Total No. of cases	10	8	4	1
No. of cases with vaccine serotypes identified	3	4	2	1
Range of intervals after last dose	4 d-2 mo (in 8 reports with dates)	8 d-6 mo (in 5 reports with dates)	2 d-1 y	5 mo

*Nine of 23 reported cases of pneumococcal meningitis identified serotypes 6B, 9V, 14 (2 reports), 18C, 19F (2 reports), and 23F (2 reports); 1 report described a specimen that was "positive for 1 of the 7 serotypes contained in the vaccine" without further specification. The other 13 reports did not provide any serotype identification.

Immune-Mediated Events

Almost one third of reports (31.3%) describe allergic or other syndromes that might reflect abnormal immune responses. In particular, anaphylactic or anaphylactoid reactions were described in 14 reports; 12 of the 14 patients had received only initial doses of PCV, and the other 2 reports described no problem after previous doses. All 14 patients survived; at least 8 received epinephrine. Symptoms emerged 5 to 30 minutes after vaccination in 8 patients and after 1 to 4 hours in the other 6. Three patients received PCV alone; 2 of them had symptoms within 5 to 10 minutes. One patient developed symptoms 150 minutes after receipt of PCV and diphtheria and tetanus toxoids and acellular pertussis vaccine. An allergist later learned that a second feeding with a particular infant formula preceded symptoms by 30 minutes. The baby had previously developed erythema and swelling of his lips after the first trial of that formula. With this history and consistent skin test results, the allergist concluded that casein in the formula had most likely been at fault.

Although 78 reports described possible thrombocytopenia (with descriptions of thrombocytopenia, petechiae, purpura, or ecchymosis), only 14 provided documentation of depressed platelet counts, with 2 mildly affected patients (50000-150000 platelets/mm^3) and 12 with severely depressed counts (<20000/mm^3). None died. One of the 14 patients developed immune thrombocytopenic purpura and aplastic anemia 1 week after her first dose of PCV, given alone. The other 13 patients developed symptoms 1 to 35 days after multiple immunizations. At least 8 patients had vaccines, medications, or viral or bacterial infections as potential causes, including 4 who had received measles, mumps, and rubella vaccine (28.6% vs 17.5% of other PCV reports). Among the other 64 reports with possible thrombocytopenia but platelet counts unspecified or higher than 150000/mm^3, 27 involved injection site bruising or other local reactions, and 25 involved petechiae elsewhere.

Antibiotics provided an alternative etiology for 1 patient with serum sickness, but a large fraction of these case reports (5/6) described no additional vaccine given with PCV.

Possible Vaccine Failures

Among 7 patients who died with pneumococcal infections, 6 had received only 1 or 2 PCV doses, and 2 had vaccine serotypes identified. A 9-month-old male died with serotype 14 pneumococcal meningitis 19 days after his first dose of PCV. A 13-month-old male died with serotype 19F pneumococcal meningitis 4 months after his third PCV dose. His history included premature birth, congenital bronchomalacia, a tracheostomy, duodenal atresia, and a tracheoesophageal fistula.

Invasive *S pneumoniae* infections developed in 34 patients with meningitis, pneumonia, or sepsis after 1 PCV dose (11 cases), 2 doses (11 cases), 3 doses (10 cases), or 4 doses (2 cases). Ten of 23 patients with pneumococcal meningitis had received only initial doses of PCV (TABLE 4). Of 21 reports with serotype data from any invasive pneumococcal infection, 19 identified vaccine serotypes (4, 6B, 9V, 14, 18C, 19F, 23F). Every vaccine serotype except type 4 appeared in at least 1 report; the most frequently occurring serotype was 19F (7 cases).

COMMENT

The great majority of reports in the first 2 years after PCV licensure described minor signs and symptoms previously recorded during clinical trials. The proportion of reports portraying serious events (14.6%) was similar to that for other vaccines (14.3%).[10] Still, rare reports of serious events, including seizures, anaphylactic or anaphylactoid reactions, serum sickness, and thrombocytopenia, might represent uncommon risks and warrant further assessment. Symptoms that recurred in children after repeated doses of PCV, including allergic reactions, prolonged or abnormal crying, fussiness, dyspnea, and GI distress, also warrant further study.

The interpretation of VAERS reports requires caution because many reported events may not be due to the vaccine. In addition to the fact that other vaccines were administered in two thirds of PCV reports, all of the events described in these 4154 reports (except for true vaccine failures) can occur independently of immunizations. Children frequently develop fever, vomiting, diarrhea, and rashes in the absence of any vaccination. Febrile seizures are not rare. Even anaphylaxis can have nonvaccine causes. With time after vaccination, intercurrent exposures to nonvaccine antigens (food or others) may occur, as illustrated by the patient with anaphylaxis whose positive rechallenge and skin test evidence implicated casein in formula as the offending antigen. Local reactions at vaccine injection sites are common and nearly always benign and transient. With both temporal and anatomic associations between injection site reactions and recent vaccination, we usually infer causation, as reflected in terminology ("reaction" rather than "report"), but even these events may stem from immunization technique, host experience (prior exposure to antigens, as in Arthus reactions), or other factors apart from a vaccine's intrinsic composition. Positive rechallenges seem less likely to arise by chance alone, but they do not absolutely confirm that a vaccine caused an adverse event, especially when the vaccination and event are both common.

Passive surveillance systems have important limitations, including underreporting.[11] Despite incomplete case ascertainment, however, the value of VAERS-based safety surveillance was demonstrated when a small number of initial intussusception reports for rotavirus vaccine led to epidemiologic studies that verified the hazard. Even after publicity stimulated additional reporting, VAERS received information on only an estimated 47% of cases that had actually occurred.[12] Underreporting of adverse events undoubtedly affects PCV as well. The increasing report numbers in the first year probably reflect growing utilization, along with the "Weber effect" of greater reporting enthusiasm or diligence for new products.[13] The subsequent decrease may relate in part to PCV shortages, which occurred between August 2001 and late 2002,[14] as well as waning of reporting enthusiasm and reporting delays.

Although limitations of VAERS preclude ascribing reported seizures to PCV, vaccination may have played a role in at least some cases. In the primary clinical trial before licensure, a few more patients had seizures within 3 days after PCV than after the meningococcal comparator vaccine (8 vs 4), raising concern about a possible association. However, all of these seizure patients had received at least diphtheria, tetanus, and whole cell or acellular pertussis vaccine concomitantly. We found that most of nearly 400 seizures reported to VAERS followed multiple vaccinations. One patient had a positive rechallenge, but his febrile seizures were associated with infections as well as vaccinations. Like other vaccines, PCV can provoke fever, which could trigger a febrile seizure. From prelicensure studies, up to 23.9% of PCV recipients developed fever of 38°C or higher in the first 2 days, and 0.9% to 2.5% had fever higher than 39°C.[2] However, about 1 in 5 patients with a seizure reported to VAERS did not have a history of fever or a previous seizure disorder. Most of these patients did not require subsequent anticonvulsant medication.

Similarly, some allergic reactions may be attributable to PCV. Reported allergic events included anaphylactic or anaphylactoid reactions within minutes to hours after PCV. Many other patients with urticaria, facial edema, angioedema, pruritus, or unspecified allergic reactions may have had immediate hypersensitivity reactions of lesser intensity. Some patients had symptoms only days after vaccination.

Pneumococcal conjugate vaccine may have contributed to some of the other reported immune-mediated adverse events. The 12 reports of thrombocytopenia with profoundly depressed platelet counts illustrate uncertainties in the interpretation of passive surveillance data. Thrombocytopenia is a recognized complication of measles-containing vaccines[15-17] and has been reported after varicella vaccine.[18] Although both products have live viruses, an immunologic mechanism might not require a live virus agent.[19] On the other hand, most patients had received multiple vaccines, their intervals from vaccination to onset varied, and several had infectious or drug exposures that might account for their thrombocytopenia.

Postvaccinal vasculitis has been described after other immunizations, including varicella vaccine,[18] and Henoch-Schönlein purpura is rare in young children.[20] However, we suggest caution in assessment of this diagnosis as a potential risk of PCV. Several rash illnesses are common in young children; many vasculitis reports to VAERS lack clinical details and laboratory evidence, and none had a biopsy. Most reports of Henoch-Schönlein purpura did not describe arthralgias or intestinal symptoms.

After extensive review of medical literature and clinical vaccine trials, Jefferson and Demicheli[21] found "no evidence of a link between IDDM [insulin dependent diabetes mellitus] and vaccination in humans." The Institute of Medicine recently concurred with this

assessment,[22] and 2 recent studies described no association between vaccines and diabetes mellitus.[23,24] The 6 reports of diabetes mellitus after PCV amount to very few cases when contrasted with the millions of vaccine doses administered. Their appearance after PCV seems more likely to be purely coincidental, with reporting stimulated by publicity about potential relationships to vaccination.[25]

We previously described alopecia reports to VAERS with 3 clear positive rechallenges for hepatitis B and 1 with influenza virus vaccine.[26] One of the 2 reports for PCV now provides a second positive rechallenge case for a vaccine other than hepatitis B. On both occasions, alopecia began 1 week after administration of PCV with 2 other bacterial vaccines. The sequence suggests that alopecia may be a nonspecific response to vaccinations or other immunologic stimulation, rather than necessarily having a specific relationship with hepatitis B.

The reported deaths cannot be attributed to PCV. Even among fatalities from pneumococcal infection in PCV recipients, only 1 patient had an infection with a pneumococcal serotype included in the vaccine after receiving more than 2 doses. We analyzed all reported deaths, but the 12 from active surveillance might differ from most VAERS cases in various ways. Most importantly, clinical concern about a possible relationship with vaccination probably motivates most voluntary reporters after they see an unexpected event in a recently immunized patient. We believe that the short median interval from vaccination until death for the spontaneously reported cases reflects this psychology, in clear contrast to the substantially longer median for the 12 actively ascertained cases. Silvers et al[27] reviewed fatality reporting to VAERS during a period prior to PCV licensure. Unexplained deaths predominated then as they do for PCV reports now. A report to VAERS is less likely for a death after evident illness or when an autopsy identifies pathology. In contrast, deaths that remain unexplained after investigation are more likely to engender concern over a possible relationship to recent vaccinations. Several systematic studies failed to find an association between SIDS and vaccinations.[28-32] The Institute of Medicine recently reviewed sudden unexpected infant deaths, finding that the weight of evidence does not support causal linkage between SIDS and multiple vaccinations routinely scheduled together.[33]

Most or all of the GI symptoms reported with PCV might not relate to vaccination, despite positive rechallenges, since diarrhea and vomiting are so prevalent during infancy. The tendency for reported symptoms to follow soon after vaccination (eg, nearly half of GI cases in the first day) may reflect selective reporting. Physicians and patients' families would be progressively less likely to wonder about a possible vaccine role as the postvaccination interval increases. The Weber effect and publicity about rotavirus vaccine and intussusception may have stimulated reporting to VAERS for the 5 intussusception cases with PCV, even though it is neither a live virus nor an orally administered vaccine. However, it is routinely given to infants, the age group in which intussusception typically occurs.

A report of neonatal hyperbilirubinemia after accidental gestational exposure to PCV is the only pregnancy exposure to come to light thus far. Neonatal hyperbilirubinemia is common, usually promptly recognized and treated, and has no known relationship to immunizations. Although PCV is not a live virus product and is not indicated for adults, additional case reports would contribute to clarifying any potential risk from gestational exposure. The Institute for Safe Medication Practices described 3 other adults who received PCV by mistake.[34] We found misclassification of the 2 pneumococcal vaccines, PCV and the polyvalent polysaccharide vaccine, in several cases. Inadvertent product substitutions could deprive an adult of protection from several serotypes included in polyvalent polysaccharide vaccine but not in PCV. Conversely, if a young child receives the adult product, rather than PCV, immunogenicity would be inadequate.

Although VAERS receives reports of suspected vaccine failures, no vaccine protects every recipient. The main clinical trial of PCV demonstrated efficacy of 100% after 3 or 4 doses for protection against pneumococcal infections with serotypes in PCV (with a lower 95% confidence estimate of 75.4%).[1] Efficacy calculated for prevention of any invasive pneumococcal infection (not just vaccine serotypes) among children who received 1 or more doses was 88.9% (with a lower 95% confidence limit of 63.8%).[1] If PCV has 90% protective efficacy against any invasive pneumococcal infection, roughly 150 children per million vaccinees younger than 3 years could be expected to contract these infections each year. Although few reports to VAERS for invasive pneumococcal infections had serotype information (21 cases over the 2 years after licensure of PCV), such reports are shared with a new CDC surveillance program (available at: http://www.cdc.gov/nip/diseases/pneumo/PCV-survrpts/default.htm) that seeks to systematically identify serotypes of isolates from normally sterile sites. By monitoring for infection shifts toward strains not in PCV, this program could guide serotype selections for future polyvalent pneumococcal vaccines.

In the first 2 years after PCV licensure, the great majority of VAERS reports portray minor adverse events already observed during clinical trials. Our focused follow-up of the first 98 seizure reports addressed a concern arising from the prelicensure trial. We found that the large majority of reported seizures were febrile or in patients with a previous history of seizures. Although allergic reactions, prolonged or abnormal crying, fussiness in infants, dyspnea, and GI distress are common childhood symptoms apart from immunizations, their occurrence with positive rechallenges after PCV increases the possibility of occasional causal relation-

ship with vaccination and, therefore, warrants continued surveillance for these events. The FDA and CDC will also continue to monitor VAERS for reports of rare but potentially serious events, such as seizures, anaphylactic or anaphylactoid reactions, serum sickness, and thrombocytopenia.

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Study concept and design: Wise, Iskander, Ball, Braun.
Acquisition of data: Wise, Pless, Campbell.
Analysis and interpretation of data: Wise, Iskander, Pratt, Ball, Campbell, Braun.
Drafting of the manuscript: Wise, Iskander, Ball.
Critical revision of the manuscript for important intellectual content: Wise, Iskander, Pratt, Pless, Ball, Campbell, Braun.
Administrative, technical, or material support: Wise, Iskander, Pless, Ball, Campbell, Braun.
Study supervision: Wise, Ball, Braun.
Technical expertise: Wise, Iskander, Pratt, Campbell, Ball, Pless, Braun.
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Other Resources: The following Internet sites provide additional information for people wishing to file a report to VAERS or to learn more about the VAERS program: http://www.vaers.org; http://www.fda.gov/cber/vaers/vaers.htm; http://www.cdc.gov/nip.

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