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Risk of Anaphylaxis After Vaccination of Children and Adolescents

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ABSTRACT. *Objective.* To quantify the risk of anaphylaxis after vaccination of children and adolescents.

Methods. The study population consisted of children and adolescents who were enrolled at 4 health maintenance organizations that participated in the Vaccine Safety Datalink Project. For the period 1991–1997, we identified potential cases by searching for occurrences of *International Classification of Diseases, Ninth Revision (ICD-9)* code 995.0 (anaphylactic shock), E948.0 through E948.9 (adverse reaction from bacterial vaccines), and E949.0 through E949.9 (adverse reaction from other vaccines and biological substances). At 1 study site, we also included a range of other allergy codes. We restricted to diagnoses on days 0 to 2 after vaccination (*ICD-9* 995.0) or day 0 (all other *ICD-9* codes). We then reviewed the medical record to confirm the diagnosis.

Results. We identified 5 cases of potentially vaccine-associated anaphylaxis after administration of 7 644 049 vaccine doses, for a risk of 0.65 cases/million doses (95% confidence interval: 0.21–1.53). None of the episodes resulted in death. Vaccines that were administered before the anaphylactic episodes were generally given in combination and included measles-mumps-rubella, hepatitis B, diphtheria-tetanus, diphtheria-tetanus-pertussis, *Haemophilus influenzae* type b, and oral polio vaccine. One case of anaphylaxis followed measles-mumps-rubella vaccine alone. At the site at which we reviewed additional allergy codes, we identified 1 case after 653 990 vaccine doses, for a risk of 1.53 cases/million doses (95% confidence interval: 0.04–8.52).

Conclusions. Patients and health care providers can be reassured that vaccine-associated anaphylaxis is a rare event. Nevertheless, providers should be prepared to provide immediate medical treatment should it occur. *Pediatrics* 2003;112:815–820; *anaphylaxis, vaccination, vaccine adverse reactions.*

ABBREVIATIONS. MMR, measles-mumps-rubella; HMO, health maintenance organization; VSD, Vaccine Safety Datalink; *ICD-9*, *International Classification of Diseases, Ninth Revision*; CI, confidence interval; DT, pediatric diphtheria-tetanus; DTP, diphtheria-tetanus-whole cell pertussis; Hib, *Haemophilus influenzae* type b; OPV, oral polio vaccine; VAERS, Vaccine Adverse Event Reporting System.

Anaphylaxis is a potentially fatal hypersensitivity reaction resulting in cutaneous, respiratory, cardiovascular, and/or gastrointestinal signs and symptoms. Common causes of anaphylaxis in children include peanuts and other foods, medications, and hymenoptera stings. Vaccine-associated anaphylaxis has been reported, and the Institute of Medicine accepts a causal relation with the combined measles-mumps-rubella vaccine (MMR), hepatitis B vaccine, and diphtheria and tetanus toxoids,¹ but the number of vaccine-associated cases seems to be small. Because the risk of vaccine-associated anaphylaxis is not well quantified, we describe the incidence of anaphylaxis after vaccination among children and adolescents at 4 West Coast health maintenance organizations (HMOs) participating in the Centers for Disease Control and Prevention's Vaccine Safety Datalink (VSD) project.

METHODS

Study Sites

The 4 HMOs participating in the study were Group Health Cooperative, Seattle, Washington; Northern California Kaiser Permanente, Oakland, California; Northwest Kaiser Permanente, Portland, Oregon; and Southern California Kaiser Permanente, Los Angeles, California. These sites are participants in the VSD project, which since 1991 has been funded by the Centers for Disease Control and Prevention to study adverse events after vaccination.

Study Population and Time Frame

The study cohort consisted of children and adolescents aged 0 through 17 years at 3 sites and aged 0 through 6 years at 1 site. A total of 2 226 907 children and adolescents in this cohort were enrolled in their respective HMO for at least 1 day between 1991 (for 3 of the sites) or 1992 (for 1 site) and the end of 1997.

Assessment of Exposure

Vaccines that were administered during the study period were identified from the automated immunization data collected by each study site. These data include type of vaccine and date of administration. The quality of these data has been assessed in a previous study, which noted high concordance between the automated data and data abstracted from the medical record.² These data provided the denominator for calculations of risk of anaphylaxis after vaccination, and linkage with the outcome data allowed

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The findings and conclusions of this study do not necessarily represent the views or policies of the Department of Health and Human Services or the American Association of Health Plans.

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for identification of allergic reactions occurring the same day as vaccination.

Identification of Potential Cases of Vaccine-Associated Anaphylaxis

We searched the automated encounter databases at each site for occurrences of *International Classification of Diseases, Ninth Revision (ICD-9)* codes suggestive of anaphylaxis. These databases included hospitalizations and emergency department visits at all study sites. Availability of outpatient clinic data differed across study sites: 1 site had outpatient clinic data for the entire study period, 1 site had data from 1995 onward, 1 site had data for 1997 only, and 1 site did not contribute outpatient clinic data. Given this variability in outpatient data, we conducted 2 sets of analyses: 1 including all study sites and 1 restricted to the site with complete outpatient data. The site with complete outpatient data had data for children 0 through 17 years of age.

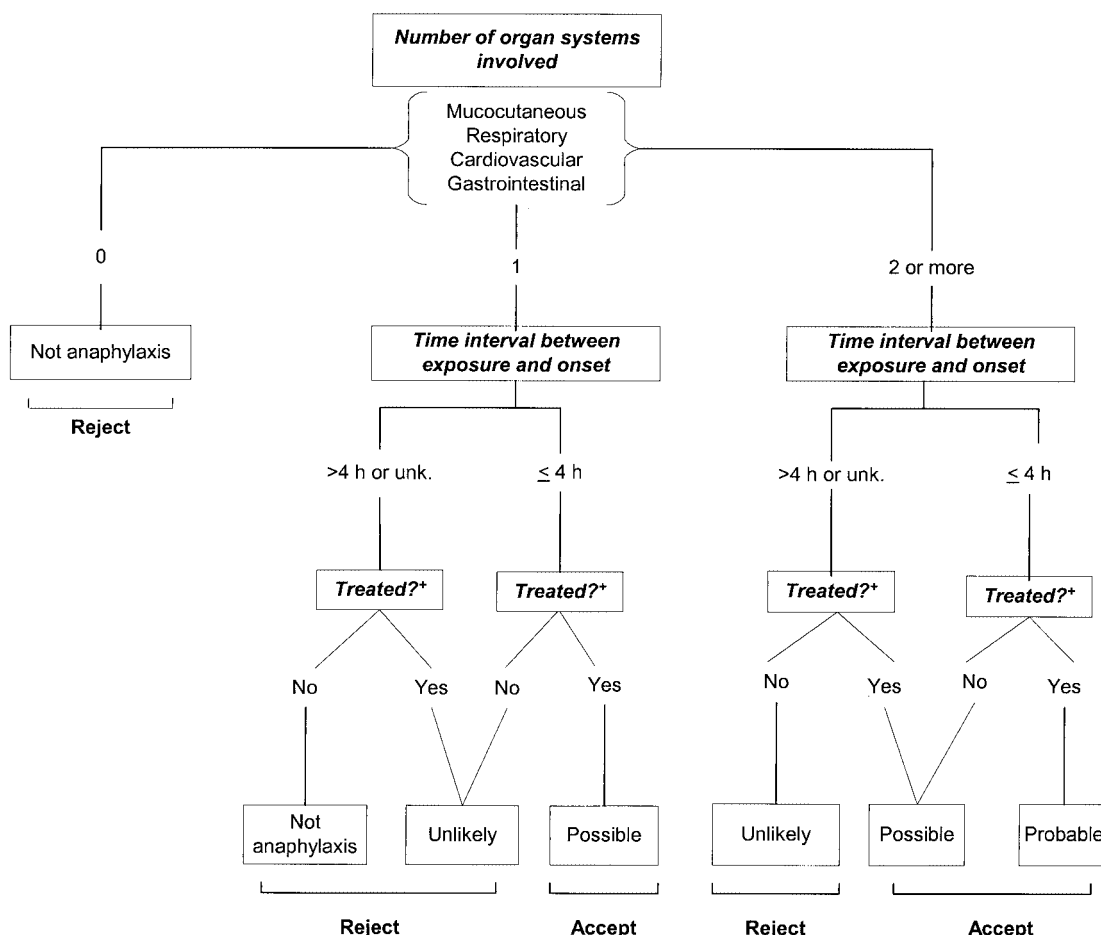
We searched for diagnoses of ICD-9 code 995.0 (anaphylactic shock), E948.0 through E948.9 (adverse reaction from bacterial vaccines), and E949.0 through E949.9 (adverse reaction from other vaccines and biological substances). We restricted our review to diagnoses occurring on days 0 to 2 after vaccination (day 0 defined as the same day as vaccination) for ICD-9 code 995.0 and day 0 for ICD-9 codes E948.0 to E948.9 and E949.0 to E949.9. Because some cases of anaphylaxis may receive other related allergy diagnoses, at 1 of the study sites, we also performed a chart review of all day 0 diagnoses of 708.0 (allergic urticaria), 708.9 (urticaria unspecified), 995.1 (angioneurotic edema), 995.3 (allergy unspecified), 695.1 (erythema multiforme), and 995.2 (unspecified adverse effect of drug, medicinal and biological substance).

Definition of Anaphylaxis

To classify episodes as “probable” or “possible” anaphylaxis, we considered the number and type of organ systems involved, the rapidity with which signs and symptoms appeared after exposure to a precipitating agent, and treatment (Fig 1). The decision to incorporate treatment was based on our knowledge that prompt treatment of an anaphylactic episode can stop progression to >1 organ system. Cases defined as “probable” anaphylaxis required manifestations involving >1 organ system (cutaneous, respiratory, cardiovascular, and/or gastrointestinal), occurring within 4 hours of exposure to a precipitating agent, with subsequent treatment. “Possible” anaphylaxis included 3 groups: 1) those with involvement of >1 organ system (described above), with signs and symptoms developing within 4 hours of exposure, and untreated; 2) those with involvement of >1 organ system, occurring >4 hours (or an indeterminate time period) after exposure, who were treated; and 3) those with involvement of only 1 organ system, with symptoms developing within 4 hours of exposure, who were treated.

Chart Abstraction

For each potential case, we reviewed the medical record to collect information about date of onset, signs and symptoms, cause posited by the treating physician, time interval between exposure and onset of signs and symptoms, treatment, and history of atopy. Information was also recorded on specific manifestations within 4 categories of signs and symptoms integral to diagnosing anaphylaxis: mucocutaneous, respiratory, cardiovascular, and gastrointestinal. Time interval from posited exposure to onset of



* With any of the following:

Epinephrine, parenterally administered antihistamines, parenterally administered corticosteroids, intravenous fluids, bronchodilators

Fig 1. Algorithm for assessing anaphylaxis.

signs and symptoms was categorized as <5 minutes (or “immediate”), 5 to 59 minutes, 1 to 4 hours, >4 hours, and unknown. We collected information about all treatments administered by medical personnel, including epinephrine, parenterally administered antihistamines, parenterally administered corticosteroids, intravenous fluids, and bronchodilators. A child was classified as potentially atopic when he or she had a medically recorded history of asthma, hay fever, eczema, allergic bronchitis, reactive airway disease or bronchiolitis, other allergies, or use of bronchodilators. We collected history of these conditions or medications from chart notes pertaining to the anaphylactic episode or its follow-up (we reviewed chart notes for the month after the episode). Although this documentation followed the anaphylactic episode, we included only those conditions or medications that were originally diagnosed or prescribed before the anaphylactic episode.

Analysis

We calculated the risk of anaphylaxis after vaccination as the number of identified cases of anaphylaxis per million doses of vaccine administered. We estimated risk for all vaccines combined, as well as separately by vaccine type. When an accepted case of anaphylaxis had received >1 vaccine simultaneously, that case contributed to the risk estimate for each of the vaccines that he or she had received. We estimated risk for all 4 study sites combined and also conducted an analysis restricted to the 1 study site that reviewed a range of other related diagnoses and that had complete outpatient clinic diagnosis information. We calculated 95% confidence intervals (CIs) for the risk estimates when the risk was >0. When the risk was 0, we calculated 1-sided 97.5% CIs.

RESULTS

We identified 664 diagnoses of interest and reviewed 657 (Table 1). We were unable to review 7 diagnoses because of missing chart information. These 7 consisted of 3 diagnoses of 995.3 (allergy unspecified) and 4 diagnoses of E948.6 (adverse reaction from pertussis vaccine).

We accepted 6 of the 657 reviewed episodes as probable or possible anaphylaxis. However, 1 of the 6 cases was clearly not vaccine related. The patient's visit consisted of evaluation for an episode of idiopathic anaphylaxis that had occurred a few days before vaccination. At the time of this evaluation, it was noted that the patient was due for hepatitis B vaccine and the vaccine was administered. This appeared in the automated data as a day 0 reaction, although the reaction preceded vaccine administration. The 5 remaining cases are described in Table 2. Of these 5, 2 are questionable with respect to whether the reaction was truly anaphylaxis (patient 1: signs and symptoms not typical of anaphylaxis and not treated; patient 3: provider doubted whether episode

was a true allergic reaction), and 1 was unlikely to have been caused by vaccination (patient 4: time interval between vaccination and symptoms was 2 days; cause of the anaphylactic episode was unclear). None of the anaphylactic episodes resulted in death.

The number of vaccinations administered to the study cohort was 7 644 049. Given 5 identified cases of anaphylaxis, our estimate of the risk of anaphylaxis after vaccination is 0.65 cases per million doses (95% CI: 0.21–1.53). If we exclude the 3 cases that were questionable with regard to either vaccine association or outcome, then our estimate of the risk is 2 cases per 7 644 049 vaccine doses, or 0.26 cases per million doses (95% CI: 0.03–0.95).

One of the cases of anaphylaxis occurred at the study site for which we reviewed a broader range of diagnoses and had complete information regarding outpatient clinic diagnoses. Although we had complete outpatient clinic data at this site, the single case of anaphylaxis identified was diagnosed in the emergency department. The population of children at this site had received 653 990 doses of vaccine, for a risk of 1.53 per million doses (95% CI: 0.04–8.52).

The vaccines administered to the patients were most often given in combination and included MMR, hepatitis B, pediatric diphtheria-tetanus (DT), combined diphtheria-tetanus-whole cell pertussis (DTP), *Haemophilus influenzae* type b (Hib), combined DTP-Hib, and oral polio vaccine (OPV; Table 2). The 1 subject who received a single vaccine received MMR. Considering the data from all 4 sites, the risk of anaphylaxis after these vaccines ranged from 1.1 cases/million doses of hepatitis B to 21.2 cases/million doses of DT (Table 3). This latter estimate is based on relatively few doses and a single case of anaphylaxis and is less precise than the estimates for the other vaccines (as reflected in the wider CI). We observed no cases of anaphylaxis after vaccination with combined diphtheria-tetanus-acellular pertussis, influenza, inactivated polio vaccine, adult diphtheria-tetanus, or varicella. For several of these vaccines, however, our population had received relatively few doses, resulting in wide CIs.

At the study site with the most comprehensive data, the 1 case of anaphylaxis had received MMR, DTP, Hib, and OPV. Although we do not know which of these vaccines caused the anaphylactic ep-

TABLE 1. Number of Diagnoses Reviewed, by ICD-9 Code

ICD-9 Code	No. of Study Sites That Reviewed This Code	No. of Diagnoses	Postvaccine Days Reviewed*
995.0 (anaphylactic shock)	4	5	0–2
E948.0–E948.9 (adverse reaction from bacterial vaccines) or E949.0–E949.9 (adverse reaction from other vaccines and biological substances)	4	89	0
708.0 (allergic urticaria)	1	2	0
708.9 (urticaria unspecified)	1	73	0
995.1 (angioneurotic edema)	1	3	0
995.3 (allergy unspecified)	1	457	0
695.1 (erythema multiforme)	1	1	0
995.2 (unspecified adverse effect of drug, medicinal and biologic substance)	1	27	0

* Day 0 is the day the vaccine was administered

TABLE 2. Description of the 5 Cases of Anaphylaxis With a Possible Vaccine Link

Patient	Age	Diagnosis	Symptoms	Vaccines	Time Interval Between Vaccination and Symptom Onset	Treatment	History of Atopy?
1	7 wk	E948.6	Petechial lesions, cyanosis, dyspnea, tachycardia	DTP-Hib, hepatitis B, OPV	2 h	Acetaminophen, chest radiograph, electrocardiogram	No
2	16 mo	E949.9	Erythema, wheezing, tachycardia, rash	MMR	Within 1 h	Albuterol, diphenhydramine elixir	Yes, asthma and eczema
3	17 y	995.0	Facial flushing, shortness of breath, nausea, lightheadedness, numbness in legs	DT, MMR	Within 1 h	Epinephrine, IM diphenhydramine, IV hydrocortisone, D5W.	No
4	10 mo	995.0	Swollen lips, rash, wheezing	DTP-Hib, OPV hepatitis B	2 d	Epinephrine, IM dexamethasone, albuterol, hydroxyzine syrup	Yes, asthma
5	19 mo	995.3	Urticaria, pruritis, swollen lips, slight stridor	MMR, DTP, OPV, Hib	5–10 min	Epinephrine, IM diphenhydramine	No

IM indicates intramuscular; IV, intravenous.

TABLE 3. Observed Risk of Anaphylaxis After Specific Vaccines*

Vaccine	No. of Doses Administered	No. of Cases of Anaphylaxis	Risk per Million Doses (95% CI)†
DT	47 171	1	21.2 (0.5–118.1)
DTP	788 807	1	1.3 (0.03–7.1)
DTaP	448 456	0	0 (0–8.2)
DTP-Hib	596 645	2	3.4 (0.4–12.1)
Influenza	197 964	0	0 (0–18.6)
Hepatitis A	23 185	0	0 (0–159.1)
Hepatitis B	1 852 147	2	1.1 (0.1–3.9)
Hib	785 010	1	1.3 (0.03–7.1)
IPV	48 062	0	0 (0–76.7)
MMR	848 945	3	3.5 (0.7–10.3)
OPV	1 546 372	3	1.9 (0.4–5.7)
Td	152 636	0	0 (0–24.2)
Varicella	254 186	0	0 (0–14.5)
Other	54 463	0	0 (0–67.7)
TOTAL	7 644 049	5	0.65 (0.21–1.53)

DTaP indicates diphtheria-tetanus-acellular pertussis; IPV, inactivated polio vaccine; Td, adult diphtheria-tetanus.

* Includes vaccines administered in combination with other vaccines.

† If risk is 0, the CI is 1-sided 97.5% CI.

isode, we allowed the case to contribute to the vaccine-specific risk estimates for each of the vaccines received. For the vaccine that caused the episode, the resulting risk estimate is valid. For the vaccines that did not cause the reaction, the risk in this population is 0. The vaccine-specific risks were 8.6 cases/million doses of DTP (95% CI: 0.2–47.8), 9.5 cases/million doses of Hib (95% CI: 0.2–53.0), 9.2 cases/million doses of OPV (95% CI: 0.2–51.1), and 14.4 cases/million doses of MMR (95% CI: 0.4–80.5).

DISCUSSION

Anaphylaxis can be caused by vaccination and is among the most serious of vaccine-associated adverse events. However, this study suggests that the risk of anaphylaxis after vaccination is very low. We identified 5 cases of potentially vaccine-associated anaphylaxis in a population of children who had received roughly 7.5 million doses of vaccine (0.65 cases/million doses). Although this estimate likely

represents an underestimate of the risk, because at 3 of the study sites we used a restricted set of diagnosis codes to identify cases and had varying availability of outpatient clinic data, the risk remained low (1.5 cases/million doses) when we restricted to the study site at which we considered a broad range of diagnosis codes and for which we had outpatient clinic data for the entire study period.

Attributing the anaphylactic episodes to a particular vaccine was difficult because the children generally received several vaccines simultaneously. Only 1 child with anaphylaxis had received a single vaccine, and this was MMR. The remaining episodes most often followed diphtheria- and tetanus-containing vaccines (DT, DTP, DTP-HIB), hepatitis B, MMR, and OPV. These vaccines were also the most frequently administered. Considering data from all 4 study sites, the vaccine-specific risks for these vaccines were generally in the range of 1.1 to 3.5 cases per million doses. The vaccine-specific risks at the

study site with the most complete data were higher and ranged from 0 to 14.4 cases/million doses. Because a case contributed to the risk estimates for each vaccine received, when probably only 1 of the vaccines (or none) caused the anaphylaxis, we likely overestimated some of the vaccine-specific risks. For example, the calculation of the risk after MMR at all 4 sites was based on the 3 cases that had received MMR. Because 2 of these cases also received other vaccines along with MMR, it is possible that only 1 case was caused by MMR. We observed no cases of anaphylaxis after diphtheria-tetanus-acellular pertussis, influenza, inactivated polio vaccine, adult diphtheria-tetanus, hepatitis A, or varicella, but given the study time frame (1991–1997) and age range (0–17 years), our population had received relatively few doses of these vaccines. The wide CIs reflect the smaller number of doses administered and should not be interpreted as suggestive of a particularly high or low risk after these vaccines.

Two of the 5 episodes of anaphylaxis occurred in children with a history of asthma and/or eczema. Although this proportion is higher than the estimated prevalence of atopy in the general population of 1 in 6,³ we had too few cases to draw meaningful conclusions about the prevalence of atopy among children with vaccine-associated anaphylaxis.

When comparing our results with those of previous studies, it is important to consider the means of case ascertainment. A strength of the current study is that it does not rely on passive reporting of anaphylaxis. Although passive reporting systems have many important uses, including detection of previously unknown adverse events and increases in the frequency of adverse events, they are prone to underreporting.⁴ The current study, however, does rely on the sensitivity of the ICD-9 codes that we reviewed. Previous studies have indicated that anaphylaxis is sometimes coded as a variety of other allergic conditions.^{5,6} Some of these diagnoses (eg, 995.3, allergy unspecified) are used frequently, and review of all of these diagnoses at all 4 sites was not feasible. The restricted set of codes reviewed at 3 of the sites, along with the variable availability of outpatient clinic data, may have resulted in incomplete capture of anaphylaxis at these sites. In addition, 1 of the sites only had data for children 0 to 6 years of age. Additional cases of anaphylaxis may have been identified at this site if data for older children had been available, but the estimate of the risk would not necessarily change because the number of vaccine doses would also increase. To address these limitations, we conducted a secondary set of analyses restricted to the single site at which a broad range of allergy codes was reviewed and for which we had complete outpatient data for children 0 to 17 years of age.

Previous studies of the risk of anaphylaxis after MMR have generally produced risk estimates at or below the estimates observed in the present study. The differences may reflect in part whether the studies used active or passive surveillance systems, because these differ with regard to underreporting. A Finnish study evaluated serious adverse events after

MMR from 1982 to 1996 in a population that had received close to 3 million doses of MMR.⁷ There were 30 reports of anaphylaxis, 14 of which were classified as having a possibly causal association with MMR. All of the anaphylactic episodes resulted in recovery. On the basis of the 14 cases with a possible link to MMR, the risk of 5 cases/million doses is similar to our estimate from all 4 study sites (3.5 cases/million doses) and not significantly different from the risk estimated from the site with the most complete data (14.4 cases/million doses, based on a single case). In the United States, 168 cases of probable or possible anaphylaxis were reported to the Vaccine Adverse Event Reporting System (VAERS) after administration of approximately 94 million doses of MMR, for a reporting rate of 1.8 cases/million doses.⁸ Finally, in Australia, 1 case of anaphylaxis was reported during the 1998 measles control campaign, during which 1.7 million schoolchildren were vaccinated with MMR.⁹ There were also 6 reactions defined as anaphylactoid. If all 7 of these reactions are considered, then the risk is 4 cases/million doses of MMR. There were no deaths as a result of anaphylaxis.

The risk of anaphylaxis after hepatitis B vaccination was reported in a study of a school-based hepatitis B vaccination program in Canada.¹⁰ In 1992, 127 922 doses of hepatitis B vaccine were administered to sixth-grade students. One case of anaphylaxis was reported for a risk of 7.8 cases/million doses. There were no deaths. The risk estimate in this study is higher than both the estimate obtained in the present study (1.1 cases/million doses) and a reporting rate obtained from VAERS data (1.67 cases/million doses)¹¹ but is based on relatively few doses.

Most of the previous reports of anaphylaxis after diphtheria and tetanus vaccines are case reports.^{12–14} These reports support a causal relationship with anaphylaxis but do not quantify the risk. There were 16 reports of anaphylaxis or collapse after DT or DTP vaccines over a 7-year period in the Northwest Thames Region of the United Kingdom, but the symptoms and severity of these reactions varied.¹⁵ All people with anaphylaxis or collapse recovered. Approximately 268 200 children in this population had completed courses of DTP or DT.

Although we observed no cases of anaphylaxis after varicella vaccination, others have reported it. In the United States, from March 1995 to July 1998, VAERS received 30 reports consistent with anaphylaxis after varicella vaccine, for a reporting rate of 3 cases/million doses distributed.¹⁶ All patients with anaphylaxis survived. Because the varicella vaccine was licensed in the United States in 1995 and we identified cases diagnosed through the end of 1997, our population of children had received only 254 196 doses of varicella vaccine. At all 4 sites taken together, the upper limit of the CI for the risk of anaphylaxis after varicella vaccine was 14.5 cases/million doses. We hope to repeat these analyses in the future as the VSD project collects more data on cases of anaphylaxis prospectively.

We do not know which vaccine components might have caused the episodes of anaphylaxis described in

this study. Vaccine components that may cause allergic reactions include the vaccine antigen (eg, tetanus toxoid¹⁴), animal protein (eg, gelatin⁸), and antibiotics (eg, neomycin¹⁷). A report of anaphylaxis after hepatitis B vaccination suggests that latex used in vial stoppers and syringe plungers may also be a cause of vaccine-associated anaphylaxis.¹⁸ A history of anaphylaxis to a vaccine component is a contraindication to receipt of that vaccine.¹⁹ Furthermore, children who have had an anaphylactic reaction to a specific vaccine should not receive subsequent doses of that vaccine, although desensitization may be possible in some cases (eg, among people with tetanus toxoid allergy^{20,21}).

CONCLUSIONS

Providers and patients can be reassured that the frequency of vaccine-associated anaphylaxis is very low. Nevertheless, providers should be prepared to provide immediate treatment should it occur.

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NEW DOCTORS SHY AWAY FROM PRIMARY CARE AGAIN

“The number of family practice positions filled by US medical school seniors fell from 47%, while internal medicine matches slipped from 59% to 55%. Many of the remaining positions will be filled outside the match by international medical graduates and doctors of osteopathic medicine. . . The only primary care specialty with much drawing power this year was pediatrics; more than two-thirds of its slots were filled by US seniors.”

Medical Economics. May 9, 2003

Noted by JFL, MD

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