MAJOR ARTICLE

Postmarketing Safety Surveillance for Typhoid Fever Vaccines from the Vaccine Adverse Event Reporting System, July 1990 through June 2002

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Vaccines against *Salmonella enterica* serotype Typhi are used for prophylaxis of international travelers and have potential use as counterbioterrorism agents. The Vaccine Adverse Event Reporting System (VAERS) cannot usually establish causal relationships between vaccines and reported adverse events without further research but has successfully detected unrecognized side effects of vaccine. We reviewed reports to VAERS for US-licensed typhoid fever vaccines for the period of July 1990 through June 2002. We received 321 reports for parenteral Vi capsular polysaccharide vaccine and 345 reports for live, oral, attenuated Ty21a vaccine, with 7.5% and 5.5%, respectively, describing death, hospitalization, permanent disability, or life-threatening illness. Unexpected frequently reported symptoms included dizziness and pruritus for Vi vaccine and fatigue and myalgia for Ty21a vaccine. Gastroenteritis-like illness after receipt of Ty21a vaccine and abdominal pain after receipt of Vi vaccine, which are previously recognized events, occasionally required hospitalization. Nonfatal anaphylaxis was reported after both vaccines. VAERS reports do not indicate any unexpected serious side effects that compromise these vaccines' use for travelers' prophylaxis.

Vaccines against *Salmonella enterica* serotype Typhi are indicated for prophylaxis against typhoid fever [1, 2]. The US Food and Drug Administration (FDA) currently licenses 2 vaccines: Typhim Vi, a parenteral Vi capsular polysaccharide vaccine, licensed in 1994 for persons aged ⩾2 years [1]; and Vivotif Berna, an oral 4-capsule series containing live, attenuated *S.* Typhi, Ty21a strain, licensed in 1989 for persons aged ⩾6 years [2]. The parenteral heat-phenol–inactivated and acetone-inactivated whole-cell vaccines, known for their higher reactogenicity [3, 4], are no longer distributed in the United States.

Because typhoid fever is rare in the United States [5], the Advisory Committee on Immunization Practices only recommends vaccination for travelers to endemic areas, persons with intimate exposure to an *S.* Typhi carrier, and microbiology laboratorians who work frequently with *S.* Typhi [6]. Typhoid has a well-documented ability to cause large single-source outbreaks [7, 8], and the Centers for Disease Control and Prevention (CDC) has classified *Salmonella* species with other food safety threats as high-priority potential bioterrorism agents (category B) [9, 10].

More than 10,000 Vi doses [1, 4, 11–14] and 1.4 million Ty21a doses [2, 15–19] have been administered in clinical trials, but most studies were not conducted specifically for safety monitoring, and many lacked pla

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cebo controls [3]. The Vi product label reports results (without statistical significance testing) of a US initial vaccination safety trial; the 54 vaccinees experienced a higher frequency of several conditions than did 98 placebo controls: injection site reactions, including tenderness (96.9%), pain (26.5%), induration (5.1%), erythema (5.1%); headache (16.3%); myalgia (3.1%); nausea (8.2%); and subjective fever (3.1%) [1]. Abdominal pain, allergic-type reactions, including urticaria, and numerous other conditions have been reported in foreign postmarketing surveillance [1]. Ty21a's product label documents 483 vaccinees receiving 3 enteric-coated capsules and reporting abdominal pain (6.4%), nausea (5.8%), headache (4.8%), fever (3.3%), diarrhea (2.9%), vomiting (1.5%), and skin rash (1.0%), with only nausea occurring statistically more frequently than in placebo controls [2, 15–16]. Anaphylaxis (1 event) and urticaria have been reported in postmarketing surveillance [2].

Careful analysis of spontaneous adverse event reports has identified rare, potentially serious vaccine side effects in the postlicensure period for other vaccines [20, 21]. We reviewed the spontaneously reported adverse events in the Vaccine Adverse Event Reporting System (VAERS) for typhoid fever vaccines.

MATERIALS AND METHODS

VAERS is a passive surveillance system jointly administered by the FDA and CDC for postlicensure vaccine safety surveillance. Medical classification terms are assigned to each report by using Coding Symbols for Thesaurus of Adverse Reaction Terms [22] on the basis of the inclusion of certain words or phrases, without application of standardized case definitions; multiple coding terms are often assigned. Serious events, including deaths or events that were reported to result in hospitalization, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly [23], are followed up by telephone to obtain additional information about the event and the patient's medical history. Important limitations of VAERS include underreporting, lack of consistent diagnostic criteria, and difficulty in determining whether a vaccine caused the reported adverse event [24, 25].

We reviewed adverse event reports after typhoid fever vaccination received from the inception of VAERS in July 1990 through June 2002. Multiple reports involving a single adverse event were consolidated and treated as 1 report, as were multiple reports relating to a single 4-capsule Ty21a vaccination series. Duplicate reports were identified by using birth date or age, vaccination date, vaccinee name, and clinical details. We reviewed events originating from within and outside the United States but present only US events because of limitations in conducting routine follow-up outside of the United States.

Reporting rates were calculated by dividing the number of reports received by the numbers of vaccine doses distributed for available years obtained from manufacturers (Susan Getz [Aventis Pasteur] and Annette Koller [Berna Biotech], personal communication). We searched for patterns of unexpected events by determining the most frequent coding terms; describing reports by age, sex, and seriousness; and individually reviewing serious, pediatric, and positive rechallenge reports (recurrence of the same condition after repeated vaccination of the same person). We also individually reviewed reports and assigned common coding terms that represented unexpected symptoms not mentioned in the adverse event summary of the specific product label at the time of analysis.

We calculated proportional reporting ratios (PRRs) [26] for all coding terms for each typhoid vaccine. The PRR identifies conditions that constituted a larger proportion of reported events for a given typhoid vaccine compared with other vaccines. We used PRRs to screen for symptoms or conditions meriting further clinical review. PRRs were calculated as follows: [number of events assigned given coding term for the vaccine of interest/total number of reported events for vaccine of interest]/[number of events assigned given coding term for the comparison vaccines/total number of reported events for comparison group vaccines].

We used 2 comparison groups from VAERS: all nontyphoid events and all nontyphoid travel vaccine events (cholera, inactivated polio, oral polio, plague, yellow fever, hepatitis A, and Japanese encephalitis virus vaccines). To improve comparability between the typhoid and comparison groups, we included only US reports received from July 1990 through June 2002 involving individuals aged 18–65 years, because most typhoid vaccine reports met these criteria. We selected for further review coding terms with PRRs of ≥ 2 and involving >3 events [26].

RESULTS

Overall, VAERS received 1482 US adverse event reports after typhoid vaccination during the period of 1 July 1990 through 31 June 2002. A total of 321 of these reports involved Vi, 345 involved Ty21a, 707 involved discontinued whole-cell vaccines, and 109 did not identify the vaccine type. Temporal patterns roughly mirror vaccine distribution, with no events for the 1994-approved Vi until 1995 and no whole-cell vaccine reports since their discontinuation in 2000 (figure 1). In 2001–2002, a sharp decrease in Ty21a reports is visible during the FDA's 13-month import ban as a result of Good Manufacturing Practices infractions.

Reporting rates for years with available distribution data were 4.5 events per 100,000 Vi doses (for 1995–2002) and 9.7 events per 100,000 Ty21a doses (for 1991–2002). Serious event reporting rates were 0.34 events per 100,000 doses for Vi and 0.59 events per 100,000 doses for Ty21a. Demographic char-

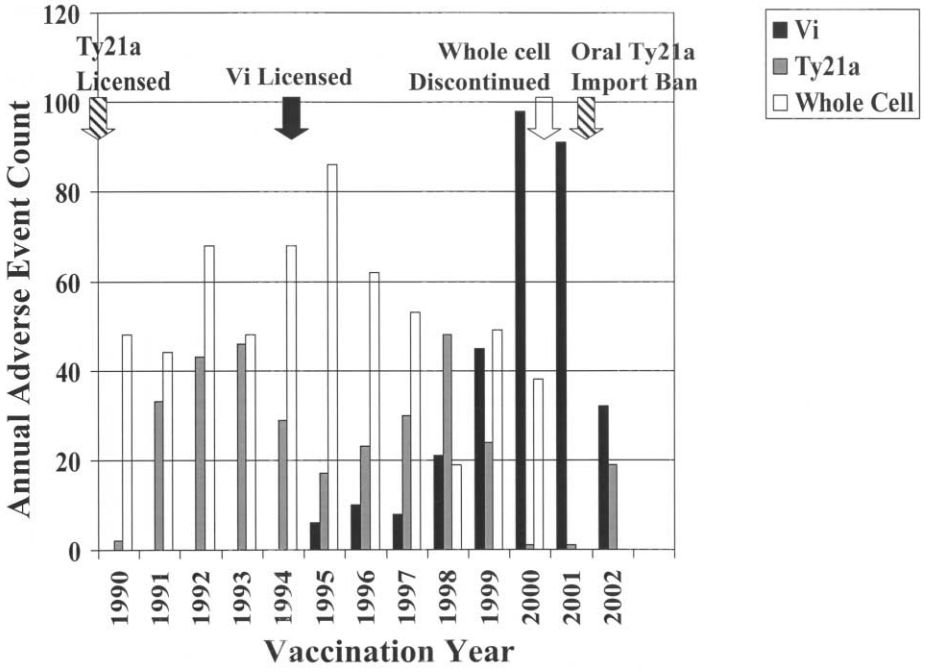

Figure 1. Adverse events after typhoid fever vaccination reported to the Vaccine Adverse Events Reporting System, by vaccination date and vaccine type, United States, July 1990 through June 2002.

acteristics of vaccinees, seriousness of events, and proportions of coadministered vaccines are presented in tables 1 and 2. Hepatitis A was the most commonly coadministered vaccine (46% and 18% for Vi and Ty21a, respectively).

Vi Results

Commonly reported symptoms after receipt of Vi vaccine. The most common coding terms were mainly expected conditions and symptoms, such as injection site reactions (injection site pain, injection site hypersensitivity, vasodilatation), fever, headache, rash, urticaria, abdominal pain, and nausea (table 3). Twenty events received the coding term "abdominal pain," with 6 after Vi alone. Fifteen reports (75%) described symptom onset within 24 h after vaccination, frequently just a few hours afterward. For these 20 events, associated complaints included nausea (55%), diarrhea (20%), and vomiting (15%), with 25% reporting no other gastrointestinal symptoms.

The unexpected symptoms of dizziness and pruritus were reported after receipt of the vaccine alone and in combination. Dizziness was usually a short-lived component of the clinical picture for expected conditions, such as influenza-like syndromes, allergic reactions, and gastrointestinal distress (nausea and/or vomiting). Pruritus generally accompanied the expected conditions of rash or allergic reaction except for one event of isolated generalized pruritus after receipt of Vi alone. No positive rechallenge reports were identified for Vi.

Serious events after receipt of Vi vaccine. Three serious events followed Vi alone, and 21 followed Vi provided in combination with other vaccines (table 4).

With regard to neurological events, a 30-year-old man developed Guillain-Barré syndrome (GBS) 3 weeks after receipt of Vi alone; the man had no recent history of viral illness, surgery, or medication use. Three other GBS events were reported with onset 8 days after receipt of tetanus diphtheria, yellow fever, hepatitis A, and Vi vaccines; 10 days after receipt of yellow fever, hepatitis A, and Vi vaccines; and 4 months after receipt of hepatitis A and Vi vaccines. No intervening viral illnesses were noted. One encephalitis event occurred 4 months after receipt of multiple vaccines, including Vi; a second meningoencephalitis event was attributed to concomitantly administered yellow fever vaccine, because CSF samples were positive for yellow fever–specific IgM [21]. Four additional neurological events after receipt of multiple vaccines requiring hospitalization involved seizure ($n = 2$), severe headache, and an ischemic cerebrovascular accident.

With regard to allergic events, a 45-year-old woman received 3 parenteral typhoid immunizations in 1984, 1992, and 1995 without incident; it was likely that she received whole-cell vaccine (as based on the years the vaccines were administered). In 1999, she had an anaphylactic reaction after receiving her fourth Ty21a capsule. Two months later, during attempted progressive rechallenge, she developed "throat tightening" and generalized pruritus 55 min after receipt of 0.02 mL of a 1:100 dilution of Vi alone. Five additional serious events involved angioedema,

Table 1. Adverse events after typhoid fever vaccination reported to the Vaccine Adverse Event Reporting System by age, sex, severity, and vaccine type for currently licensed vaccines, United States, July 1990 through June 2002.

Vaccine, age group in years	No. (%) of adverse events				
	Severity of event[a]		Sex of vaccinee		
	Serious	Not serious	Female	Male	Total[b]
Parenteral Vi					
0–17	2	29	13	17	31 (10)
18–25	7	72	39	40	79 (25)
26–35	5	70	27	46	75 (23)
36–45	3	50	25	28	53 (17)
46–55	1	34	17	18	35 (11)
>55	6	34	22	18	40 (12)
Unknown	0	8	2	3	8 (2)
Total[b]	24 (7)	297 (93)	145 (46)	170 (54)	321 (100)
Oral Ty21a					
0–17	0	29	13	16	29 (8)
18–25	4	52	31	21	56 (16)
26–35	5	69	51	23	74 (21)
36–45	2	61	34	29	63 (18)
46–55	2	63	43	21	65 (19)
>55	4[c]	42	27	19	46 (13)
Unknown	2	10	5	6	12 (3)
Total	19 (6)	326 (94)	204 (60)	135 (40)	345 (100)

[a] Serious events include deaths and events that were reported to result in hospitalization, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly [23].

[b] Column totals include 12 events with missing sex information. Percentages in the row about sex use vaccinees with known sex as the denominator.

[c] Includes 1 reported death involving a 56-year-old man.

urticaria, and/or other allergic reactions. For 4 events, yellow fever vaccine had been coadministered, and the fifth involved concomitant rabies vaccine.

With regard to other events, a 32-year-old man developed severe abdominal pain 1 day after receiving Vi. Small bowel inflammation was diagnosed by computed tomography. Six days after vaccination, he underwent abdominal surgery for a perforated jejunum. Other events after multiple vaccines that required hospitalization included 2 febrile diarrheal illnesses, several weeks of fever attributed to yellow fever vaccine, pneumonia in a 72-year-old man receiving long-term corticosteroids, and minimal-change nephrotic syndrome in a 12-year-old boy 13 days after vaccination. Additional events after multiple vaccines but without hospitalization included new-onset hypertension and self-limited chest pain with negative cardiac workup.

Other selected events after receipt of Vi vaccine. Related coding terms "laryngismus" and "edema tongue" had elevated PRRs when all nontyphoid fever vaccine events were used as the comparison group, and "facial edema" had an elevated PRR when travel vaccine events were used as the comparison. Because of the conditions' clinical relatedness, we aggregated these 27 events' review results (table 5). Three events followed Vi alone: angioedema with fever, tachycardia, and fatigue consistent with anaphylaxis [27] except for the delayed symptom onset 7.5 h after vaccination; isolated throat swelling minutes after vaccination; and the serious anaphylaxis event described above. We searched VAERS for additional anaphylaxis events and identified only 1 event, which involved concomitant receipt of yellow fever vaccine. No additional reports of allergic reaction after both Ty21a and Vi were identified.

Clinical review of events assigned other coding terms with elevated PRRs found no unexpected syndromes, although a few expected symptoms mentioned in the product label had elevated PRRs: nausea, vomiting, and abdominal pain.

Ty21a Results

Commonly reported symptoms after receipt of Ty21a vaccine. The 10 most common coding terms included expected symptoms noted in the product label at the time of this analysis, such as diarrhea, nausea, fever, abdominal pain, headache, rash, vomiting, and urticaria (table 3). The unexpected conditions of asthenia and myalgia were reported after receipt of Ty21a alone and in combination; pruritus was common in events in which other vaccines were coadministered. For most pruritus events, itching was associated with rash or injection site reactions to coadministered vaccines.

Reports assigned the coding term "asthenia" predominantly

Table 2. Frequencies of the most common coadministered vaccines, by vaccine type, for adverse events after typhoid fever vaccination, United States, July 1990 through June 2002.

Coadministered vaccine	No. (%) of adverse events			
	Parenteral Vi (n = 321)[a]		Oral Ty21a (n = 345)[a]	
	All events	Serious events	All events	Serious events
Hepatitis A	147 (46)	14 (58)	61 (18)	4 (21)
Yellow fever	84 (26)	10 (42)	46 (13)	2 (11)
Hepatitis B	67 (21)	3 (13)	28 (8)	1 (5)
Inactivated polio	46 (14)	4 (17)	40 (12)	4 (21)
Tetanus diphtheria	46 (14)	4 (17)	64 (18)	4 (21)
Meningococcal	36 (11)	1 (4)	22 (6)	1 (5)
Anthrax	37 (12)	0 (0)	3 (1)	0 (0)
All vaccines[b]	260 (81)	20 (83)	165 (48)	8 (42)

[a] Twenty-four Vi-related and 19 Ty21a-related events were designated as serious by the reporter. Serious events include deaths and events that were reported to result in hospitalization, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly [23].

[b] Individual percentages do not add to total for "All Vaccines" because many vaccinees received >1 coadministered vaccines, and only the most common coadministered vaccines are listed.

Table 3. Most common coding terms for adverse events reported after typhoid fever vaccination by vaccine type, United States, July 1990–June 2002.

Vaccine, adverse event coding term	No. (%) of adverse events
Vaccine alone	
Vi (n = 61)	
Fever	11 (18)
Headache	11 (18)
Dizziness[a]	9 (15)
Rash	9 (15)
Urticaria	9 (15)
Myalgia	6 (10)
Pain	6 (10)
Abdominal pain	6 (10)
Pruritus[a]	6 (10)
Injection site pain	5 (8)
Ty21a (n = 182)	
Diarrhea	51 (28)
Nausea	47 (26)
Fever	42 (23)
Abdominal pain	42 (23)
Headache	31 (17)
Rash	26 (14)
Vomiting	21 (12)
Pain	20 (11)
Asthenia[a]	17 (9)
Myalgia[a]	17 (9)
Vaccine in combination	
Vi (n = 260)	
Fever	39 (15)
Pruritus[a]	35 (13)
Vasodilation	35 (13)
Headache	34 (13)
Injection site hypersensitivity	34 (13)
Rash	32 (12)
Myalgia	26 (10)
Urticaria	26 (10)
Nausea	25 (10)
Dizziness[a]	23 (9)
Ty21a (n = 163)	
Fever	34 (21)
Abdominal pain	28 (17)
Pruritus[a]	28 (17)
Rash	26 (16)
Diarrhea	24 (15)
Pain	23 (14)
Myalgia[a]	21 (13)
Nausea	21 (13)
Headache	19 (12)
Urticaria	19 (12)

NOTE. Adverse event coding terms are not mutually exclusive because several terms are often assigned to a single event.

[a] Symptom or condition was not mentioned in the specific product label's adverse event summary at the time of this analysis.

described fatigue or weakness as part of gastroenteritis-like syndromes or influenza-like syndromes involving myalgias, fever, and chills without gastrointestinal distress. Many "asthenia" events overlapped with the events that were assigned the term "myalgia." Fourteen "myalgia" events involved influenza-like syndromes without either gastrointestinal symptoms or rash; 6 followed receipt of Ty21a alone. A 27-year-old woman experienced a serious event involving influenza-like symptoms (weakness, myalgia, fever, and severe headache) beginning 10–12 h after receiving her first capsule. After resolution, the same symptoms recurred 3 h after she received her second capsule.

Ty21a positive rechallenge reports. Both positive rechallenge reports identified involved rash (an expected condition) recurring after a repeated Ty21a series in the same individual. We also found 29 events describing self-limited symptoms recurring after receipt of multiple Ty21a capsules in a single vaccination series. Most involved gastrointestinal complaints: abdominal pain (n = 12), diarrhea (n = 10), nausea (n = 6), and/or vomiting (n = 2). Other symptoms included headache (n = 6), fatigue/weakness (n = 4), fever (n = 4), chills (n = 2), rash (n = 2), myalgias (n = 1), dyspepsia (n = 1), palpitations (n = 1), nasal swelling (n = 1), and vertigo (n = 1).

Serious events after receipt of Ty21a vaccine. Five serious events followed receipt of Ty21a alone, and 14, including 1 death, followed receipt of Ty21a provided in combination with other vaccines (table 4).

Death report. A 56-year-old man became ill 4 days after receiving yellow fever vaccine and Ty21a and was pronounced brain dead as a result of cerebral herniation 6 days later. *Pseudomonas* species and enterococci grew from postmortem brain tissue cultures. On the basis of the clinical details, disease timing and overall autopsy findings, the CDC Yellow Fever Vaccine Working Group attributed the death to yellow fever vaccine–associated viscerotropic disease, although the results of all tests (immunohistochemistry staining and serological and culture studies) for yellow fever virus were negative (R. S. Barwick [CDC], personal communication).

Nonfatal serious events after receipt of Ty21a vaccine. With regard to neurological events, a 25-year-old healthy man developed transverse myelitis 1 week after Ty21a, immunoglobulin, and mefloquine. Three additional demyelinating disease events were reported: GBS beginning 11 days after receipt of Ty21a, inactivated poliovirus vaccine (IPV), hepatitis A vaccines, and intramuscular immunoglobulin; a GBS-like condition with facial and lower extremity weakness occurring 22 days after receipt of Ty21a, IPV, and meningococcal vaccines; and transverse myelitis occurring 21 days after receipt of Ty21a, IPV, and hepatitis A vaccines. Only the final report described an intervening viral illness (viral pneumonia a week before GBS onset). Additional neurological events after receipt of multiple

Table 4. Serious adverse events reported to the Vaccine Adverse Event Reporting System after typhoid fever vaccination, United States, July 1990 through June 2002.

Vaccine type, serious adverse event[a]	No. of adverse events		
	Vaccine received in combination	Vaccine received alone	Total
Parenteral Vi vaccine			
Neurological syndromes			
Guillain-Barré syndrome	3	1	4
Encephalitis or meningoencephalitis	2	0	2
Seizure	2	0	2
Cerebrovascular accident	1	0	1
Headache, severe	1	0	1
Other events			
Angioedema, urticaria and/or other allergic reactions	5	1	6
Nephrotic syndrome	1	0	1
Perforated jejunum	0	1	1
Diarrhea with fever	2	0	2
Other	4	0	4
Total	21	3	24
Oral Ty21a vaccine			
Neurological syndromes			
Guillain-Barré syndrome	1	0	1
Other demyelinating disease	2	1	3
Cerebral edema	1	0	0
Headache, severe	4	0	4
Other events			
Nausea, vomiting, diarrhea and/or abdominal pain	2	2	4
Sepsis	0	1	1
Rheumatoid arthritis	0	1	1
Arthralgia	1	0	1
Spontaneous abortion	1	0	1
Diabetes mellitus type 2	1	0	1
Cellulitis	1	0	1
Total	14	5	19

[a] Serious events include deaths and events that were reported to result in hospitalization, prolongation of hospitalization, permanent disability, life-threatening illness, or congenital anomaly [23].

vaccines included 4 severe headaches, 1 of which had concomitant weakness and diplopia.

With regard to gastrointestinal events, 2 vaccinees were hospitalized briefly with vomiting, abdominal cramping, fever, and dehydration after Ty21a alone. Two other vaccinees were hospitalized after receipt of multiple vaccines: a 43-year-old man with a gastroenteritis-like illness and pruritic rash (diagnosed as vaccine-induced typhoid fever; no culture confirmation was reported) 18 days after vaccination, and a 79-year-old man hospitalized for severe abdominal pain with a negative upper gastrointestinal series.

With regard to arthralgia events, a 33-year-old woman subsequently diagnosed with rheumatoid arthritis developed bilateral ankle and knee pain and swelling after receipt of Ty21a vaccine alone; her symptoms began the afternoon after receiving the first capsule and worsened after receiving the second and third capsules. An additional serious event after receipt of multiple vaccines involved high fever, polyarthralgia, and headache 2 days after vaccination with persistent joint pain and headaches 8 years later.

With regard to other events, a 32-year-old woman developed a febrile illness consistent with sepsis syndrome 30 min after receiving Ty21a vaccine alone by rectal enema as part of a research protocol [28]. No etiologic organism was identified, but blood samples were not obtained for culture before antibiotic administration. Three other events after receipt of multiple vaccines included type 2 diabetes mellitus diagnosed 6 months after vaccination, a spontaneous abortion at 9 weeks' gestation 1 month after receipt of anthrax and Ty21a vaccine, and an illness including fever, conjunctivitis, and cellulitis of unstated site.

Selected nonserious Ty21a vaccine events. Clinical review of events assigned coding terms with elevated PRRs found no unexpected syndromes, although a few expected symptoms (abdominal pain, diarrhea, vomiting, and nausea) mentioned in the product label had elevated PRRs.

In addition to the cross-sensitization event noted in the Vi serious events, we identified a possible Ty21a anaphylactic reaction: 2 h after vaccination, nausea, diarrhea, and uneasiness developed, followed by pruritus, agitation, facial edema, and throat swelling. The patient was treated with oral diphenhydramine and discharged, and the patient returned to the emergency department with shortness of breath, wheezing, throat tightness, and syncope that required epinephrine treatment.

DISCUSSION

We reviewed adverse events reported to VAERS for typhoid fever vaccines focusing on the 2 US-licensed products, Typhim Vi and Vivotif Berna. Causal relationships for specific conditions cannot be established on the basis of this review, but we did identify some unanticipated conditions that may be related to the vaccines: influenza-like syndromes after receipt of Ty21a vaccine and anaphylaxis and other serious allergic events after receipt of Vi vaccine. We were also able to clinically characterize events already linked to the vaccines in clinical trials, such as abdominal pain for Vi vaccine and gastrointestinal symptoms for Ty21a vaccine.

In reviewing Ty21a-related events with the common coding terms "asthenia" and "myalgia," we found influenza-like syndromes (myalgias with chills or fevers) without gastrointestinal complaints. Several followed receipt of Ty21a alone, and 1 se-

Table 5. Adverse events reported after Vi capsular polysaccharide vaccination assigned coding terms "laryngismus," "edema tongue," or "facial edema," United States, July 1990 through June 2002.

Adverse event, site	Vaccine, no. of adverse events				Onset of symptoms <4 h after vaccination[b]
	TYP only	YF	Other[a]	Total	
Anaphylaxis events [27]					
Throat or tongue edema with dermatological symptoms[c]	1	3	3	7	7
Facial edema with shortness of breath	0	5	1	6	6
Fever, tachycardia, angioedema, and fatigue	1	0	0	1	0
Total	2	8	4	14	13
Nonanaphylaxis allergic events					
Throat or tongue edema alone	1	1	2	4	1
Facial edema alone	0	0	4	4	1
Facial edema with urticaria	0	1	1	2	1
Other	0	1	2	3	2
Total	1	3	9	13	5

NOTE. TYP only, only typhoid vaccine administered; YF, yellow fever vaccine coadministered.

[a] Other non–yellow fever vaccine coadministered with typhoid vaccine.

[b] All but 2 of the anaphylaxis events occurred <1 h after vaccination.

[c] Dermatologic symptoms included pruritus, urticaria, angioedema, and flushing [27].

rious event recurred after receipt of multiple capsules. We have no evidence that bacteremia associated with receipt of this live, attenuated vaccine played a role here or in other Ty21a events. Gastroenteritis-like syndromes constituted a large proportion of Ty21a-related events, with diarrhea, nausea, abdominal pain, and vomiting among the most frequent coding terms. Several such events required brief hospitalizations. Only nausea was statistically more frequent in vaccinees than placebo controls during clinical trials, but vaccinees did report abdominal pain, diarrhea, and vomiting more commonly than controls [15]. Some reports described self-limited gastrointestinal symptoms recurring after receipt of multiple capsules, adding evidence for a causal link.

Abdominal pain events composed a larger proportion of events after receipt of Vi than after receipt of other vaccines. This symptom was sometimes reported without other gastrointestinal symptoms. The most serious abdominal pain event involved a perforated jejuneum after receipt of Vi alone. Abdominal pain was seen in active surveillance (0.5% of 435 Kenyan children aged 5–15 years; there was no placebo arm) [14] and foreign postmarketing surveillance [1]. Subsequent travel-related illness is likely not a confounder, because the symptom often developed a few hours after vaccination. Elevated baseline rates for gastrointestinal conditions would not be anticipated in US vaccinees before travel. A controlled study examining the vaccine's association with abdominal pain hospitalizations or emergency department visits could help clarify whether the association is causal.

We found the coding terms for throat, tongue, and facial edema to have elevated PRRs for Vi. Elevated PRRs should not automatically be interpreted as causal associations, because reporting bias, differences between vaccinee populations, and other factors can result in a symptom or condition representing a greater proportion of events for an individual vaccine than for comparison vaccines without a causal relationship [29]. Also, coding term assignment is based on inclusion of certain words or phrases in the report, without the application of standardized event definitions, further limiting conclusions. However, these 3 clinically related coding terms represented a group of clinically homogeneous events consistent with allergic reactions, a biologically plausible adverse event. Frequent coadministration with yellow fever vaccine may have contributed to these elevated PRRs, but some events did not involve this vaccine and others followed Vi alone. Passive postmarketing adverse event–reporting data from France is summarized in the product label and includes reports of "allergic-type reactions," but more serious allergic events, such as laryngismus or anaphylaxis, are not specifically mentioned [1].

Possible cross-sensitization between the 2 vaccine types resulting in anaphylaxis was reported. Some other allergen could possibly explain this event as well, but clinicians should be cautious about administering these products to patients with

previous allergic reactions to any typhoid vaccine. The Ty21a label describes a single reported event of anaphylaxis [2]. We found 2 additional events without alternative explanations, including the cross-sensitization event, suggesting that this serious allergic event is likely a rare risk for both vaccines.

A review of the reported deaths did not find any evidence, aside from temporal proximity, that these events were causally related to typhoid fever vaccines. GBS was reported for both vaccines. Most events occurred after multiple vaccinations, and the reports lack adequate information to rule out other potential provoking conditions, making causal attribution difficult. GBS reports are periodically received by VAERS [25] and commonly found in adverse events summaries [30, 31]. This may be due in part to the association of GBS with the swine influenza vaccine of 1976–1977 [25], and possibly and rarely other influenza vaccines [32], and because this condition can occur without clear provoking factors. Ideally, the relationship of GBS with all vaccine exposures could be investigated in a controlled epidemiologic study.

Adverse event reporting rates for these vaccines were lower than the rates in other published adverse event summaries [30, 33] except for the similarly distributed meningococcal vaccines [31]. However, quantitative comparisons of adverse event reporting rates between vaccines are limited by differences in vaccinee populations, variable levels of underreporting, and other factors. Underreporting to VAERS may be greater for travelers than among the general population because many events occur while the vaccinees are out of the country [34], potentially explaining the lower rates for these vaccines and the meningococcal vaccines.

Overall, reported adverse events for the licensed typhoid fever vaccines were largely self-limited. Gastrointestinal conditions were frequently reported for both vaccines. The allergic-type reactions discussed are likely to be causally related to the vaccines in some cases, but frequent coadministration with other vaccines, including yellow fever vaccine, makes quantification of this risk difficult. Vaccine administrators should be prepared for such reactions wherever vaccines are provided. Expanded use of these vaccines as counterterrorism agents is not contraindicated by these reports. However, careful consideration of the target population is warranted because military and civilian travelers, who represent most current vaccinees, are likely to be generally healthier than the US population as a whole. We encourage reporting of adverse events after vaccination to VAERS at http://www.vaers.org or (800) 822–7967.

STUDY GROUP MEMBERS

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