MAJOR ARTICLE

Typhoid Fever in Travelers: Who Should Be Targeted for Prevention?

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To clarify indications for typhoid vaccination, we reviewed laboratory-confirmed cases of typhoid fever reported to the United States Centers for Disease Control and Prevention between 1994 and 1999. To estimate the risk of adverse events associated with typhoid vaccination, we reviewed reports to the Vaccine Adverse Event Reporting System for the same period. Acute *Salmonella enterica* serotype Typhi infection was reported for 1393 patients. Of these patients, recent travel was reported by 1027 (74%), only 36 (4%) of whom reported having received a vaccination. Six countries accounted for 76% of travel-associated cases (India [30%], Pakistan [13%], Mexico [12%], Bangladesh [8%], The Philippines [8%], and Haiti [5%]). For 626 travelers who traveled to a single country, the length of stay was ≤1 week for 31 (5%), ≤2 weeks for 100 (16%), ≤3 weeks for 169 (27%), ≤4 weeks for 232 (37%), ≤5 weeks for 338 (54%), and ≤6 weeks for 376 (60%). Reports of serious adverse events due to typhoid vaccination were very rare. Vaccination should be considered even for persons planning short-term travel to high-risk areas.

Typhoid fever is caused by the bacterium *Salmonella enterica* serotype Typhi and is spread primarily through contaminated food and water. Infection with *S.* Typhi causes an estimated 16 million cases of typhoid fever worldwide each year, including 200–400 laboratory-confirmed cases in the United States [1]. The proportion of cases occurring among travelers increased from <30% in 1975 to 75% in 1994 [2, 3]. Treatment with effective antimicrobial agents has reduced mortality from typhoid fever to <1% in the United States, but the global emergence of multidrug-resistant *S.* Typhi threatens this success [4].

One of the goals of the Healthy People 2010 initiative is to increase the proportion of international travelers who receive appropriate preventive services [5]. Vaccination of travelers is an important means of preventing typhoid fever; however, determining which travelers to vaccinate can be challenging. Factors to consider when deciding whom to immunize include the efficacy, adverse effects, and cost of the vaccine, the age and underlying medical conditions of the traveler, and the destination, duration of stay, purpose of travel, and destination-based likelihood of acquiring a resistant strain of *S.* Typhi.

The Advisory Committee on Immunization Practices made recommendations for typhoid immunization in 1994 [6]. They recommended vaccination for the following 3 groups: microbiologists who frequently work with *S.* Typhi, persons with intimate exposure to a documented carrier, and travelers. The recommendations note that risk is greatest for "travelers to developing countries who have prolonged exposure to potentially contaminated food and drink" [6, p. 2].

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Three vaccines against typhoid were available in the United States between 1994 and 1999: an oral live-attenuated vaccine (Ty21a; Vivotif Berna); a parenteral heat-inactivated vaccine (Typhoid vaccine; Wyeth-Lederle); and, after December 1994, a parenteral capsular polysaccharide vaccine (Typhim Vi; Aventis Pasteur SA) [6]. Typhoid vaccine is licensed for children ⩾6 months of age, Typhim Vi for children ⩾2 years of age, and oral Ty21a for children ⩾6 years of age. The available vaccines have relatively equivalent efficacy, which varies from ~50% to 80% [6]. Reactogenicity differs substantially for the 3 vaccines. For example, fever occurred in 0%–1% of those who received the parenteral capsular polysaccharide vaccine, in 0%–5% of those who received the Ty21a vaccine, and in 6.7%–24% of those who received the parenteral heat-inactivated vaccine [6]. On 27 June 2000, marketing of Typhoid vaccine was discontinued in the United States, and all stocks are estimated to have expired by 1 February 2001, leaving children <2 years of age without access to a licensed vaccine (Wyeth-Lederle, personal communication). To clarify indications for typhoid vaccination and to identify high-priority groups for improved vaccine coverage, we reviewed US typhoid fever surveillance data from 1994–1999.

METHODS

We reviewed data from all laboratory-confirmed cases of acute *S.* Typhi infection reported to the US Centers for Disease Control and Prevention's (CDC's) National Typhoid Fever Surveillance System from 1 January 1994 through 31 December 1999. State and territorial health departments voluntarily reported all laboratory-confirmed cases of typhoid fever to CDC during this period. Demographic, epidemiologic, and clinical information collected on surveillance forms included age, sex, occupation, US citizenship, previous immunization against typhoid fever, history of travel in the 30 days preceding illness onset, reason for travel, laboratory data, hospitalization, and illness outcome. In addition, active national surveillance was conducted through state public health laboratories and epidemiology departments from 1 July 1996 through 30 June 1997. A previously published summary of information on cases occurring during that period was also reviewed [4]. The surveillance form used by Ackers et al. [4] differed slightly from the form used in our study and specified a longer time frame (6 weeks) for defining travel outside of the United States. Additional analyses of data from Ackers et al. [4] were performed, and the results were included in the present study.

A case was defined as illness compatible with acute typhoid fever and isolation of *S.* Typhi from a sterile site or a stool or urine sample. Asymptomatic carriers and patients for whom diagnoses were based on results of serologic assays alone were not included.

Cases were defined as travel associated when they occurred in persons who traveled outside of the United States or its territories within 30 days before illness onset, except for cases occurring between 1 July 1996 and 30 June 1997, which were included if they occurred in persons who traveled up to 6 weeks before illness onset because a separate study was conducted during that period. Only persons who received a diagnosis of typhoid fever in the United States were included in our study. Countries were grouped into the regions and subregions outlined in *Health Information for International Travel* [7].

To estimate the risk of adverse reactions, we reviewed all reports to the Vaccine Adverse Event Reporting System (VAERS) for persons who received a typhoid vaccination between 1994 and 1999, excluding foreign and duplicate reports [8]. Standard symptom definitions were used. Hypersensitivity at the injection site was defined by VAERS as "erythema, redness, rash, or localized hives at site of injection." Reports of severe reactions that involved hospitalization were reviewed to assess potential new or unusual adverse events. To obtain information on the number of persons immunized, we reviewed data provided by the 3 vaccine manufacturers. Data were analyzed using Epi Info software, version 6.04 (CDC), and SAS software, version 8 (SAS Institute).

RESULTS

From 1 January 1994 through 31 December 1999, a total of 44 states and 2 US territories reported 1393 laboratory-confirmed cases of acute *S.* Typhi infection (mean, 232 cases/year; range, 159 [1999] to 307 [1994] cases/year). Overall, 74% of the cases were associated with travel (range, 63% [1999] to 79% [1994]). California and New York reported the most cases (29% and 24%, respectively). The median age was 22 years (range, 1 month to 94 years). A total of 7% of the patients were <2 years old, and 41% were 2–17 years old (table 1). Overall, 294 (26%) reported "student" as their occupation; 54% were male. A total of 867 patients (84%) were hospitalized, with a median length of stay of 7 days (range, 1–20 days); 10 (0.7%) died. Microbiology laboratory workers and members of their households accounted for 9 (0.6%) of cases. Only 96 cases (7%) reportedly occurred as part of recognized outbreaks of *S.* Typhi infection [9].

Travel-associated cases. Overall, 1027 cases (74%) were associated with travel. The demographic characteristics of patients with travel-associated cases resembled those of patients with cases acquired in the United States (table 1). The median age of 924 patients with travel-associated cases was 22 years; 64 (7%) were <2 years old, and 310 (34%) were 2–17 years old. Four hundred (47%) of 843 patients with travel-associated cases were reportedly US citizens, compared with 202 (68%) of 295 patients with non–travel-associated cases. Travelers to a

Table 1. Characteristics of US patients with typhoid fever (TF), 1994–1999.

Characteristic	Acquired TF during travel (n = 1027)	Acquired TF in the United States (n = 366)	Total (n = 1393)
Age			
Median years	22	22	22
<6 months	0.3	1.2	0.7
6– 23 months	6.6	7.1	4.5
2–5 years	6.3	11.1	9.9
6–11 years	15.1	10.8	13.9
12–17 years	12.2	10.5	11.7
18–22 years	11.6	9.9	11.1
⩾23 years	47.9	49.4	48.2
Male sex	54.3	53.6	54.1
US citizen	47.4	68.4	52.9
Hospitalized	85	81	83.9
Died, no. of patients	3	7	10

NOTE. Data are percentage of patients, unless otherwise indicated.

total of 64 countries acquired typhoid fever. Among 940 travelers who visited a single country, 53% acquired typhoid fever in the Indian subcontinent (Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka), 17% in Mexico and Central America, 7% in the Caribbean, 3% in Africa, and 4% in other regions. Travel to 6 countries—India (30% of travelers), Pakistan (13%), Mexico (12%), Bangladesh (8%), the Philippines (8%), and Haiti (5%)—accounted for 76% of travel-associated cases. Only 36 travelers (4%) reported having received a typhoid vaccination at any point during the 5 years preceding travel. Only 5 travelers specified the vaccine type; 1 received Typhoid vaccine, 3 received Ty21a, and 1 received Typhim Vi.

Among 147 patients who specified a single reason for travel, 117 (80%) were visiting relatives or friends abroad, 23 (16%) were emigrating to the United States, 5 (3%) were traveling as tourists, and 2 (1%) were traveling for business. Even short-term travel was associated with a risk of typhoid fever. For 626 travelers who traveled to a single country and reported their duration of stay, 31 (5%) stayed ⩽1 week, 100 (16%) stayed ⩽2 weeks, 169 (27%) stayed ⩽3 weeks, 232 (37%) stayed ⩽4 weeks, 338 (54%) stayed ⩽5 weeks, and 376 (60%) stayed ⩽6 weeks (figure 1).

Laboratory results. *S.* Typhi was isolated from blood samples alone in 718 cases (70%), from stool samples alone in 156 (15%), from both blood and stool specimens in 126 (13%), and from blood and stool specimens and samples from other sites in 17 (2%). No source was identified for 10 isolates (1%).

Adverse events. During this same period, 688 adverse events due to vaccine against typhoid, given alone or in combination with other vaccines, were reported to the VAERS (mean, 114.5 adverse events/year). Of these, 297 were reported following administration of vaccine against typhoid alone (mean, 49.5 adverse events/year). Of the 271 reported events for which a specific vaccine brand was identified, 184 (68%) were due to Typhoid vaccine (tables 2 and 3).

Among the 297 persons who received typhoid vaccination alone and for whom information was available, the most commonly reported symptoms were fever (28%), headache (18%), chills (16%), nausea (15%), and hypersensitivity at the injection site (12%). Thirty-one persons (10%) with ⩾1 adverse event following typhoid vaccination alone were reportedly hospitalized, 2 persons (0.007%) had a disability, and none died (table 2). Among the 686 persons who received typhoid vaccination either alone or in combination with ⩾1 other vaccine and for whom information was available, the most commonly reported symptoms were fever (27%), headache (18%), chills (16%), nausea (15%), and hypersensitivity at the injection site (12%). A total of 84 persons (12%) with ⩾1 adverse event following administration of typhoid vaccine, either alone or in combination with other vaccines, were reportedly hospitalized, 7 persons (0.01%) had a disability, and 1 person died (0.001%) (table 3). No unusual pattern of adverse events emerged from the review of serious reports following the concomitant administration of vaccine against typhoid with other vaccines.

On the basis of information on sales and returns provided by the manufacturers, we estimated that ~6.5 million (6,617,878) doses of vaccine were sold over the 6-year period and that 85% of these doses were administered. We estimate that ~5.5 million persons received typhoid vaccination, but we do not know what proportion received it in combination with other vaccines. If we assume that virtually all 5.5 million persons received vaccine against typhoid alone and that all adverse events resulting in hospitalization, disability, or death were reported to VAERS, then an estimated 0.47 per 100,000 vaccinees were hospitalized; 0.03 per 100,000 vaccinees suffered a disability, and 0 per 100,000 vaccinees died. If we assume that nearly all 5.5 million persons received typhoid vaccination along with other vaccinations and that typhoid vaccination was responsible

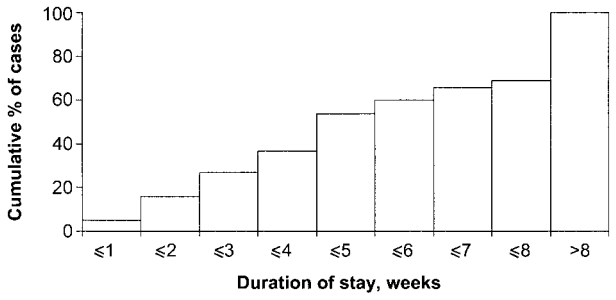

Figure 1. Travel-associated cases of typhoid fever, by duration of stay in weeks, reported in the United States, 1994–1999.

Table 2. Symptoms and severe adverse events among US patients reported to the Vaccine Adverse Event Reporting System after administration of vaccine against typhoid alone, 1994–1999.

Characteristic	Vaccine against typhoid received, % of patients			
	Ty21a (n = 70)	Typhim Vi (n = 17)	Typhoid vaccine (n = 184)	Total (n = 297)[a]
Symptom[b]				
Fever	19	18	37	28
Headache	17	23	21	18
Chills	4	12	19	16
Nausea	29	…	17	15
Hypersensitivity at injection site	1	…	14	12
Severe adverse event[c]				
Hospitalization	7	6	13	10
Disability	1	…	0.5	0.007
Death	…	…	…	…

[a] Includes reports in which the manufacturer was not specified.
[b] Not mutually exclusive. Manufacturer was not specified for 26 reports.
[c] Not mutually exclusive. Manufacturer was not specified for 1 reported hospitalization.

for all resultant adverse events, the rates for hospitalization, disability, and death per 100,000 vaccinees were 1.3, 0.1, and 0.02, respectively.

DISCUSSION

Although typhoid fever is relatively rare in the United States, it remains an important health risk for international travelers. Travelers who acquire typhoid fever were rarely immunized against it, indicating that failure to vaccinate, not vaccine failure, is the primary problem. This is the first review of typhoid fever in the United States since the introduction of the Typhim Vi vaccine, and it covers the period before Typhoid vaccine was removed from the market, which has left children <2 years old without access to a licensed vaccine. It highlights the failure to adequately vaccinate and educate particular groups of travelers at high risk for typhoid fever, including children and students, travelers to the Indian subcontinent, and persons visiting friends or relatives abroad.

Our data also indicate that 37% of travel-associated cases, representing 17% of all typhoid fever cases diagnosed in the United States, occurred among persons who stayed at their travel destination for ≤4 weeks and that ~16% occurred among

Table 3. Symptoms and severe adverse events among US patients reported to the Vaccine Adverse Event Reporting System after administration of vaccine against typhoid in combination with other vaccines, 1994–1999.

Characteristic	Vaccine against typhoid received, % of patients			
	Ty21a (n = 176)	Typhim Vi (n = 90)	Typhoid vaccine (n = 336)	Total (n = 688)[a]
Symptom[b]				
Fever	17	17	34	27
Headache	14	11	24	18
Chills	6	8	21	16
Nausea	19	0	15	15
Hypersensitivity at injection site	8	9	17	12
Severe adverse event[c]				
Hospitalization	5	6	18	12
Disability	1	1	0.3	0.01
Death	0.6	…	…	0.001

[a] Includes reports in which the manufacturer was not specified.
[b] Not mutually exclusive. Manufacturer was not specified for 86 reports of symptoms.
[c] Not mutually exclusive. Manufacturer was not specified for 26 reported hospitalizations and 4 reported disabilities.

persons who stayed for ≤2 weeks. This strongly suggests that vaccination should be considered even for persons planning short-term travel to high-risk areas, such as the Indian subcontinent. The high prevalence of multidrug resistance among *S.* Typhi strains in south Asia further compounds the risk to travelers to that region [4, 10].

Persons, especially children, who travel to visit friends and relatives in countries where typhoid is endemic should be considered to be at high risk. Educational efforts regarding typhoid immunization should be made to clinicians who care for children of first- or second-generation immigrants from high-risk areas and also to health care professionals involved in student-health services. Until newer, more-effective vaccines against typhoid, which are currently being evaluated, are available for children <2 years of age, physicians should encourage caregivers to practice strict food and water precautions and to encourage breast feeding, if possible, while the child is outside of the United States [7, 11, 12]. Although typhoid fever in tourists and business travelers was rare, we still recommend considering vaccination for these groups, particularly if they visit high-risk areas, such as the Indian subcontinent, for ≥2 weeks.

Our analysis included reports of adverse events associated with typhoid vaccine given alone and in combination with other vaccines. Reports of serious adverse reactions due to typhoid vaccine administered alone were very rare. The majority of reports were associated with the now discontinued Typhoid vaccine. Even when vaccine against typhoid was administered concomitantly with other vaccines or medications, the rate of serious adverse events after vaccination was very low. We observed a proportion of serious adverse events in our analysis that was higher than that in a recent study by Beiger et al. [13], which examined reports to VAERS from 1990 through 2002 following vaccination against typhoid. Although the methodologies and study periods differed, the difference was mainly due to the exclusion of the whole-cell Typhoid vaccine, which is no longer distributed.

This study had several limitations. Although the surveillance systems were national in scope, the surveillance data were incomplete both for typhoid fever and for vaccine-related adverse events. We lack precise information on the total number of travelers who were vaccinated for typhoid fever and on the total number of persons traveling to each country from the United States, their age, and their reasons for travel. We suspect that our risk groups overlap; for example, children traveling to the Indian subcontinent are more likely to be visiting friends and relatives than are adults visiting Europe. However, we could not delineate the degree to which confounding occurred, nor could we calculate actual risks. Finally, our data did not permit us to address issues of cost-effectiveness. The main limitations of VAERS include under-reporting, variability in the quality of reported data, and the inability to determine causality [14]. The extent of under-reporting varies, depending on the type and severity of adverse event; severe events that occur in close proximity to the time of vaccination are more likely to be reported than are minor events or events with a long latency period [15].

Nonetheless, vaccination and careful attention to hygiene and to foods and beverages consumed abroad remain the primary means by which travelers can lower their risk of acquiring typhoid fever. Details on typhoid fever and typhoid vaccination are available at the CDC Web site (http://www.cdc.gov/travel/typhoid.htm) or through the CDC fax information service (1-888-CDC-FAXX [232–3299]). In addition, health care professionals may obtain a copy of *Health Information for International Travel* through the Public Health Foundation at http://www.phf.org. Persons experiencing an adverse event following typhoid vaccination should report the event to VAERS at http://www.VAERS.org or by calling 1-800-822-7907.

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References

1. Edelman R, Levine NM. Summary of an international workshop on typhoid fever. Rev Infect Dis **1986**; 8:329–349.
2. Ryan CA, Hargrett-Bean NT, Blake PA. *Salmonella typhi* infections in the United States, 1975–1984: increasing role of foreign travel. Rev Infect Dis **1989**; 11:1–8.
3. Mermin JH, Townes JM, Gerber M, Dolan N, Mintz ED, Tauxe RV. Typhoid fever in the United States, 1985–1994: changing risks of international travel and increasing antimicrobial resistance. Arch Intern Med **1998**; 158:633–8.
4. Ackers ML, Puhr N, Tauxe R, Mintz ED. Laboratory-based surveillance of *Salmonella* serotype Typhi infections in the United States: antimicrobial resistance on the rise. JAMA **2000**; 283:2668–73.
5. US Department of Health and Human Services (USDHHS). Healthy people 2010: understanding and improving health. Washington, DC: USDHHS, **2000**.
6. Centers for Disease Control and Prevention. Typhoid immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep **1994**; 43(RR-14):1–7. Available at: http://www.cdc.gov/mmwr/pdf/rr/rr4314.pdf. Accessed 1 July 2004.
7. Centers for Disease Control and Prevention (CDC). Health information for international travel, 2001–2002. Atlanta: CDC, **2001**.
8. Singleton J. An overview of the vaccine adverse event reporting system (VAERS) as a surveillance system. Vaccine **1999**; 17:2908–17.
9. Olsen SJ, Bleasdale SC, Magnazo R, et al. Outbreaks of typhoid fever in the United States, 1960–1999. Epidemiol Infect **2003**; 130:13–21.
10. Parry C, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. N Engl J Med **2002**; 347:1770–82.
11. Lin F, Ho VA, Khiem HB, et al. The efficacy of a *Salmonella typhi* Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med **2001**; 344:1263–9.

12. Mai NL, Phan VB, Vo AH, et al. Persistent efficacy of Vi conjugate vaccine against typhoid fever in young children. N Engl J Med **2003**; 349:1390–1.
13. Begier EM, Burwen DR, Haber P, Ball R. Postmarketing safety surveillance for typhoid fever vaccines from the Vaccine Adverse Event Report System, July 1990 through June 2002. Vaccine Adverse Event Report System Working Group. Clin Infect Dis **2004**; 38:771–9.
14. Zhou W, Pool V, Iskander JK, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. MMWR Morb Mortal Wkly Rep **2003**; 52(SS-1):1–24.
15. Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. Am J Public Health **1995**; 85:1706–9.