Typhoid Fever in the United States, 1985-1994

Changing Risks of International Travel and Increasing Antimicrobial Resistance

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Background: Typhoid fever is a potentially fatal illness common in the less industrialized world. In the United States, the majority of cases occur in travelers to other countries.

Methods: We reviewed surveillance forms submitted to the Centers for Disease Control and Prevention, Atlanta, Ga, for patients with culture-confirmed typhoid fever between 1985 and 1994.

Results: The Centers for Disease Control and Prevention received report forms for 2445 cases of typhoid fever. Median age of patients was 24 years (range, 0-89 years). Ten (0.4%) died. Seventy-two percent reported international travel within the 30 days before onset of illness. Six countries accounted for 80% of cases: Mexico (28%), India (25%), the Philippines (10%), Pakistan (8%), El Salvador (5%), and Haiti (4%). The percentage of cases associated with visiting Mexico decreased from 46% in 1985 to 23% in 1994, while the percentage of cases associated with visiting the Indian subcontinent increased from 25% in 1985 to 37% in 1994. The incidence of typhoid fever in US citizens traveling to the Indian subcontinent was at least 18 times higher than for any other geographic region. Complete data on antimicrobial susceptibility to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole were reported for 330 (13%) Salmonella Typhi isolates. Isolates from 1990 to 1994 were more likely than isolates from 1985 to 1989 to be resistant to any of these antimicrobial agents (30% vs 12%; P<.001) and to be resistant to all 3 agents (12% vs 0.6%; P<.001).

Conclusions: American travelers to less industrialized countries, especially those traveling to the Indian subcontinent, continue to be at risk for typhoid fever. Antimicrobial resistance has increased, and a quinolone or third-generation cephalosporin may be the best choice for empirical treatment of typhoid fever.

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Typhoid Fever has been rare in the United States since improvements in water and sewage treatment occurred early in this century, but it remains a common illness in many developing countries.1 When typhoid fever occurs in the United States it is most often among individuals exposed to Salmonella serotype Typhi (formerly Salmonella typhi) during international travel. The risk to travelers of acquiring typhoid fever while visiting different areas of the world is likely to change over time, but there is no systematic international surveillance for the disease. Information on risk of typhoid fever to travelers is often used by physicians in recommending preventive measures.

When the diagnosis of typhoid fever is suspected, the initial choice of antimicrobial therapy depends in part on current information about antimicrobial resistance patterns. Recently, strains of Salmonella Typhi resistant to the 3 antimicrobial agents traditionally recommended for treatment of typhoid fever—ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole—have been reported from the Indian subcontinent,2 China,3 Vietnam,4,5 Singapore,6 the Middle East,7,8 South Africa,9 Spain,10 and the United Kingdom.11 National data on typhoid fever are available from 2 sources. One is the Morbidity and Mortality Weekly Report published by the Centers for Disease Control and Prevention, Atlanta, Ga, which collects limited information on all cases of typhoid fever reported by state and territorial health departments—the cases need not be bacteriologically confirmed. The second is the Centers for Disease Control and Prevention typhoid fever surveillance system, which is based on a standard questionnaire voluntarily completed by state and local health departments for bacteriologically confirmed cases of typhoid fever.
METHODS

Completed Centers for Disease Control and Prevention typhoid fever surveillance forms were collected from all states and territories. California and Texas use a slightly different form. No forms were received from New York City; data from there have been presented elsewhere and were not included in this analysis. A case was defined as symptoms compatible with typhoid fever and a culture from a sterile site or stool sample yielding Salmonella Typhi. Patients diagnosed as having typhoid fever by serologic assays alone were not included in this definition. Patients who traveled outside the United States at any time during the month preceding the onset of illness were defined as having travel-associated typhoid fever. Those who had no history of international travel during the month preceding the onset of illness were classified as having domestically acquired typhoid fever. Asymptomatic carriers, defined as people from whom Salmonella Typhi was isolated but whose case report form indicated that they were not ill, were not included as cases. A carrier of Salmonella Typhi is usually defined as an individual whose stool sample culture yielded Salmonella Typhi but who was asymptomatic for 1 year before testing. However, the definition of a carrier identified in association with a reported case in this article was decided by local health officials. An outbreak was defined as 2 or more cases of typhoid fever associated by time and place.

Information on the number of US citizens and residents traveling abroad and foreigners traveling to the United States was obtained from the US Travel and Tourism Administration, Department of Commerce. The primary sources for these travel data are embarkation or debarkation cards (I-92 forms) provided by airplane travelers at the time of arrival, and in-flight surveys of airline passengers. Embar- kation or debarkation cards include only the country of most recent embarkation, which may differ from the original point of departure. This information is coded by the traveler’s citizenship. In-flight survey data provide information on the original country of embarkation, and are thus more accurate than I-92 data; however, the information is coded by the traveler’s country of residence, and is not available for all countries. In this article, rates of typhoid fever for travelers to different regions of the world were calculated using both denominators and presented in tables separately. Travel by land, air, and sea to and from Canada and Mexico is included in data presented for those countries.

Data were analyzed using Epi-Info 6.02 computer software (USD Inc, Stone Mountain, Ga). Proportions were compared using the Fisher exact test. P values were 2-tailed. Antimicrobial susceptibility testing and bacteriophage typing were performed by state and local laboratories; routine bacteriophage typing of sporadic Salmonella Typhi isolates was discontinued at most state public health laboratories by 1988.

RESULTS

From 1985 to 1994, the typhoid fever surveillance system received epidemiological information for 2445 (55%) of 4408 cases of typhoid fever reported in the Morbidity and Mortality Weekly Report. The number of report forms received per year ranged from 129 to 302. Six states—California, Texas, Illinois, Massachusetts, New York, and Florida—accounted for 80% of cases reported to the typhoid fever surveillance system (Table 1). Among patients for whom case reports were received, the median age was 24 years (range, 0-89 years); 54% were male. Of 2254 patients with reported outcome, 10 (0.4%) died. The median age of individuals who died was 27 years (range, 14-81 years); 4 (3.6%) of 71 patients 65 years or older died, compared with 6 (0.3%) of 2183 patients younger than 65 years (P=.001). The median ages for domestically acquired and travel-associated cases of typhoid fever were similar (23.5 years vs 23.4 years), as were the case mortality rates (0.8% vs 0.3%). Five deaths occurred among individuals with travel-associated cases, all of whom were foreign nationals: 2 from Mexico, 1 from El Salvador, 1 from India, and 1 Haitian from the US camp in Guantanamo Bay, Cuba, who died while hospitalized in Florida. The 5 individuals with domestically acquired typhoid fever who died included 3 with underlying illness. None of the 5 patients who died and had a known vaccination history had received typhoid fever vaccine.

TRAVEL-ASSOCIATED TYPHOID FEVER

Of 2328 patients with a known travel history, 1687 (72%) had traveled internationally before their illness. The proportion of typhoid fever cases that were travel associated increased from 65% in 1985 to 75% in 1994, yet the overall rate of travel-associated cases of typhoid fever decreased after 1991—from 3.3 per 1 million travelers for 1989 to 1991 to 2.6 per 1 million travelers for 1992 to 1994. Of 1461 patients who had visited a single country, 80% had visited 1 of 6 countries: Mexico (28%), India (25%), the Philippines (10%), Pakistan (8%), El Salvador (5%), and Haiti (4%). The percentage of travel-associated cases associated with visiting Mexico decreased from 33 (46%) of 71 travel-associated cases in 1985 to 34 (23%) of 145 cases in 1994. The incidence of typhoid fever among travelers to Mexico decreased from 1.9 to 1.3 per million during this time (Figure 1). The percentage of cases associated with visiting the Indian subcontinent (India, Pakistan, Bangladesh, Sri Lanka, and...
Myanmar) increased from 18 (25%) of 71 cases in 1985 to 54 (37%) of 145 cases in 1994, and at the same time the incidence of typhoid fever in travelers to the Indian subcontinent increased from 234 to 812 per million (Figure 2). Of 1921 patients with known citizenship, 57% were US citizens; 65% of cases in US citizens were associated with traveling. The risk of acquiring typhoid fever for US citizen travelers varied according to geographic region visited; for travel to the Indian subcontinent, the risk was at least 18 times higher than the highest rate for travel to any other region (Table 2). The overall rate of typhoid fever in non-US citizens who traveled to a country other than Canada was 2.9 per 1 million individuals, and for US citizens who traveled to a country other than Canada, 2.2 per 1 million individuals.

Forty-one (3%) of 1305 patients with travel-associated cases who had a known vaccination history had reportedly been vaccinated in the 2 years before illness. Twenty-one (51%) of these individuals had traveled to the Indian subcontinent and 7 (17%) had traveled to Southeast Asia. History of vaccination did not vary significantly by citizenship. The frequency of travel-associated typhoid fever increased during the summer and winter months, probably because of increased overseas travel during these times. Students had 16% of all travel-associated cases, and 12% of travel-associated cases among individuals 18 years or older. Eighty-three percent of students with typhoid fever had travel-associated cases; 5% of these had reportedly been vaccinated.

DOMESTICALLY ACQUIRED TYPHOID FEVER

Six hundred forty-one (28%) of 2328 cases in which travel history was known were domestically acquired. Most of these cases were sporadic infections; only 108 (19%) of 571 domestically acquired cases for which data were available were reported to be associated with known outbreaks. The largest outbreak during the study period, associated with 47 culture-confirmed cases, was caused by orange juice contaminated by a foodhandler not previously known by the health department to be a Salmonella Typhi carrier. Of all outbreak-associated typhoid fever cases, 4% were traced to Salmonella Typhi carriers known to the state health department and 39% were traced to new carriers. Among 463 domestic cases not associated with outbreaks, 3.5% were traced to a known carrier and 17% were traced to a new carrier. The source of the majority of domestically acquired cases was unexplained.

A total of 45 patients were health care workers, of whom 13 (29%) had not traveled within the previous month. These 13 health care workers represented 4% of 368 domestically acquired cases with a known occupational history. Seven of the health care workers worked in a microbiology laboratory; 5 of them had no travel history. Only 1 had previously received typhoid fever vaccine. In addition, an unvaccinated 22-year-old student became infected while working with Salmonella Typhi for laboratory practice.

LABORATORY RESULTS

The clinical source of the Salmonella Typhi isolate was identified in 2386 (98%) of 2445 reported cases. In 61% of cases, Salmonella Typhi was isolated from blood samples alone, in 20% from stool samples alone, in 15% from blood

<table>
<thead>
<tr>
<th>State or Territory</th>
<th>No. (%) of Cases Reported* (N=2443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>California</td>
<td>1068 (44)</td>
</tr>
<tr>
<td>Texas</td>
<td>250 (10)</td>
</tr>
<tr>
<td>Illinois</td>
<td>194 (8)</td>
</tr>
<tr>
<td>Massachusetts</td>
<td>159 (7)</td>
</tr>
<tr>
<td>New York†</td>
<td>144 (6)</td>
</tr>
<tr>
<td>Florida</td>
<td>120 (5)</td>
</tr>
<tr>
<td>Washington</td>
<td>75 (3)</td>
</tr>
<tr>
<td>Virginia</td>
<td>59 (2)</td>
</tr>
<tr>
<td>Maryland</td>
<td>52 (2)</td>
</tr>
<tr>
<td>Hawaii</td>
<td>33 (1)</td>
</tr>
<tr>
<td>All other states and territories</td>
<td>289 (12)</td>
</tr>
</tbody>
</table>

*Data based on typhoid fever surveillance forms completed for culture-confirmed cases and submitted to the typhoid fever surveillance system.
†Does not include 579 cases during the same period from New York City that were reported separately.

Figure 1. Incidence of cases of typhoid fever in the United States associated with travel to Mexico (1985-1994).

Figure 2. Incidence of cases of typhoid fever in the United States associated with travel to the Indian subcontinent (1985-1994).
Table 2. Number of Typhoid Fever Cases Reported in the United States and Estimated Rate per Million Travelers, by Region Visited and Citizenship (1985-1994)

<table>
<thead>
<tr>
<th>Area Visited*</th>
<th>No. of Cases in US Citizen Travelers</th>
<th>No. of Cases per 1 Million US Citizen or Resident Travelers†</th>
<th>No. of Cases in Non-US Citizen Travelers</th>
<th>No. of Cases per 10^9 Non-US Citizen or Resident Travelers</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>5</td>
<td>&lt;1</td>
<td>0</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Mexico</td>
<td>104</td>
<td>1</td>
<td>214</td>
<td>4</td>
</tr>
<tr>
<td>Central America</td>
<td>34</td>
<td>6-5</td>
<td>64</td>
<td>16-21</td>
</tr>
<tr>
<td>South America</td>
<td>22</td>
<td>2</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Caribbean</td>
<td>22</td>
<td>&lt;1</td>
<td>27</td>
<td>2-3</td>
</tr>
<tr>
<td>Europe</td>
<td>7</td>
<td>&lt;1</td>
<td>6</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Middle East</td>
<td>2</td>
<td>&lt;1</td>
<td>3</td>
<td>1-2</td>
</tr>
<tr>
<td>Africa</td>
<td>10</td>
<td>4-14</td>
<td>13</td>
<td>9-28</td>
</tr>
<tr>
<td>Asia</td>
<td>Indian subcontinent</td>
<td>182</td>
<td>110-410</td>
<td>212</td>
</tr>
<tr>
<td>Southeast</td>
<td>127</td>
<td>5-12</td>
<td>87</td>
<td>9-12</td>
</tr>
<tr>
<td>Oceania</td>
<td>2</td>
<td>&lt;1</td>
<td>4</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

* Restricted to 1,196 travelers to only one region for whom citizenship data were available.
† Separate denominators for number of travelers to specific regions were calculated using embarkation or debarkation card (I-92 form) and in-flight survey data. When these 2 calculations resulted in different rates of typhoid fever, both are listed.

and stool samples, in 2% from urine samples alone, and in 0.3% from bone marrow specimens. It was infrequently isolated from other sites, including bile (20 cases), wound (4), lymph node (3), abscess (3), cyst (3), appendix (1), cerebrospinal fluid (1), peritoneal fluid (1), knee joint (1), scrotum (1), sputum (1), and spleen (1). All 10 patients who died had Salmonella Typhi isolated from a sterile site: 7 (70%) from blood samples, 2 (20%) from blood and stool samples, and 1 (10%) from cerebrospinal fluid.

Bacteriophage types of isolated Salmonella Typhi strains were reported for 648 cases (27%). Forty-one different bacteriophage types were reported; the most common types were degraded Vi (31%), E1 (18%), A (10%), 38 (7%), M1 (4%), and E2 (4%). Travel-associated and domestically acquired cases of typhoid fever did not differ with respect to distribution of bacteriophage types. Bacteriophage types were reported for Salmonella Typhi isolates from 10 patients who had received typhoid fever vaccine; each was a different type. Bacteriophage typing was available for only 1 isolate from a patient who died; the isolate was type E1.

ANTIMICROBIAL RESISTANCE DATA

Complete information on antimicrobial susceptibility to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole was reported for 330 Salmonella Typhi isolates (13%). Of these, 71 (22%) were resistant to at least 1 antimicrobial agent and 21 (6%) were resistant to all 3 agents. Isolates from 1990 to 1994 were more likely than isolates from 1985 to 1989 to be resistant to any of these antimicrobial agents (30% vs 12%, P < .001) and to be resistant to all 3 agents (12% vs 0.6%; P < .001) (Figure 3). In 322 cases in which complete antimicrobial susceptibility data and travel information were available, isolates from travel-related cases were no more likely to be resistant to at least one antimicrobial agent than were isolates from domestically acquired cases (21% vs 20%), nor were they significantly more likely to be resistant to all 3 agents (7% vs 4%; P = .33). However, 16 (94%) of 17 isolates from travel-associated cases that were resistant to all 3 agents were associated with travel to the Indian subcontinent, and 1 (6%) with travel to Central America. Since 1990, 14 (30%) of the 46 isolates with available susceptibility data from travelers to the Indian subcontinent were resistant to all 3 agents. Four (19%) that were resistant to all 3 agents were domestically acquired. Information on antimicrobial resistance was reported for 7 of the 10 isolates from individuals who died; only 1 isolate was resistant, and only to ampicillin.

COMMENT

Typhoid fever, a rare infection in the United States, is increasingly related to foreign travel. The annual number of cases has remained relatively stable, with an average of 445 cases reported each year in the Morbidity and Mortality Weekly Report from 1967 to 1994; however, the proportion related to foreign travel has increased: 33% for the period of 1967 to 1972,16,17 62% for 1975 to 1984,12 and 72% for 1985 to 1994. At least for the last decade, this change has paralleled the increasing number of US citizens traveling outside the United States (from 26 million trips in 1985 to 34 million trips in 1994) and the increasing number of foreign nationals visiting the United States (from 24 million trips in 1985 to 46 million trips in 1994).16,17

The incidence of typhoid among travelers appears to have declined since 1991, for unclear reasons. One possibility is that more travelers are vaccinated. Until 1991, only the standard parenteral typhoid fever vaccine was available in the United States; in that year an oral vaccine (Ty21a) was licensed for use in this country.20 Use of this oral vaccine may have increased vaccine coverage and reduced overall rates of typhoid fever among travelers.

In recent years, travelers to the Indian subcontinent have been at highest risk for acquiring typhoid fe-
However, while the incidence of typhoid fever in visitors to the Indian subcontinent increased between 1985 and 1992, it decreased from 1992 to 1994 (Figure 1). This recent decrease may be due in part to preventive measures taken by countries to control epidemic cholera because of *Vibrio cholerae* O139 Bengal, which first appeared in India in 1992 and rapidly spread throughout southeast Asia. Similarly, the risk of acquiring typhoid fever for visitors to Mexico has decreased during the past decade, and this may be partially attributable to improved sanitary measures taken in the early 1990s in response to the Latin American cholera epidemic. For example, improvements in sanitation in Chile in response to cholera dramatically reduced the incidence of typhoid fever in that country. Travelers to both Latin America and the Indian subcontinent may also have taken increased precautions during these times to reduce their risk of acquiring cholera during the widely publicized epidemics.

The increased incidence of typhoid fever in travelers who were not US citizens may reflect increased risk to homeland visitors (individuals returning to the United States from their country of origin or from visiting family or friends abroad). Homeland visitors may be less likely than traditional tourists to receive prevention messages before traveling, to seek vaccination for typhoid fever, or to avoid high-risk foods and beverages. They might also visit rural areas with poor sanitation more frequently than would traditional tourists. In addition, some cases among non–US citizens may have occurred in residents of countries with endemic typhoid fever who acquired the infection there but were diagnosed during a visit to the United States.

Travel-associated typhoid fever is largely preventable. Travelers to less industrialized countries should be encouraged to take routine precautions in selecting and preparing foods and beverages: cooked foods should be eaten hot, raw fruits and vegetables should be peeled by the traveler, and only low-risk beverages should be consumed, such as hot drinks, carbonated beverages without ice, and water that has been boiled or chemically disinfected. In addition, vaccination against typhoid fever is recommended for travelers visiting countries with endemic disease. Three vaccines are licensed for use in the United States: the parenteral killed bacterial vaccine, the live oral vaccine, and an improved parenteral vaccine (VicPS) licensed in 1995. Both the oral and new parenteral vaccine are equally effective and rarely cause adverse reactions. In this article, only 3% of patients with travel-associated cases, and none of those who died, were reported to have received typhoid fever vaccine.

During the 10-year study period, the majority of domestically acquired cases had no identifiable source. Bacteriophage typing of *Salmonella* Typhi isolates has historically been most useful in investigating outbreaks by suggesting similarity of isolates and common geographic origin; however, it has become less common in recent years because it has rarely proved useful in finding links among sporadic cases and is time and resource consuming. The similarity in distribution of bacteriophage types between travel-associated and domestically acquired cases suggests that many domestically acquired cases might be associated with unrecognized *Salmonella* Typhi carriers who have traveled to or resided in other countries. Developing a standard molecular subtyping method for *Salmonella* Typhi that would provide finer strain distinctions than bacteriophage typing could prove useful.

Students made up a lower proportion of all cases in this 10-year period compared with the years 1975 to 1984 (16% vs 30%). This decrease may reflect increased education and vaccination coverage by university health services. Microbiology laboratory workers continue to be at risk for typhoid fever and should be vaccinated if they anticipate contact with specimens from patients with typhoid fever or with isolates of *Salmonella* Typhi. *Salmonella* Typhi should not be used in student experiments or quality control proficiency testing.

The reported incidence of typhoid fever in this article underestimates the actual incidence for several reasons: (1) forms were completed for only culture-confirmed cases; (2) cases of typhoid fever diagnosed and treated outside the United States were not reported; (3) forms were completed only for cases investigated by local or state health departments; and (4) cases from New York City were not included in the analysis. In addition, complete antimicrobial resistance patterns were reported for only 13% of cases. Nevertheless, because of standard reporting procedures, comparisons among countries and years should reliably reflect trends.

Although surveillance forms from New York City were not available, data previously reported for 479 cases of typhoid fever in New York City between 1980 and 1990 are comparable with information presented in this article for the rest of the United States. In New York City, 71% of cases were associated with travel compared with 72% in the rest of the country, and the median age was 24 years for both groups. Travel to Mexico, India, the Philippines, and Pakistan was associated with 44% of cases in New York City, compared with 71% of cases in the rest of the United States.

Deaths related to typhoid fever remain rare in the United States, probably because of rapid treatment with effective antimicrobial agents. In countries with en-
emic typhoid fever, infection with antimicrobial-resistant Salmonella Typhi has been associated with increased morbidity and mortality.\textsuperscript{5,6} The proportion of typhoid fever cases in the United States caused by antimicrobial-resistant strains of Salmonella Typhi has dramatically increased during the past 20 years. From 1975 to 1984, only 5\% of isolates were resistant to at least 1 of the antimicrobial drugs commonly used for treatment (ampicillin, chloramphenicol, or trimethoprim-sulfamethoxazole), and 0.1\% were resistant to all 3 antimicrobial agents.\textsuperscript{12} From 1990 to 1994, 30\% were resistant to at least 1, and 12\% were resistant to all 3 of these agents. As antimicrobial-resistant strains of Salmonella Typhi occur increasingly in the United States, the mortality rate may rise. Because Salmonella Typhi strains resistant to multiple antimicrobial agents appear to constitute an increasing proportion of both travel-associated and domestically acquired cases, ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole should no longer be first-line empirical therapy. A quinolone or third-generation cephalosporin, to which resistance remains rare,\textsuperscript{2,26-28} may be the best empirical antimicrobial therapy for cases of typhoid fever in the United States.

The incidence of typhoid fever in the United States depends closely on its incidence in other countries. The appearance of antimicrobial-resistant strains of Salmonella Typhi in the less industrialized world and in travelers to the less industrialized world emphasizes the need for prudent use of antimicrobial agents everywhere. Travelers can lower their risk of typhoid fever by carefully selecting foods and beverages and undergoing vaccination. However, the elimination of typhoid fever in the United States will ultimately depend on improving health and sanitation throughout the world.

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REFERENCES