

Enteric (Typhoid) Fever in Travelers

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The incidence of enteric (typhoid) fever in travelers is estimated to be ~3–30 cases per 100,000 travelers to developing countries. Recently, it is become clear that travelers who are visiting friends and relatives, especially travelers to the Indian subcontinent, seem to be the most vulnerable to enteric fever and require special attention for prevention. Recent concerns are the increasing incidence of paratyphoid fever in Asia, which is not covered by available typhoid vaccines, and the emergence of infections caused by antibiotic-resistant strains (including strains resistant to fluoroquinolones). Typhoid vaccination is recommended for most travelers to moderate- to high-risk countries. Because of the nonspecific clinical presentation of enteric fever, a high index of suspicion is important in febrile travelers who have traveled to areas of endemicity.

Enteric (typhoid or paratyphoid) fever is a systemic illness caused by *Salmonella enterica* serotype Typhi or *S. enterica* serotype Paratyphi. *S. Typhi* and *S. Paratyphi* are highly adapted to humans and have no nonhuman animal or environmental reservoirs. Enteric fever is acquired by ingestion of fecally contaminated food or water. Continued excretion of large numbers of bacteria by asymptomatic carriers or individuals who have recently recovered from enteric fever is common and is a major source of spread for an epidemic. In areas of endemicity, enteric fever is associated with drinking contaminated water, eating food prepared outside the home, having a close relative with enteric fever, and poor housing. A recent study from Indonesia identified consumption of food from street vendors and flooding as being independently associated with paratyphoid fever [1]. In contrast, typhoid fever was associated with household risk factors, such as presence of a household member with recent typhoid fever, lack of soap for hand washing, and sharing food from the same plate.

It is estimated that there are 22 million new cases of enteric fever annually, with 200,000 deaths [2]. Most cases are confined to the developing world, where the disease is endemic, with the greatest burden being in the Indian subcontinent and in Southeast Asia (figure 1). Regions with the highest incidence of enteric fever (>100 cases per 100,000 persons per year) are south-central

Asia and Southeast Asia. Regions of medium incidence (10–100 cases per 100,000 persons per year) include the rest of Asia, Africa, Latin America and the Caribbean, and Oceania, except for Australia and New Zealand. In Delhi, India, the incidence of enteric fever is 9.8 cases per 1000 person-years [3].

In developed countries, enteric fever is a sporadic disease that occurs mainly in returned travelers. Overall, it has been estimated that the incidence of typhoid among travelers to developing countries is 3–30 cases per 100,000 travelers [4]. Recent travel was reported by 74% of patients with typhoid fever reported to the United States Centers for Disease Control and Prevention between 1994 and 1999 [5]. More than one-half of these patients had traveled to the Indian subcontinent (i.e., Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka), 17% had traveled to Mexico and Central America, 8% had traveled to The Philippines, and 5% had traveled to Haiti. Another study in the United States from 1985–1994 revealed that the incidence of typhoid fever among US citizens who traveled to the Indian subcontinent was at least 18 times higher than for any other geographic region [6]. Similarly, in a 10-year retrospective study of 41 patients with typhoid or paratyphoid fever in a Parisian hospital, almost 30% of patients were from the Indian subcontinent [7]. Although the number of reported enteric fever cases in the United States has remained stable at ~400 hundred cases per year, the proportion of enteric fever cases ascribed to travel outside of the United States has increased from 62% for 1975–1984 to 72% for 1985–1994 and to 81% for 1996–1997 [8].

Recently, a subgroup of travelers who visit friends and relatives has been highlighted as being at increased risk (compared

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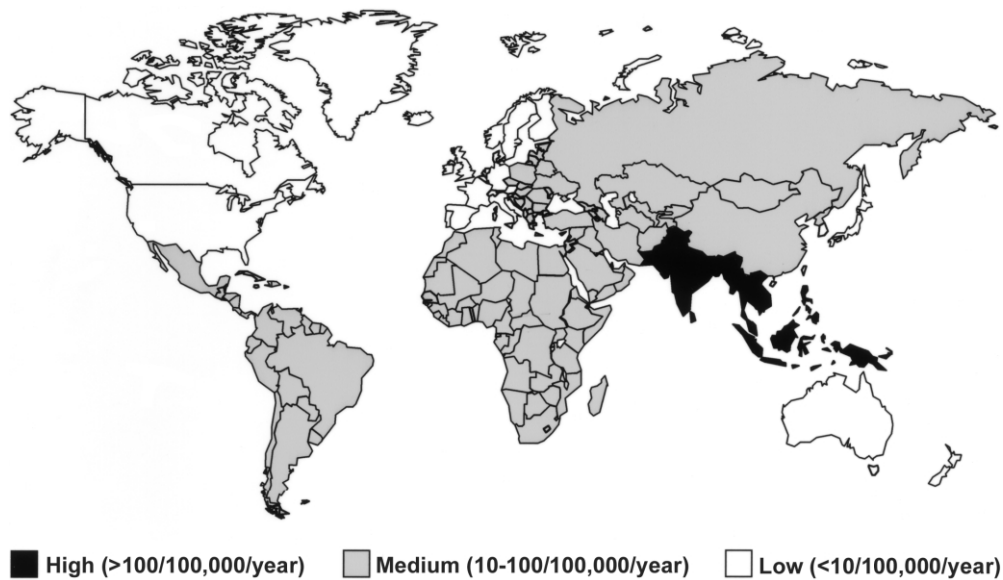


Figure 1. Geographic distribution of enteric fever. Values are no. of cases per 100,000 population per year. From [2]. (Permission was granted by the World Health Organization for reproduction in this journal.)

with other travelers) for several infections, including enteric fever [9]. In the United States, this group is made up largely of foreign-born US residents and their children who return to visit their countries of origin; these people make up >40% of all resident travelers abroad. While staying with family members or friends, these travelers may have less control over their diet and be more likely to drink untreated water and to eat uncooked foods. A 1-year review of all reported travel-related cases of typhoid fever in the United States showed that tourists accounted for 4% of cases, whereas travelers visiting friends and relatives accounted for >40% [8].

INCREASING PARATYPHOID FEVER

Over the past decade, there is a disproportionate increase in the incidence of enteric fever caused by *S. Paratyphi A* in the Indian subcontinent [10–13]. In one New Delhi laboratory, the proportion of *S. Paratyphi A* isolations in cases of enteric fever increased from 6.5% in 1994 to 44.9% in 1998 [11]. Increasing numbers of *S. Paratyphi A* infection have also been noted elsewhere in India [12, 13] and in Nepal [14]. Of 42 cases of enteric fever in travelers presenting to a travel clinic in Nepal during a 16-month period in 1987–1988, a total of 20 were caused by *S. Typhi*, and 22 were caused by *S. Paratyphi A* [15]. Interestingly, molecular analysis by PFGE has indicated that recent outbreaks of *S. Paratyphi A* infection in India are due to a restricted number of clones [16–18]. Similarly, the high proportion of *S. Paratyphi A* infection in Nepal during 2001 was due to the emergence of a single clone [19]. In contrast, the greater genetic diversity among *S. Typhi* isolates suggests endemic disease from multiple sources.

One important implication for travelers of the emergence of infection due to *S. Paratyphi A* is the reduced efficacy of typhoid vaccines to these strains. There is currently no licensed vaccine against *S. Paratyphi A*. In addition, the emergence of *S. Paratyphi A* as a cause of enteric fever in some areas in India has been followed by an increasing incidence of infection due to antibiotic-resistant *S. Paratyphi A* [20]. These issues are discussed further below.

ANTIMICROBIAL RESISTANCE

In 1948, chloramphenicol revolutionized the treatment of typhoid fever, but in 1972, plasmid-mediated, chloramphenicol-resistant typhoid became a major problem. In 1989, multidrug-resistant *S. Typhi* appeared, with the emergence of strains resistant to chloramphenicol, ampicillin, trimethoprim, streptomycin, sulfonamides, and tetracycline. The prevalence of multidrug-resistant *S. Typhi* has also increased among travelers. The rate of multidrug-resistant *S. Typhi* infection in American travelers acquired in India increased from 30% in 1990–1994 to 35% in 1996–1997, and 4 of 5 travelers with typhoid fever acquired in Vietnam were infected with multidrug-resistant strains [8]. Increasing rates of multidrug-resistant strains of *S. Paratyphi A* have also been reported among travelers. In European travelers, the rate of multidrug-resistant *S. Paratyphi A* increased from 9% in 1999 to 25% in 2000 [21].

As a consequence of the emergence of multidrug-resistant strains of *S. Typhi* and *S. Paratyphi*, quinolones have become the mainstay in many areas for the treatment of enteric fever. Unfortunately, quinolone resistance has also developed in both *S. Typhi* and *S. Paratyphi*, especially in Asia, where it has be-

come a major problem. Many of these quinolone-resistant strains are found to be resistant to nalidixic acid by in vitro testing, but MICs of fluoroquinolones (e.g., ciprofloxacin and ofloxacin) remain in the susceptible range according to widely used interpretive criteria [22]. Furthermore, these fluoroquinolone-susceptible, nalidixic acid-resistant strains may be associated with intermediate susceptibility to fluoroquinolones and clinical failure or delayed response in fluoroquinolone-treated patients [23]. This has prompted the Clinical and Laboratory Standards Institute (formerly NCCLS) to recommend testing for nalidixic acid resistance in all extraintestinal *Salmonella* isolates and to inform clinicians that fluoroquinolone-susceptible, nalidixic acid-resistant isolates may not be eradicated by fluoroquinolone treatment [24].

Nalidixic acid-resistant strains of *S. Paratyphi A* are also being seen in travelers to the Indian subcontinent [21]. This is important, because the vast majority of cases of typhoid fever among travelers come from this region, and the current typhoid vaccines are ineffective against *S. Paratyphi A*.

CLINICAL FEATURES

Typhoid and paratyphoid fever in travelers generally produce indistinguishable clinical features. Most people with enteric fever present with a nonspecific febrile illness, often with an insidious onset, after an incubation period of 7–14 days (range, 3–60 days). Headache, malaise, myalgia, and dry cough are common, and the spleen enlarges. Arthralgia is less common for typhoid and paratyphoid fever than for rickettsial illnesses. The slowly increasing fever in a “stepladder” pattern is uncommon, although fever does tend to worsen as the disease progresses. Often times, there are sudden episodes of shaking chills and rigor that resemble symptoms of fever due to malaria. Constipation and relative bradycardia are common but not necessary for the diagnosis. Rose spots (2–3 mm pink-red macules on the chest and abdomen that blanch with pressure but that are fleeting in appearance and difficult to detect in dark-skinned individuals) may appear, are often unnoticed, and may be more prominent in cases of paratyphoid fever. A variety of neuropsychiatric and focal features may occur.

Complications occur in 10%–15% of patients and probably are more common in patients who have been ill for >2 weeks [25]. Gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy are the important complications. Travelers usually seek advice more promptly than do local patients; thus, these complications are usually less common in the traveler population.

Relapse occurs in 5%–10% of patients, usually 2–3 weeks after the resolution of fever [26]. Relapses are typically milder than the original attack, and the bacterial isolate from the relapse usually has the same antibiotic susceptibility pattern as the original isolate. Importantly, ~1%–5% of patients with en-

teric fever become long-term, asymptomatic carriers who may shed *S. Typhi* in either the urine or stool for >1 year [25]. Chronic carriage rates are higher among women and among persons with biliary abnormalities, such as gallstones.

The average case-fatality rate in the nontraveler population is generally <1%, compared with 15% in the preantibiotic era. The rate is probably even lower in the traveler population when there is, in general, less of a delay in the institution of effective antibiotic therapy, the latter being the most important contributor to a poor outcome. The case-fatality rate is highest among children <1 year of age and among elderly persons. In another recent study that involved returned Israeli travelers, the clinical presentation, rate of complications and relapses were similar for infections with *S. Typhi* and *S. Paratyphi*, clearly suggesting that the latter may not be less benign than *S. Typhi* [27].

The differential diagnosis in a traveler with suspected enteric fever is broad. Other considerations for patients returning from areas of endemicity with an undifferentiated febrile illness include malaria, rickettsial diseases (including murine and scrub typhus), leptospirosis, dengue, hepatitis, and amebic liver abscess.

DIAGNOSIS

The clinical diagnosis of enteric fever can be difficult because of the nonspecific nature of symptoms and signs. A travel history to the Indian subcontinent or to other areas of endemicity in a febrile patient should alert the physician to the possibility of enteric fever. In patients with enteric fever, the peripheral WBC count is usually normal to low, and mild hepatic involvement may be reflected in slightly abnormal liver function test results. The definitive diagnosis of enteric fever requires the isolation of *S. Typhi* or *S. Paratyphi* from specimens of blood, bone marrow, or another extraintestinal site. Blood cultures are the standard diagnostic method, and the results can be positive in 60%–80% of patients, provided that a large volume of blood (typically 15 mL for adults) is cultured. Bone marrow cultures increase the diagnostic yield of blood cultures by ~30%, reflecting a higher concentration of bacteria in this sample type. The results of stool cultures are positive for ~60% of children and ~25% of adults with enteric fever; for the detection of carriers, several samples should be examined because of the irregular nature of shedding [26]. *S. Typhi* is occasionally excreted in the urine, especially in the presence of structural abnormalities of the urinary tract, including *Schistosoma haematobium* infection.

Several serologic tests have been developed to detect *S. Typhi* antibodies. The role of the classic Widal test is controversial, with divergent views on the test's utility in various areas of endemicity. Newer rapid *S. Typhi* antibody tests may be useful in areas where enteric fever is endemic and resources are limited [28]. However, no current serologic test is sufficiently sensitive or specific to replace culture-based tests for the diagnosis of enteric fever in developed countries.

Table 1. Treatment of enteric fever in adults.

Treatment type, antibiotic	Dosage (route)	Duration, days
Empirical treatment		
Ceftriaxone ^a	60 mg/kg/day (intravenous or intramuscular) ^b	7–14
Azithromycin	8–10 mg/kg/day (oral)	7
Treatment of fully drug-susceptible infection		
Ciprofloxacin (first-line treatment) ^c	15 mg/kg/day (oral or intravenous)	5–7
Amoxicillin (second-line treatment)	75–100 mg/kg/day (oral or intravenous)	14
Chloramphenicol	75 mg/kg/day (oral, intravenous, or intramuscular)	14–21
Trimethoprim-sulfamethoxazole	8/40 mg/kg/day (oral or intravenous)	14
Treatment of multidrug-resistant infection		
Ceftriaxone ^a	60 mg/kg/day (intravenous or intramuscular) ^b	5–7
Ciprofloxacin ^c	15 mg/kg/day (oral or intravenous)	7–14
Azithromycin	8–10 mg/kg/day (oral)	7
Treatment of fluoroquinolone-resistant infection		
Ceftriaxone ^a	60 mg/kg/day (intravenous or intramuscular) ^b	7–14
Azithromycin	8–10 mg/kg/day (oral)	7
High-dose ciprofloxacin ^c	20 mg/kg/day (oral or intravenous)	10–14

^a Or other third-generation cephalosporins (e.g., cefotaxime and cefixime).

^c Or ofloxacin

^b Intramuscular administration with 1% lidocaine.

TREATMENT

Administration of effective antibiotics, careful attention to fluid and electrolyte balance, and prompt recognition of complications are central to the treatment of enteric fever. Randomized, controlled trials of treatment for enteric fever come from regions where it is endemic. Such data are lacking for travelers with enteric fever, although there is no reason to believe that there would be any appreciable difference in treatment efficacy from residents of areas of endemicity.

In the treatment of the traveler with enteric fever, the antibiotic susceptibility of the infecting strain is crucial in determining which drug to use. The antibiotics of choice for treating enteric fever are shown in table 1. Fluoroquinolones appear to be the most effective antibiotics when infection is caused by fully susceptible strains and are widely used for empirical treatment of enteric fever. However, the increasing incidence of quinolone resistance is limiting the use of this class of antibiotic. Ceftriaxone and other third-generation cephalosporins are a good choice for empirical therapy for travelers with suspected typhoid fever. An oral third-generation drug, cefixime, has also been studied and found to be effective [26, 29]. However, recent anecdotal reports and an ongoing clinical trial in Kathmandu have raised questions about the efficacy of cefixime in the treatment of enteric fever (B.B.; data not shown). Gatifloxacin, which is currently being studied in Nepal, appears to be promising. A traveler returning from the Indian subcontinent or other areas of endemicity with high fever but otherwise normal physical examination findings and sometimes with splenomegaly or a normal or low WBC count needs to be considered for

empirical therapy, even as the results of other tests (such as malaria smears and blood cultures) are pending. The time to fever clearance for these third-generation cephalosporins is ~1 week, although many patients feel subjective improvement at the time of initiation of therapy with ceftriaxone or cefixime. The treatment failure rate is ~5%–10% [26]. Importantly, the fecal carriage rate is <3%, and the relapse rate is 3%–6%. Although it has been recommended that maximum dosages of ciprofloxacin (20 mg/kg/day) or ofloxacin (20 mg/kg/day) given for a minimum of 10 days can be used to treat infections with nalidixic acid-resistant strains, there are some drawbacks to this approach. In particular, long times to fever clearance and high rate of fecal carriage during convalescence have been noted [26].

One of the main reasons for the emergence of fluoroquinolone-resistant *S. Typhi* and *S. Paratyphi* in Asia is the widespread availability of relatively cheap, generic fluoroquinolones that can be purchased without prescription.

Azithromycin, which can be given orally, has shown promise in a limited number of trials [26, 30], with fever clearance times of 4–6 days and with rates of relapse and convalescent-phase fecal carriage of <3%. Aztreonam and imipenem are expensive potential third-line drugs.

Despite demonstrating *in vitro* killing of salmonellae, first- and second-generation cephalosporins and aminoglycosides are ineffective in treating enteric fever. Gentamicin is widely used as therapy for gram-negative sepsis. However, it is important to note that this antibiotic is not used empirically to treat gram-negative bacteremia in patients who have recently been visiting areas where enteric fever is endemic.

Eradication of the chronic carrier state is important to stop the spread of the disease and can be achieved in >80% of cases with high-dose ampicillin/amoxicillin with probenecid for 3 months or with ciprofloxacin for at least 4 weeks [26, 31]. Successful treatment depends on the susceptibility of the organism. Cholecystectomy may be an important adjunct to antibiotic therapy in chronic carriers with cholelithiasis [25].

VACCINATIONS

Table 2 summarizes the different vaccinations against typhoid fever. The 2 most readily available vaccines are the parenteral capsular polysaccharide vaccine and the oral live, attenuated vaccine. A potentially useful Vi vaccine conjugated to a nontoxic recombinant *Pseudomonas aeruginosa* was recently evaluated in Vietnam and shown to have protective efficacy of 91.5% [32]. Neither of the 2 commercially available vaccines give full protection to the traveler (efficacy rates, 50%–80%); therefore, the other protective measures suggested below must be followed. The oral Ty 21 a vaccine is available in Europe as a 3-dose vaccine, although in the United States and Canada, for travelers going to areas of endemicity, 4 doses of the vaccine are administered on the basis of a study that showed that 4 doses were more protective for the local population in endemic areas than 2 or 3 doses [33]. Circumstantial evidence indicates that typhoid vaccine does offer protection to travelers visiting areas of endemicity. In a study undertaken in Nepal, the rate of typhoid fever was 7 times higher among 243 Israeli travelers treated at a Western clinic for all causes than among 2866 other tourists [34]. The rate of vaccination against typhoid for the Israeli tourists was 6%, compared with 91% for the other Western tourists. In addition, in a recent study of American travelers, of 1027 patients with travel-associated typhoid fever, only 36 (4%) had undergone typhoid vaccination [5].

Both the US Centers for Disease Control and Prevention and the World Health Organization recommend typhoid vaccination for persons traveling to countries where enteric fever is endemic. These vaccines need to be given at least 2 weeks before departure. However, none of these vaccines seem to provide any protection against *S. Paratyphoid A*. Unfortunately, at present there is no commercially available vaccine in the United States for the child traveler aged <2 years [5].

Importantly, enteric fever is a risk even for short-term travel to high-risk areas (i.e., it does not take long-term travel to acquire enteric fever, as was suggested by some older guidelines). Of 262 American travelers with typhoid fever who reported their duration of stay in the area of endemicity, 5% stayed <1 week, 16% stayed <2 weeks, 27% stayed <3 weeks, 37% stayed <4 weeks, 54% stayed <5 weeks, and 60% stayed <6 weeks [5]. Unfortunately, these data were not accompanied by estimated risks for each duration of stay. In general, vaccination should be considered for backpackers traveling to areas of endemicity, for immunocompromised travelers, and for persons with severe atherosclerotic disease, internal prosthesis, and cholelithiasis, because such persons are most likely to have complicated disease should infection occur [35]. In addition, many travel medicine doctors think that widespread vaccination of the local population will help decrease the incidence of enteric fever among both the local population and travelers to the area. Crucially paratyphoid vaccine are urgently needed, and a bivalent preparation would be ideal. Finally, pregnant travelers to an area where enteric fever is endemic should receive the parenteral capsular polysaccharide vaccine.

OTHER PRECAUTIONS

The recent notification of *S. Typhi* as a potential weapon of bioterrorism has helped to rekindle interest in the important

Table 2. Summary of vaccines against typhoid fever.

Vaccines against typhoid fever	Age of recipients, years	Regimen	Adverse effects and comments
Oral, live attenuated Ty 21 a vaccine (Vivotif Berna) ^a	>6	Given on days 1, 3, 5, and 7; booster given every 5 years; in Europe, it is available as a 3-dose vaccine	Live, attenuated vaccine should not be given to immunocompromised persons or persons receiving antibiotics; vaccine is well tolerated (50%–80% effective); rare adverse effects include abdominal pain, nausea, and vomiting
Parenteral capsular polysaccharide vaccine (Typhim Vi, Aventis Pasteur SA) ^a	>2	Given in 1 dose with a booster every 2 years	Vaccine is well tolerated (50%–80% effective); adverse effects include headache (16%–20% of recipients) and fever (0%–1%)
Acetone-killed whole cell vaccine ^b
Modified Vi vaccine conjugated to nontoxic recombinant <i>Pseudomonas aeruginosa</i> exotoxin A	>2	Given in 2 parenteral doses	Vaccine was well tolerated and had the highest efficacy rate (90%); vaccine may even be immunogenic for infants aged <2 years; vaccine is not commercially available at present

^a Not be administered to people with acute febrile illness.

^b Available for use only by the US military.

precautionary measures to help avoid infection with this organism. When traveling to areas of endemicity, travelers have to make sure that drinking water is boiled or properly bottled. Food should be thoroughly cooked and preferably steaming hot when served. Fresh vegetables and fruits that have been washed in unclean water may be sources of infection. The maxim “boil it, peel it, or throw it” clearly applies in the control of this illness. Breast-feeding of infants may need to be encouraged during travel to areas of endemicity. Clearly, eating food from street vendors is a risk for enteric fever, especially for enteric fever due to *S. Paratyphi A* [1].

Finally, travelers visiting friends and relatives—especially those going to the Indian subcontinent—need to be targeted for the prevention of enteric fever. Travel medicine has evolved around the tourist industry, and this approach may be ineffective in these travelers who may have preconceived health beliefs of low personal risk for illness abroad and may drink tap water, eat uncooked vegetables, and not obtain typhoid and other vaccines.

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