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Imported Enteric Fever: Case Series from the Hospital for Tropical Diseases, London, United Kingdom

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Abstract. Our current knowledge of the clinical characteristics of enteric fever is drawn mainly from population-based studies in disease-endemic countries, and there are limited data published on cases in returning travelers. We report the clinical characteristics of enteric fever in 92 travelers returning to London, United Kingdom. *Salmonella typhi* and *S. paratyphi* resulted in an almost indistinguishable clinical picture. Rose spots and relative bradycardia were found only in a few patients. A total of 91% of the patients had a normal leukocyte count, which was associated with a markedly increased level of alanine aminotransferase in 82%. A total of 57% of the *S. typhi* isolates had decreased susceptibility to ciprofloxacin and resistance to nalidixic acid; these isolates were from southern Asia. Thirty percent were multidrug resistant; all were from southern Asia and Nigeria. None of the paratyphoid isolates were multidrug resistant but rates of decreased susceptibility to fluoroquinolones were higher than in *S. typhi* (74%).

INTRODUCTION

Enteric fever is an infection caused by either typhoid bacteria (*Salmonella enterica* serotype typhi) or paratyphoid bacteria (*S. enterica paratyphi* A, B, and C). The disease remains a serious public health problem in southern and Southeast Asia where the incidence can be as high as 100 cases/100, 000 population/year. It is estimated that enteric fever causes 22 million episodes of illness and more than 200,000 deaths globally each year.[1,2] Enteric fever is still seen in resource-rich areas usually as an imported infection among travelers and migrants. Occasional infections occur in contacts of asymptomatic carriers of *S. enterica*. Estimates of the incidence of enteric fever among returning travelers are 3–30 cases/100,000 travelers.[3]

Since 2000, all patients admitted to the Hospital for Tropical Diseases in London have had their clinical and laboratory data prospectively entered into a database. Over the past 9 years, we have seen 92 cases of microbiologically confirmed enteric fever. We report the demographic, clinical, and laboratory features of these patients and their response to treatment, in what we believe is the largest series of enteric fever in adult returning travelers in the literature to date.

METHODS

A case of enteric fever was defined as isolation of *S. enterica* serotypes typhi or paratyphi A, B, and C from a sterile site (blood, bone marrow aspirate, or urine) or isolation from stool in a patient with clinical features compatible with enteric fever.

Cases were identified from a database of all adult patients admitted to the Hospital for Tropical Diseases during 2000–2009, where the diagnosis made by the attending physician is entered prospectively. Patients less than 16 years of age are not seen at the Hospital for Tropical Diseases. Epidemiological, demographic, clinical, radiological, and microbiological, as well as treatment and outcomes data were gathered retrospectively from patients' notes and laboratory records. Some data were missing from patients' notes and these are noted in the analyses.

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Time to defervescence was defined as a temperature < 37.5°C for at least 48 hours without an antipyretic. Relapse was defined as recurrence of symptoms with a positive culture from a sterile site (blood, bone marrow aspirate, or urine) or isolation from stool in a patient with clinical features compatible with enteric fever.

Organisms isolated from blood cultures, stool, urine, and bone marrow were identified by using the API 20E system (bioMérieux, Marcy l'Etoile, France). Before full identification, antibiotic susceptibility patterns for coliforms in general would have been determined and these include testing for ampicillin, ciprofloxacin, trimethoprim, nalidixic acid, and ceftriaxone resistance by using the British Society of Antimicrobial Chemotherapy standard disc susceptibility method. In addition, specific susceptibility to chloramphenicol was determined for all *Salmonella* spp. Since 2002, nalidixic acid resistance was used to identify those isolates with reduced susceptibility to ciprofloxacin. Because this procedure does not detect all cases, ciprofloxacin minimum inhibitory concentrations (MICs) were determined by using E test strips since 2003.

Isolates were defined as either fully susceptible (to the first-line antimicrobial drugs ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole [co-trimoxazole]), multidrug-resistant (exhibiting resistance to first-line antimicrobial drugs), demonstrating decreased ciprofloxacin susceptibility or nalidixic acid resistance (DCS/Na^R)[4] (ciprofloxacin MIC = 0.125–1.0 mg/L), or fluoroquinolone resistant (ciprofloxacin MIC > 1 mg/L).

For continuous variables, means and standard deviations are shown. For normally distributed data and non-normal data, geometric means and ranges are shown. Student's *t*-test was used to analyze quantitative variables and Fisher's exact test was used to test for categorical variables.

RESULTS

Between August 2000 and January 2009, 92 cases of enteric fever were diagnosed. Over this same period, 4,061 cases of enteric fever were reported to the Health Protection Agency Center for England and Wales.[5]

Demographics and travel history. The mean ± SD age of patients was 35 ± 12 years. Most (84 of 88, 96%) of them were

usually resident in a developed country, and four (5%) were either visiting or recent immigrants to the United Kingdom. Most patients were either Asian (49%) or white (41%), and most (70%) acquired their infection in southern Asia. One person had not traveled outside the United Kingdom but was Pakistani, and another person, originally from Somalia, had last traveled six months earlier and may have become infected in the United Kingdom (Table 1).

Most patients were either visiting friends and relatives (40 of 87, 46%) or were on holiday (25 of 87, 29%). The average duration of travel was approximately eight weeks (median = 33 days, range = 7–404 days). Vaccination status was known for 40 patients; 22 (55%) had received typhoid vaccination within the previous three years, although most of these patients (17 of 22) were infected with *S. paratyphi*. Of the 18 patients who reported not having received vaccination, 12 (67%) were infected with *S. typhi*.

Clinical features. Symptoms usually began in the week before (14%), or within the first three weeks after (74%) arrival in the United Kingdom (Table 2). All patients had a history of fever and 67 (82%) of 82 were febrile at presentation; 50 (60%) of 83 reported a fever and gastrointestinal symptoms; and 26 (31%) reported a cough. Relative bradycardia (as defined by Cunha[6]) was uncommon, occurring in only 11 (13%) of 82 patients. Splenomegaly was present in 11 (13%) of 84 patients, and rose spots were rarely seen (3 of 83, 4%). Two patients, both infected with *S. paratyphi* A, had complicated infections; one had a rectal bleed and the other had an appendiceal perforation diagnosed by ultrasonography. Both recovered after receiving conservative treatment.

TABLE 1

Demographics and travel characteristics of patients with enteric fever, London, United Kingdom*

Characteristic	Value
Male sex (n = 92)	56 (61)
Country of residence (n = 88)	
United Kingdom	83 (94)
Nigeria	2 (2)
United States	1 (1)
India	1 (1)
South Africa	1 (1)
Country of birth (n = 87)	
Developed	45 (52)
Developing	42 (48)
Ethnic origin (n = 90)	
Asian	44 (49)
White	37 (41)
Black	6 (7)
Chinese	1 (1)
Other	2 (2)
Number of countries visited (n = 87)	
0	1 (1)
1	64 (74)
2	15 (17)
3	3 (3)
4	2 (2)
5	2 (2)
Destination/source of isolate (n = 87)	
Southern Asia	61 (70)
Southeast Asia	6 (7)
Western Asia (Turkey)	1 (1)
Western Africa	8 (9)
Eastern Africa	2 (2)
South America (Bolivia)	1 (1)
Multiple regions	7 (8)
No travel	1 (1)
Reason for travel (n = 87)	
Visiting friends or relatives	40 (46)
Tourism	25 (29)
Business	17 (20)
Visiting or immigrated to the United Kingdom	4 (5)
No travel	1 (1)
Median duration of travel, days (range) (n = 80)	33 (7–404)

*Values are no. (%) unless otherwise indicated. n = total number of patients for which data were available.

TABLE 2

Clinical characteristics of patients with enteric fever, London, United Kingdom*

Characteristic	No. (%)
Onset of symptoms in relation to arrival in United Kingdom (n = 84)	
2–5 weeks prior	3 (4)
1 week prior	12 (14)
1–7 days	18 (21)
8–14 days	28 (33)
15–21 days	16 (19)
> 22 days	7 (8)
Symptom (n = 83)	
Fever	33 (40)
GI symptoms	0
Fever and GI symptoms	50 (60)
Cough	26 (31)
Examination findings	
Fever (temperature > 37°C) (n = 82)	67 (82)
Tachycardia (n = 82)	41 (50)
Relative bradycardia (n = 82)	11 (13)
Splenomegaly (n = 84)	11 (13)
Rose spots (n = 83)	3 (4)

*n = total number of patients for which data were available; GI = gastrointestinal.

Laboratory investigations. Virtually all patients (83 of 91, 91%) had normal total leukocyte counts, although a significant proportion were lymphopenic (36 of 90, 40%) (Table 3). All patients had an elevated C-reactive protein level on admission; in 33 (36%) it was > 100 mg/L. The erythrocyte sedimentation rate was normal for 20 patients (29%). Most had a significant transaminitis, with almost all (75 of 91, 82%) having an increased level of alanine aminotransferase (ALT) during their illness. The maximum ALT level was three times the upper reference limit at some time during admission in 56 (62%) of patients. None of the 31 (34%) patients tested for co-infection with hepatotrophic viruses (hepatitis A, B, C, and E viruses, cytomegalovirus, Epstein-Barr virus, or parvovirus) had positive serologic results. Laboratory indices were compared between persons with typhoid infections and those with paratyphoid infections. There were no significant differences between them except for two characteristics: paratyphoid was associated with a lower neutrophil count and typhoid was associated with a lower hemoglobin level in males.

Microbiologic results. Blood cultures showed the highest levels of positive results (91%, n = 91), usually within 48 hours (mean ± SD = 37.0 ± 14.9 hours). Stool cultures showed a lower yield of 40% (n = 78) and tended to become positive later than blood (mean ± SD = 105.0 ± 42.3 hours).

Seven patients had only positive stool cultures. Two of 75 urine samples were also positive, one from a patient with negative results for blood and stool cultures. Only one patient provided a bone marrow sample, which had a positive culture. Samples were taken 1–48 days after onset of symptoms (mean ± SD = 11 ± 8 days, n = 84 days). No significant differences were

Table 3
Hematologic and biochemical characteristics of patients with enteric fever*

Parameter	All patients	Infected with *Salmonella typhi*	Infected with *S. paratyphi*
Total leukocytes, × 10^3/μL (n = 91)	6.2 ± 2.0 (2.4–11.4)	6.6 ± 1.9 (3.2–10.8)	5.8 ± 2.1 (2.4–11.4)
Neutrophils, × 10^3/μL (n = 90)	4.1 ± 1.5 (1.2–8.8)	4.5 ± 1.5† (2.0–8.8)	3.8 ± 1.5 (1.2–7.7)
Lymphocytes, × 10^3/μL (n = 90)	1.5 ± 0.8 (0.4–5.2)	1.6 ± 0.7 (0.7–4.5)	1.5 ± 0.9 (0.4–5.2)
Hemoglobin, g/dL			
Males (n = 56)	14.1 ± 1.3 (11.3–17.6)	13.8 ± 1.2† (11.3–16.9)	14.5 ± 1.4 (11.7–17.6)
Females (n = 35)	12.6 ± 1.4 (8.9–14.8)	12.2 ± 1.6 (8.9–14.5)	13.0 ± 1.0 (11.2–14.8)
Bilirubin, mg/dL (n = 91)	11.5 ± 7.1 (2.0–63.0)	12.1 ± 9.0 (2.0–63.0)	10.9 ± 4.5 (4.0–27.0)
Maximum (n = 90)	13.2 ± 7.9 (4.0–63.0)	14.3 ± 9.7 (4.0–63.0)	12.2 ± 5.6 (5.0–31.0)
ALT, IU/L (n = 91)	108.9 ± 131.1 (9.0–768.0)	111.6 ± 126.0 (15.0–744.0)	106.2 ± 137.4 (9.0–768.0)
Maximum (n = 90)	224.3 ± 203.1 (11.0–898.0)	239.0 ± 196.8 (18.0–752.0)	209.0 ± 210.7 (11.0–898.0)
Serum albumin, g/L (n = 91)	41.1 ± 3.6 (29.0–48.0)	40.7 ± 3.5 (34.0–47.0)	41.4 ± 3.8 (29.0–48.0)
Sodium, mmol/L (n = 82)	134.7 ± 3.6 (124.0–143.0)	133.7 ± 3.7 (124.0–140.0)	135.8 ± 3.2 (129.0–143.0)
CRP, mg/L (n = 91)	96.2 ± 21.0 (9.0–318.0)	97.7 ± 56.1 (9.0–261.0)	94.6 ± 75.7 (11.0–318.0)
ESR, mm/hr (n = 68)	33.7 ± 21.0 (2.0–116.0)	35.0 ± 22.3 (10.0–116.0)	32.3 ± 19.9 (2.0–94.0)

*Values are mean ± SD (range). ALT = alanine aminotransferase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate. Reference ranges: leukocytes = 3.0–10.0 × 10^3/μL; neutrophils = 2.0–7.5 × 10^3/μL; lymphocytes = 1.5–4.0 × 10^3/μL; hemoglobin = 11.5–15.5 g/dL; bilirubin = 0–20.0 mg/dL; ALT = 10–35 IU/L; albumin = 34–50 g/L; sodium = 135–145 mmol/L; CRP = 0–5.0 mg/L; ESR = 1–20 mm/hr.
†$P < 0.05$.

found in culture positivity of blood or stool from patients with typhoid infections or those with paratyphoid infections.

Almost equal proportions of infections were *S. typhi* (47 cases) or *S. paratyphi* (45 cases). Infections acquired in southern Asia were equally likely to be *S. typhi* or *S. paratyphi* A. In comparison, patients who traveled to Southeast Asia were more likely to have acquired *S. paratyphi* A infection (6 of 7 cases). The one case of infection with *S. paratyphi* B had traveled in Bolivia.

Antibiotic susceptibility patterns are shown in Table 4. Fourteen of the *S. typhi* isolates (30%) were fully susceptible to first-line antimicrobial drugs. Twenty-six (57%), all from southern Asia, were DCS/Na^R and 14 isolates (30%) were multidrug resistant. All of these isolates were from southern Asia and Nigeria.

None of the paratyphoid isolates were multidrug resistant. However, DCS/Na^R rates were higher than in persons infected with *S. typhi* (74%). One patient who had been traveling throughout southern and Southeast Asia acquired an infection with an isolate that showed full fluoroquinolone resistance (MIC = 8.0 mg/L), but the isolate was susceptible to first-line antimicrobial drugs. Ten (11%) patients also had other gastrointestinal infections diagnosed during their admission (*Campylobacter* spp., giardiasis, shigellosis, and ascariasis), which implied exposure to poor food/water hygiene.

Treatment and outcomes. Treatment data were available for 4 (91%) of 92 patients. Once the diagnosis was suspected, all patients were treated with azithromycin, ciprofloxacin, or ceftriaxone until culture results were available. Because patients often received more than one antimicrobial drug, antibiotic-specific times to defervescence were rarely calculated. Overall, however, fever abated in 6.2 days (n = 78). Mean time to defervescence in patients infected with DCS/Na^R strains and treated with ciprofloxacin was 7.6 days (n = 5), which was longer than that for patients who were infected with fully susceptible strains (4.8 days, n = 15).

There was one relapse in a patient infected with a DCS/Na^R strain of *S. paratyphi* A who had initially been treated with a 14-day course of ciprofloxacin and responded to an additional 60-day course of ciprofloxacin. One patient infected with fluoroquinolone-resistant paratyphoid was treated successfully with a 14-day course of amoxicillin.

Clinical characteristics and laboratory findings were compared among patients with *S. typhi* infections and those with *S. paratyphi* infections. Results showed that there were no significant differences between the two infections (Table 5).

Table 4
Antimicrobial drug susceptibility patterns in *Salmonella typhi* and *S. paratyphi*, London, United Kingdom*

Antimicrobial susceptibility pattern	*S. typhi*, no. (%) (n = 46)	*S. paratyphi*, no. (%) (n = 43)
Fully susceptible	14 (30)	10 (23)
DCS or Na^R	26 (57)	32 (74)
FQR†	0	1 (2)
MDR‡	14 (30)	0
MDR and DCS	11 (24)	0

*DCS = decreased ciprofloxacin susceptibility; Na^R = Nalidixic acid resistant; FQR = fluoroquinolone resistant; MDR = multidrug resistant.
†Minimum inhibitory concentration > 1.0 mg/L.
‡Resistance to ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole (co-trimoxazole).

DISCUSSION

The incidence of enteric fever decreased throughout the first half of the 20th century in most areas of Europe and

Table 5
Comparison of clinical characteristics of patients with infected with *Salmonella typhi* versus those infected with *S. paratyphi*, London, United Kingdom*

Characteristic	*S. typhi*	*S. paratyphi*	*P*
Mean length of in-patient stay, days	5.9 (n = 47)	6.4 (n = 45)	NS
Mean temperature on admission, °C	38.2 (n = 42)	38.1 (n = 41)	NS
Mean heart rate on admission, bpm	104 (n = 41)	98 (n = 41)	NS
Mean time to defervescence, days	5.8 (n = 41)	6.6 (n = 38)	NS
Relative bradycardia, % of total	15 (n = 41)	12 (n = 41)	NS
Splenomegaly, % of total	10 (n = 42)	17 (n = 42)	NS
Rose spots, % of total	5 (n = 42)	2 (n = 41)	NS

*NS = not significant; bpm = beats per minute.

North America as a result of improvements in sanitation and hygiene and effective public health programs.[7] The increase of enteric fever cases in temperate countries over the past few decades is largely the result of foreign travel.[8] The data presented in this report highlight some of the key features that would alert the clinician to the possibility of enteric fever as the cause of a significant ongoing febrile illness in the returning traveler. Many of these findings corroborate those recently published by Clark and others in their study of culture-confirmed cases of enteric fever in a regional infectious diseases center in Leicester, United Kingdom.[9]

Consistent with results of other studies on returning travelers and surveillance data for the United Kingdom, we found that southern Asia appears to be the most common source of infections with *S. typhi* or *S. paratyphi*.[10–15] Although enteric fever typically affects children and young adults in disease-endemic countries, with most infected patients being less than 19 years of age,[16–18] this age distribution is not reflected in the population of travelers that acquire the disease.

The risk among those visiting friends and relatives has been reported to be up to 10 times higher than in those who are on holiday.[19,20] Reasons for this finding include a failure to access pre-travel advice, either as a result of language barriers or poor access to health services, concerns over immunization costs and mistaken beliefs that previous infection or immunization confer lifelong cross-protective immunity.[21] Although this study had no denominator data, we also found far more persons visiting friends and relatives had acquired the disease compared with tourists. In terms of length of stay, the average for all travelers was more than eight weeks, which is consistent with results of another study that suggested an increased risk of acquiring disease with a longer duration of stay.[22]

Previous studies have identified *S. typhi* as the dominant pathogen among the local population in disease-endemic countries, but *S. paratyphi* A is increasingly being recognized as the cause of enteric fever, particularly in many regions of Asia.[1,23–26] However, in other countries, such as Nepal and Israel, *S. typhi* infection still predominates.[12,23] Equal proportions of *S. typhi* and *paratyphi* were found among travelers in this study, which may reflect this change in epidemiology in disease-endemic countries and different modes of transmission suggested for the two pathogens. The spread of *S. typhi* is more commonly associated with person-to-person transmission and that of *S. paratyphi* with consumption of contaminated food.[27] Importantly, although it is traditionally taught that infection with *S. paratyphi* causes milder disease with a shorter incubation than with *S. typhi*, we found no differences between groups of patients in terms of length of illness, hematologic and biochemical markers, or time to defervescence, which is consistent with findings in more recent reports.[12,28,29] Both patients in our study who had complications had *S. paratyphi* A infections, which is consistent with recent data suggesting higher rates of complications in patients infected with *S. paratyphi* than in those infected with *S. typhi*.[12,30]

Although it was not possible to establish when infection was acquired, a significant proportion of patients had symptoms within the first three weeks of returning, which is compatible with the suggested typical incubation period of 7–14 days (range = 3–60 days).[31] In the absence of fever in the medical history, a diagnosis is highly unlikely. In addition, most patients did not have relative bradycardia and only a few had rose spots. A previous study suggested that rose spots are not found in patients with *S. paratyphi* infection, but two of three patients with rose spots had enteric fever caused by *S. paratyphi*.[32]

One study suggested that anemia, leukopenia, and liver involvement with elevated levels of aminotransferases and bilirubin are common in persons with typhoid and paratyphoid.[33] In comparison, most patients in our study had normal hemoglobin levels and leukocyte counts, although lymphopenia was a frequent finding. That anemia and jaundice are more frequent findings in children and are less common in adults may account for the apparent discrepancy in our study.[16,34,35] Elevated levels of ALT in our patients, up to 25 times the upper reference limit, were seen although levels in persons with enteric fever are rarely as high as those found in persons with acute viral hepatitis.[34] Whether this is a feature of the disease or an effect of the drug treatment is debatable, but it would appear that a transaminitis (levels ≤ 900 IU/L) may be expected in adult patients with enteric fever.

Isolation of *S. typhi* or *paratyphi* in stool alone may not be sufficient to confirm the diagnosis of enteric fever because it may simply represent a carrier state. However, in the presence of pyrexia or a reliable history of febrile episodes, stool cultures may be diagnostic when blood cultures fail, as shown for seven patients in our study.

The optimal antimicrobial drug for treatment of persons with enteric fever should have a high cure rate, a short time to defervescence, and low relapse and fecal carriage rates. Therefore, selection of the most appropriate agent must involve consideration of the probabilities for partial and complete drug resistance. In this series, *S. paratyphi* isolates were more likely to show reduced susceptibilities to fluoroquinolones than *S. typhi*, but they showed low rates of multidrug resistance, which is carried on a plasmid conferring resistance to first-line antimicrobial drugs ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole. This finding is consistent with other data for the United Kingdom.[9,36] However, these differences cannot be used in making decisions on use of antimicrobials because we have shown that clinical features do not enable distinction between *S. typhi* and *S. paratyphi* infections. Instead, drug choice must take into account global resistance patterns.

Thus, patients returning from countries, such as those in southern Asia, in which fluoroquinolone and multidrug-resistant strains are prevalent, should be treated with azithromycin if oral therapy is indicated. However, it is currently difficult to confirm whether an isolate is susceptible to azithromycin because no breakpoints are available for disc testing of this drug. Ceftriaxone should be used if parenteral treatment is indicated. However, in persons returning from Africa, ciprofloxacin is still the best choice.[37] This drug has a clinical cure rate of > 90%, a fever clearance times of 5–7 days, and relapse and fecal carriage rates of < 3% in patients with typhoid fever.[31,33] It has been suggested that in severe disease (patients with persistent vomiting, severe diarrhea, abdominal distension, or complications), parenteral antimicrobial drugs (usually ceftriaxone) should be given for 10 days, or for at least 5 days after defervescence, although this recommendation is based on cure and relapse rates in small trials that involved children.[38,39] Additional data for optimal length of treatment in adult travelers with severe disease and non-severe disease are needed.

Complications occur in 10–15% of patients, but this value is based largely on studies in children in endemic countries. However, complications are rare in travelers probably because

of early access to medical care.[31] A similar reasoning can be applied to the case-fatality rate of enteric fever, which may be ≤ 30% in some disease-endemic countries but > 1% in returning travelers.[40] Finally, the reported incidence of relapse is 1.5% for *S. typhi* and 8.6% for *S. paratyphi* A in disease-endemic countries.[41,42] Patients should be warned of this possibility and to seek medical help if symptoms recur 2–3 weeks after resolution of the initial fever.

Although retrospective studies such as our study have limitations such as recording bias, this limitation is unlikely to be of significance for some of our main findings (laboratory data). These limitations will not differ between retrospective and prospective studies. However, other relevant limitations include the fact that our study was not conducted in a specialized research unit. Our study was a case series that spanned many years, involved many physicians during this period, and occasionally used incomplete data.

Despite these drawbacks, our study highlights the clinical features that should alert a physician caring for febrile returning travelers to the diagnosis of enteric fever, particularly those who visited friends and relatives and are seeking treatment within three weeks of returning. Rose spots and relative bradycardia should not be considered common findings in these patients and *S. typhi* and *S. paratyphi* infections result in an almost indistinguishable clinical picture. A normal leukocyte count and serum bilirubin level, increased levels of inflammatory markers, and markedly increased ALT levels make an accurate diagnosis more likely.

With increasing drug resistance of *S. typhi* and *S. paratyphi* isolates, persons who returned from southern and Southeast Asia should be treated with azithromycin or ceftriaxone if intravenous therapy is indicated. Persons who returning from Africa should be treated with ciprofloxacin.

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