Typhoid and paratyphoid fever in travellers

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Enteric fever—a more inclusive term for typhoid fever and paratyphoid fever—is a systemic infection caused by Salmonella enterica, including S enterica serotype Typhi (S typhi) and serotype Paratyphi (S paratyphi). In developed countries there have been two major changes in the pattern of the disease: a marked decline in its incidence and its characterisation as a predominantly travel-associated disease. The risk to travellers appears to vary by geographic region visited, with travel to the Indian subcontinent accounting for the greatest travel risk. Although the most common cause of enteric fever is S typhi, the incidence of disease caused by S paratyphi among travellers may be more important, since the available vaccines only protect against S typhi. Descriptions of the clinical presentation in travellers are scarce but severe complications and death are rare, probably due to rapid access to readily available medical care. Drug resistance reflects the situation in endemic countries, and shows a steady increase in multidrug-resistance patterns. Currently, the recommendation for first-line therapy is ceftriaxone and, where isolates have been found to be quinolone sensitive, fluoroquinolones can still be given. Preventive measures are educating travellers about hygiene precautions and vaccination. With an increase in multidrug-resistant strains, a more effective vaccine for S typhi and S paratyphi is urgently needed.

Introduction

Enteric fever—a more inclusive term for typhoid fever and paratyphoid fever—is a systemic infection caused by Salmonella enterica, including S enterica serotype Typhi (S typhi) and serotype Paratyphi (S paratyphi). Enteric fever is a faecal–oral transmissible disease and therefore is primarily a disease where overcrowding, poor sanitation, and untreated water are the norm. Until the early 20th century, the disease had a worldwide distribution, including the USA and Europe. The number of typhoid cases in the USA fell from 35 994 in 1920 to an average of 500 cases annually in the 1990s, largely as a result of changes in sanitation and hygiene.

Today, most enteric fever infections occur in less developed countries where sanitary conditions remain poor and water supplies are not treated. Human beings are the only known reservoir and transmission occurs through food and water contaminated by acutely ill or chronic carriers of the organism. Obtaining accurate data on disease burden in developing countries is difficult because the diagnosis of enteric fever is often a clinical one, without blood culture confirmation, and most patients are treated as outpatients. Public-health figures may therefore underestimate enteric fever levels compared with community-based studies. Annual incidence rates of up to 198 per 100 000 in the Mekong

Figure 1: Annual incidence of enteric fever worldwide
delta region in Vietnam 2 and 980 per 100 000 in Delhi, India 3 have been reported. According to the best global estimates, there are at least 16 million new cases of enteric fever each year, with 600 000 deaths. The greatest burden of disease is in Asia, where 13 million cases are assumed with 400 000 deaths annually. 4 There has been a rise in cases since the 1990s (figure 1). 5

Epidemiology of typhoid fever in developed countries

In developed countries where typhoid fever used to be endemic, there have been two major changes in the pattern of disease: there has been a marked decline in the incidence of the disease in the past half century, and also it has become predominantly a travel-associated disease (figure 2). For example, in the USA the annual incidence dropped from 7·5 per 100 000 in 1940 to 0·2 per 100 000 in the 1990s, and the proportion of cases related to foreign travel increased from 33% in 1967–72 to 81% in 1996–97. 6–11 In Israel, the change was even more marked, with an annual incidence of 90 per 100 000 in the early 1950s that had dropped to 0·23 per 100 000 in 2003; of the remaining cases, 57% were acquired abroad. 12 Altogether the range of reported annual incidence in developed countries in the past decade is 0·13–1·2 cases per 100 000 population, with most being imported. 6,10,11

The risk for travellers appears to vary by geographic region visited (table). Several reports indicate that the Indian subcontinent has the higher risk for acquiring typhoid fever. For example, among travellers from the USA, six countries account for 80% of cases—India, Mexico, Philippines, Pakistan, El Salvador, and Haiti. The overall risk from travel to the Indian subcontinent was higher than for travel to any other geographic region. Although the incidence of typhoid fever among travellers to Mexico decreased from 0·19 to 0·13 per 100 000 between 1985 and 1994, the incidence among travellers to the Indian subcontinent increased from 23·4 to 81·2 per 100 000. The overall risk of typhoid fever from travel to the Indian subcontinent is 18 times higher than from any other geographic area. 7 In other data, the attack rate for travel to Mexico is 2 per 100 000 journeys versus 10 per 100 000 to the Indian subcontinent. 7 British data concur—a review of cases in northwest England from 1996–98 showed that 85% of the 47 imported cases related to travel to India or Pakistan, 13 and in a review of 200 cases in England and Wales, 80% of cases acquired abroad were related to travel to the Indian subcontinent. 14 In another British report, 75% of cases of typhoid fever were in travellers and the authors’ estimation of global risk of typhoid fever—ie, the risk of contracting typhoid fever when travelling to all other developing countries besides the Indian subcontinent—was 1 per 100 000 visits, compared with 30 per 100 000 visits for travel to the Indian subcontinent. 15 In Israel, 74% of imported typhoid fever cases were acquired in India and the calculated attack rate was 24 per 100 000 travellers, a figure 100 times higher compared with travellers to Thailand or to middle eastern countries. 16 Reports from France and Germany also indicated the Indian subcontinent as the main geographic source. 17,18

Other risk factors for travellers

Risk factors for contracting enteric fever have been assessed by several authors. As expected, travel to rural areas with poor sanitation was associated with a higher risk. Not following food and water precautions and not receiving pretravel consultation increased the risk ten times. 19 A German study found an increased risk among older travellers with a longer duration of stay (58 days vs 19 days). 20 A report from the USA analysing typhoid cases acquired abroad demonstrated that 5% of cases had a visit of 1 week or less, while 60% of cases were those staying for 6 weeks or less. 21 A special group with increased risk are those travellers visiting friends and relatives—ie, immigrants who return to visit their homeland. In addition to more travel to rural areas, travellers visiting friends and relatives are less likely to have received pretravel advice, less likely to exercise food and water precautions, and, perhaps most importantly, by and large do not perceive their risk or receive typhoid vaccine before travel. 22

The pathogens

The most common cause of enteric fever is S typhi, hence the frequent use of the name typhoid fever. However, the same clinical syndrome can be caused by S paratyphi A, B, and C. Thus, enteric fever has become the more inclusive term. Reports from endemic countries demonstrate that S typhi is the dominant pathogen, accounting for approximately 80% of cases. 23,24 However, among travellers, the incidence of disease caused by S paratyphi may be more important. In reports from Nepal, the ratio of S paratyphi to S typhi was 70% versus 30% among travellers, while this ratio was reversed, as expected, in the local population. 25 The same holds true in

Figure 2: Trends in incidence of typhoid fever in the USA and the proportion of cases of typhoid fever attributed to travel
infection. The disproportionate number of cases of *S. paratyphi* may be due to a vaccine effect, which gives protection only for *S. typhi*.

**Clinical features**

The clinical manifestations and severity of typhoid fever vary with the patient population studied. Most reports and textbook descriptions relate to studies of patients in endemic countries. Descriptions of the clinical presentation in travellers are scarce but important differences in clinical manifestations exist between travellers to developing countries and local residents. These differences relate to the likelihood of exposure to infection, age, and intensity of exposure, and may be affected by more rapid and readily available access to medical care. Travellers have no pre-existing immunity (unless they have received vaccine), and are thus naive hosts. However, they might consume smaller amounts of contaminated food (due to hygiene precautions) and have more rapid and available access to medical care. In indigenous populations, typhoid fever is a disease of young children and adolescents, with 90% of cases seen in children between the ages of 3 and 19 years. In travellers, the age of the patients is a reflection of the age of travellers and there is no predominance of disease in the young, chiefly because most travellers, regardless of age, can be considered naive hosts.

After ingestion of *S. typhi*, an asymptomatic period follows that usually lasts 7–14 days (range 3–60 days). The onset of bacteraemia is marked by fever and malaise. Patients typically present after the onset of fever with influenza-like symptoms with chills (although rigors are rare), a dull frontal headache, malaise, anorexia, and nausea, but with few physical signs. Hepatomegaly and splenomegaly may exist. Relative bradycardia is considered common in typhoid fever, although it is not specific for it. Rose spots—blanching erythematous maculopapular lesions usually 2–4 mm in diameter—are reported in 5–30% of cases, although blanching and usually occur on the abdomen and chest. Rose spots are easily missed in dark-skinned patients. In one study that compared *S. paratyphi* with *S. typhi* infection, rose spots were not found in travellers, rose spots were not found in *S. paratyphi* infection. Fever often occurs in a stepwise fashion with 5–7 days of daily increments in maximal temperature of 0.5–1°C, with the height of fever usually occurring in the afternoon. There follows a period of 10–14 days of sustained fever of 39–41°C. However, travellers will usually seek medical attention much earlier into the clinical course of the stepwise fever curve and sustained fevers are usually not seen in this population. More serious complications—eg, gastrointestinal bleeding, intestinal perforation, and typhoid encephalopathy—that may occur in 10–15% of typhoid patients in endemic countries, are rarely seen in travellers, probably because of early access to medical care.

Case fatality rates in endemic countries have been reported as high as 30%; however, in travellers, this number is much lower. US Centers for Disease Control and Prevention surveillance data from 1985–94 included 2445 cases of typhoid fever with 0.4% mortality. Deaths occurred exclusively in immigrants rather than short-term travellers. In a study of 45 travellers with enteric fever in Nepal, there were no deaths reported. In addition, reports of typhoid fever in hospitalised returning travellers in France, Germany, and Israel showed no death. Chronic biliary carriage may occur in 2–5% of cases, even after treatment. Biliary carriage is defined as continued shedding of the organism for more than a year, and is a public-health risk, especially for infected individuals who work in the food industry.

Clinical disease associated with *S. paratyphi* A is indistinguishable from that of *S. typhi*, with complications occurring in about the same percentage of patients. It has also been shown that cases of enteric fever due to vaccine failure are no milder than those in whom vaccine was not received.

**Laboratory findings**

Leucopenia and thrombocytopenia are common and liver enzymes are usually moderately raised (two to three times the upper limit of normal). These findings might also be seen in other common febrile diseases in travellers—eg, malaria and dengue. Typhoid hepatitis has been described in patients in endemic countries and is characterised by substantial liver damage. Study of this phenomenon in travellers revealed that this syndrome is related to coinfection with either hepatitis A or E, which are also faecal–oral transmissible pathogens.

Diagnosis of enteric fever is based on recovery of the pathogen in blood or stool cultures. Many patients may have started antibiotics and thus blood cultures may be negative. In these instances bone marrow culture provides a better chance of recovering the organism, with
a success rate of up to 90%. The organism may also be cultured from rose spots. Conventional Widal serological tests are of little value because they are neither sensitive nor specific. Moreover, in travellers who may have received typhoid vaccine before travel, typhoid serology may be positive because of the vaccine.

**Treatment and drug resistance**

Historically, typhoid fever was treated with chloramphenicol, ampicillin, or trimethoprim-sulfamethoxazole (co-trimoxazole), but resistance to one or two of these began to be reported in the 1950s. By 1972, chloramphenicol resistance became widespread and, since 1989, resistance to all three has been noted in strains in India, Pakistan, China, and the Persian gulf. Resistance appears to be plasmid mediated, allowing the simultaneous acquisition of resistance to multiple drugs and the emergence of multidrug-resistant strains. 50–80% of isolates from China and the Indian subcontinent are now multidrug resistant, and 93% of isolates in an outbreak in Tajikistan were multidrug resistant.

The introduction of fluoroquinolones was a major advance. The drugs were found to be highly effective, well-tolerated, and could be administered orally. Antibiotics such as ciprofloxacin quickly became first-line agents. Treatment was also reduced from 14 days to as short as 5 days’ duration. A disturbing trend, however, has been an increase in fluoroquinolone resistance, which is not plasmid mediated but rather the result of chromosomal mutation. In an outbreak in Tajikistan, 82% of isolates were ciprofloxacin resistant. This resistance has necessitated higher, more prolonged doses of quinolones (10–14 days or longer). In a study done in Vietnam, quinolone resistance increased from 4% in 1993 to 76% in 1998. These quinolone-resistant strains were noted to be sensitive to ceftriaxone, cefixime, and azithromycin but the clinical response was slower, with fever clearance taking 7 days or more and failure rates of greater than 20%. In developed countries, the situation reflects the situation in endemic countries. In the USA, multidrug-resistant strains of *S typhi* increased dramatically within two decades. From 1975 to 1984, only 5% of isolates were resistant to at least one of the commonly used drugs and only 0.1% were resistant to all. From 1990 to 1994, 30% were resistant to at least one and 12% were resistant to chloramphenicol, ampicillin, and co-trimoxazole. Both patterns of resistance—plasmid mediated and chromosomal mutation—are now being seen in *S paratyphi* A infections as well.

Drug resistance highlights an emerging crisis in the antibiotic treatment of enteric fever. Multidrug-resistant strains require expensive therapies that are less effective and result in higher stool carriage rates with a greater transmission potential, posing public-health risks, especially in countries where typhoid fever is endemic and, by extension, in travellers to these countries. Cost differences in treatment regimens have now made it exceedingly difficult, if not impossible, to effectively treat typhoid fever in endemic countries. Our clinical experience with travellers shows a slower response to treatment in recent years, even when the pathogen is sensitive in vitro to quinolones or ceftriaxone. The same phenomena occurs with *S paratyphi* A.

Currently, the recommendation for first-line therapy is ceftriaxone 2 g daily. Where isolates have been found to be fluoroquinolone sensitive, standard doses of a fluoroquinolone—eg, ciprofloxacin 500 mg twice daily—may be used. However, most laboratories use disk diffusion for evaluation, the sensitivity of which does not reflect true sensitivities. Thus, this method cannot be used to determine fluoroquinolone sensitivity by itself; only nalidixic acid sensitivity confirms true quinolone sensitivity. Determining minimum inhibitory concentrations gives a more predictable measure of antibiotic resistance, and will need to be more widely used as antibiotic resistance increases.

Another promising option that has been tested in the past few years is azithromycin. This agent shows similar results to ciprofloxacin and ofloxacin. Furthermore, oral azithromycin was comparable to intravenous ceftriaxone in uncomplicated typhoid fever in children and adolescents. Of note is that all these studies were done in an endemic setting, and there are no published data to confirm their efficacy or to guide the duration of therapy in non-immune travellers.

**Typhoid vaccines**

The whole cell vaccine against typhoid fever was one of the first vaccines ever shown to be effective, but had substantial adverse effects and is no longer used in developed countries.

The complex nature of the pathogenesis of *S typhi* clinical infection has spurred the development of two primary types of vaccines. Parenteral vaccines take advantage of the protective role of the circulating antibody response and live attenuated oral vaccines rely upon vigorous secretory IgA response and cell-mediated immunity to eliminate intracellular bacilli. Both vaccines are safe and relatively well tolerated.

The live oral vaccine is an attenuated *S typhi* strain, Ty21a, which is a mutant of Ty2 with a uridine diphosphogalactose 4-epimerase defect. The strain lacks the virulence (Vi) antigen and is thus avirulent but contains immunogenic cell wall polysaccharides. Primary vaccination consists of one enteric coated capsule or lyophilised sachet on alternate days for three to four doses. The live attenuated vaccine is theoretically contraindicated in pregnancy and in those with cell-mediated immunosuppression. In addition, the concurrent use of antibiotics or antimalarials may interfere with the antibody response. This vaccine needs to be refrigerated, cannot be given to children under
A major disadvantage of both vaccines is lack of protection against *S paratyphi* infection. One study in Nepal showed that a switch in pathogens was noted among vaccinated travellers and *S paratyphi* was found in most cases. An Israeli study demonstrated that Vi vaccine gave better protection against *S typhi* among travellers to India while Ty21a gave better protection against *S paratyphi*.

Conclusions
Two features characterise enteric fever in industrialised countries. One is the general decline in the incidence of the disease and the second is the concomitant rise in the percentage of travel-related enteric fever. Most cases are acquired in the Indian subcontinent where multidrug resistance is the norm and where fluoroquinolone resistance is on the rise. Vaccine efficacy is generally tested in endemic areas, which raises questions of how the results correlate with those in naive travellers and what contribution those already immune make to the trial results. Current vaccines offer only moderate protection against *S typhi* and no protection against *S paratyphi*, which has become the dominant pathogen among travellers. Thus, there is a great need for a combined vaccine, particularly with increasing antibiotic resistance in both *S typhi* and *S paratyphi*.

Conflicts of interest
BAC is on the speakers’ bureau for Sanofi Pasteur, and is a consultant for Acambis. ES has no conflicts of interest to declare.

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