

Mini-Review Article

Epidemiology of typhoid and paratyphoid fever in India

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Abstract

Enteric fever (typhoid and paratyphoid fever) is a major human bacterial infection. Although the disease is not common in industrialised countries, it remains an important and persistent health problem in developing nations. Hospital-based studies and outbreak reports from India indicate that enteric fever is a major public health problem in this country, with *Salmonella enterica* serovar Typhi (*S. Typhi*) the most common aetiologic agent but with an apparently increasing number of cases due to *S. Paratyphi A* (SPA). Because risk factors such as poor sanitation, lack of a safe drinking water supply and low socio economic conditions in resource-poor countries are amplified by the evolution of multidrug resistant *salmonellae* with reduced susceptibility to fluoroquinolone, treatment failure cases have been reported in India, which is associated with increased mortality and morbidity. Vaccination, which requires strict planning and proper targeting of the vulnerable age groups, is considered to be an effective tool in controlling this disease in endemic areas, given there is development of a conjugate vaccine against both serovars (*S. Typhi* and *S. Para A*).

Key Words: Typhoid, multidrug resistance, *Salmonella Typhi* and *Paratyphi*, antimicrobials, vaccination

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Introduction

Clinical syndromes caused by *Salmonella* infection in humans are broadly divided into two groups. The first, enteric fever, is transmitted by contaminated water or food, and is caused mainly by *Salmonella enterica* serovar Typhi (typhoid fever) or *Salmonella enterica* serovar Paratyphi A, B or C (paratyphoid fever). The secondly, a range of clinical syndromes including diarrhoeal disease, is caused by a large number of non-typhoidal *Salmonella* serovars (NTS) [1]. *Salmonellae* are Gram negative, flagellate, nonsporulating, facultative anaerobic bacilli that ferment glucose, reduce nitrate to nitrite, and synthesise peritrichous flagella when motile. *Salmonella* is a genus in the family Enterobacteriaceae that has more than 2,300 serotypes, based on the presence of three main antigens: somatic O antigen (lipopolysaccharide cell wall component), surface Virulent (Vi) antigen (*S. Typhi* and *S. Paratyphi C* only), and flagellar H antigen. Here we will restrict our description to the epidemiology of enteric fever in India.

Burden of enteric fever in India

Although enteric fever is not common in industrialised countries, it remains an important and

persistent health problem in developing nations [2]. Hospital-based studies and outbreak reports from India indicate that enteric fever is a major public health problem in this country, with *Salmonella Typhi* (*S. Typhi*) the most common aetiologic agent but with an apparently increasing number of cases due to *S. Paratyphi A*. *S. Paratyphi B* and *S. Paratyphi C* are relatively uncommon in India. There have been two large-scale studies in India on the incidence of blood culture confirmed typhoid fever, one among individuals under 40 years old [3] and another among children 6 to 17 years old [4], but as yet, none on paratyphoid fever. Thus, the actual burden of paratyphoid fever in India and its incidence and characteristics relative to typhoid fever are poorly understood. In a study conducted in Punjab that examined 340 enteric fever cases, 334 *S. Typhi* and 6 *Paratyphi A* isolates were identified [5]. This scenario, however, has changed as recent studies have highlighted the increasing occurrence of paratyphoid fever [6-10].

Typhoid fever incidence varies substantially in Asia. Very high typhoid fever incidence has been found in India and Pakistan [11]. In comparison, typhoid fever frequency was moderate in Vietnam and China and intermediate in Indonesia. [12]. Worldwide, the

emergence of multidrug resistant *S. Typhi* and *S. Paratyphi A* strains has been shown to be geographically heterogeneous [12-13], underscoring the importance of continuing microbiological surveillance for *Salmonella* isolates by monitoring their antimicrobial resistance profile at the country level.

Transmission, seasonality and risk factors of enteric fever

Humans are the only reservoir for these organisms. The main source of infection is the stool of infected persons; other sources are contaminated water, food, and possibly flies. Lack of sanitation and clean running water cause contamination for long periods of time in resource-poor countries. Contaminated surface water further contaminates the water supply. In addition, it is seldom possible for the population in poor countries either to boil their drinking water, or to sterilise the water by any other methods [14].

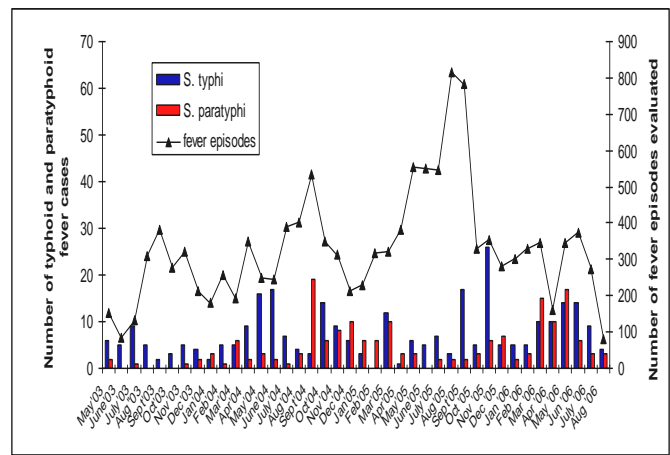
Enteric disease is caused by both waterborne and food-borne infectious agents which gain access via the gastrointestinal tract. The onset depends mainly on the virulence of the organism and the infective dose. Humans can be both cases and carriers. They usually secrete the organism for an average of 6 to 8 weeks and carrier status usually diminishes after 6 to 8 months [1].

In India, enteric disease is most prevalent in urban areas, with incidence approaching one percent of the population annually in some endemic areas [15]. Usually children 15 years of age and younger are more susceptible, most probably because adults develop immunity from recurrent infection and sub-clinical cases. A large-scale community study performed in an Indian urban slum showed incidence as high as 2 per 1,000 population per year for children under five, and 5.1 per 1,000 population per year for children under ten [16]. Another study in Northern India showed that the majority of cases occurred in children aged 5 to 12 years and 24.8% of cases were in children up to 5 years of age [17]. *Salmonella* serovars showed an age-related bias, with paratyphoid fever more common in adults. One study from Kolkata showed the incidence of paratyphoid fever was lower (0.8/1000/year), and the mean age of paratyphoid patients was older (17.1 years) compared to typhoid fever (incidence 1.4/1000/year, mean age 14.7 years) [18].

Typhoid fever is usually observed throughout the year. Some studies show a peak of the disease from July to September, as it coincides with the rainy season when the chance of water contamination is high, especially in crowded areas [16].

Researchers from New Delhi, India, reported that *S. Typhi* (75.7%) was the predominant serovar isolated during the study period followed by *S. Paratyphi A* (23.8%) [17]. The maximum number of enteric fever cases occurred during April to June (dry season) followed by July to September (monsoon season) [19]. Studies completed in Kolkata urban slums show a seasonal variation of the incidence of both typhoid and paratyphoid fever, with monsoon months being the most vulnerable period (Figure 1).

Figure 1. Month-wise variation of typhoid and paratyphoid incidence in Kolkata.



Exposure of the individual to contaminated food or water correlates closely with the risk for enteric fever. Since public health interventions, such as water improvement or vaccination campaigns, are usually implemented for groups of individuals, a large enteric fever surveillance study was conducted and factors were analysed which correlate with enteric fever on an individual level alongside factors associated with high- and low-risk areas with enteric fever incidence [18]. Thus the individual level data were linked to a population-based geographic information system. In the study, individual and household level variables were fitted in Generalized Estimating Equations (GEE) with the logit link function to take into account the likelihood that household factors correlated within household members. Over a 12-month period, 80 typhoid fever cases and 47 paratyphoid fever cases were detected among 56,946 residents in two bustees (slums) of Kolkata, India. Residents in areas with a high risk for typhoid and paratyphoid fever had lower literacy rates and economic status, a bigger household size, and resided closer to water bodies and study treatment centres than residents in low-risk areas. Predictors for both typhoid and paratyphoid fever were found to be

similar [18]. In contrast, a study conducted in Jakarta, Indonesia, showed that the risk factors are more prevalent outside the household in paratyphoid rather than inside, as with typhoid [20].

Chronic carriers of typhoid play a crucial role in spreading the disease throughout the community. The first essential factor in carrier prevention of infection includes educating the general public as well as identifying all possible carriers and sources of contamination of water supplies.

Invasive salmonellosis due to NTS in India

Typhoid is a highly adapted invasive disease that is restricted to humans and shows little association with the immunocompromised. In contrast, non-typhoidal salmonellosis have a broad vertebrate host range, an epidemiology that often involves foods and animals, and a dramatically more severe and invasive presentation in immunocompromised adults, in particular in those with HIV. The prevalence of non-typhoidal *Salmonella* (NTS) bacteraemia has risen in many countries and is probably related to the increase in HIV infection [21]. Although invasive disease caused by NTS has been recently reported from many African and Asian countries, the infection is relatively unknown in India. One study from Thailand [22] reported a total of 135 patients with NTS bacteraemia. *Salmonella* group C was predominant. The most common underlying disease was HIV infection. Up to 30% of NTS isolates were identified as multidrug resistant. In one disease burden study from Kolkata, only one isolate of *S. Typhimurium* and one isolate of *S. Dublin* were identified (not published) from 1,500 blood culture samples.

Clinical Features

Typhoid fever is a severe, contagious and life-threatening systemic disease caused by *Salmonella* Typhi which may result in persistent fever with or without severe complications. Typhoid often presents with misleading symptoms, thus making it extremely difficult to diagnose. Paratyphoid fever relates to a group of enteric illnesses caused by strains of *Salmonella* Paratyphi A, B and C. Paratyphoid fever bears similarities with typhoid fever, but its course is more benign with fewer complications [1].

Hallmarks of enteric fever include abdominal pain and high fever, with fever being the main presenting feature (as high as 75% of the cases) in the initial stages. Usually the incubation period is 1 to 14 days. In addition to fever up to 39°C, (with a typical step-ladder

pattern) a range of nonspecific symptoms may be associated with typhoid fever. These include chills, persistent headache, abdominal discomfort, constipation, diarrhoea, weakness, dizziness, nausea and cough. Diarrhoea may be a presenting feature especially in immunocompromised cases and infants. Classical clinical features of the disease were comparable among patients under and above 5 years of age but other manifestations, such as hepatomegaly, anaemia and complications, are generally more frequent in children up to 5 years of age [17].

Rare symptoms, including “Rose spots”, relative bradycardia and—in severe cases—neuropsychiatric symptoms such as muttering and delirium have also been reported [15]. Late diagnosis or failure to respond to treatment may lead to serious complications, including gastrointestinal hemorrhage, perforation of the gut, and shock. There is evidence of pancreatitis [23]; splenic infarction [24] in some cases due to typhoid. There is also evidence of vertical transmission of the pathogen with high mortality and morbidity in neonates [25].

Treatment

Antibiotic therapy is the only effective treatment for enteric fever. In the past, the drug of choice was chloramphenicol. It was the standard treatment until plasmid-mediated resistance to this drug emerged. Because of severe adverse effects, a high relapse rate and widespread bacterial resistance to chloramphenicol, ampicillin (1g given orally every 6 hours) and trimethoprim-sulfamethoxazole (TMP-SMX; double strength tablet given twice a day) became the mainstay of treatment.

With the emergence of multidrug resistant *S. Typhi* in the late 1980s, typhoid disease was found to be resistant to treatment with most of the commonly used antibiotics such as chloramphenicol, ampicillin, TMP-SMX, streptomycin and tetracycline. A study in the mid-1990s in Bangalore showed resistance to ampicillin, chloramphenicol, co-trimoxazole and nalidixic acid to be as high as 95% with 90% sensitivity to norfloxacin and ciprofloxacin [26]. Multidrug resistant outbreaks have been reported in 1995 from Bangalore with 76% resistance to ampicillin, 64% to chloramphenicol, and 75% to tetracycline [27]. Another study in Karnataka completed in 1999 showed very high resistance to chloramphenicol and cotrimoxazole [28]. Recently multidrug resistance was seen in *S. Typhi* but less in *S. Paratyphi* A isolates. However, resistance to nalidixic acid was comparable in both

serovars [17].

Ciprofloxacin for adults, excluding pregnant women, is presently the treatment of choice. There is a dramatic increase in nalidixic acid-resistant isolates with reduced susceptibility to fluoroquinolones (FQs), although all isolates are susceptible to third-generation cephalosporins. Patients infected with such strains may not be responsive to treatment with ciprofloxacin, which could lead to reports of treatment failure cases [15]. One study from Kolkata reported the isolation of one *S. Typhi* strain which demonstrated high-levels of ciprofloxacin and norfloxacin resistance with 16 µg/mL of MIC [29]. Indian studies showing evidence of emergence of fluoroquinolone resistance [30] are similar in pattern to results from other Asian countries.

Pregnant women and children most often receive ceftriaxone injections. However, all these drugs can cause adverse effects and long-term use can lead to the development of antibiotic resistance. Together, these constitute about 80% of the world's typhoid burden, where various rates of multi drug resistance (16 to 37%) and nalidixic acid resistance (5 to 51%) were found during 2002-2004 [30]. However, there is now evidence that strains previously resistant to chloramphenicol have become sensitive to treatment with chloramphenicol [31]. Another study showed a change in resistance patterns to conventional anti-typhoid microbials such as ampicillin and chloramphenicol from 84% to 14% [32].

A study conducted in Kolkata observed that recent *S. Paratyphi A* isolates from Kolkata, India, were resistant to ampicillin, co-trimoxazole and chloramphenicol, to which this organism was sensitive in earlier years [33]. There was also evidence of an upsurge of *S. Paratyphi A* in Kolkata [34]. In the global context, there is evidence of increased incidence of enteric infections due to *S. Typhi* Vi-phage- type E1 and *S. Paratyphi A* phage type PT1 in the western world among those who had traveled to India and Pakistan in the recent past [35].

The latest studies showed evidence of significant resistance to ciprofloxacin and early evidence of resistance to ceftriaxone [36]. These observations correspond with the global picture. In Vietnam, uncomplicated typhoid fever cases due to MDR *S. Typhi* with reduced susceptibility to fluoroquinolones have been shown to be successfully treated with a 7-day course of azithromycin [37]. There have been reports of isolation and emergence of *S. Paratyphi A* since 1996 from across India, especially from central India and Orissa. The isolates were sensitive to chloramphenicol

and ampicillin [38].

Diagnosis and Treatment of Chronic Carriers of Typhoid

In developed countries where adequate medical facilities exist, it is important to screen all patients, suspects and contacts. Three negative stool cultures and one negative Vi antigen blood test should be the minimum requirements before a proven case of typhoid fever is determined non-infectious. However, the Vi test is of little use in tropical and subtropical countries where typhoid fever is endemic [14].

The treatment of the chronic carrier is a difficult problem. Trials with ampicillin have shown some success but even prolonged ampicillin administration in the convalescent stage may not prevent the carrier state [14].

A trial of combined chloramphenicol and aureomycin in patients who were excreting the typhoid bacillus showed that about 25% continued to excrete the bacillus after completion of the treatment. Presently, it still appears that prophylaxis remains the best method for preventing the spread of typhoid fever by chronic carriers who have not responded to both conservative and operative treatment. To date, ciprofloxacin and norfloxacin are found to be more effective drugs than prolonged courses of ampicillin or co-trimoxazole [14].

Prevention and Control

As the main route of typhoid transmission (enteric fever as a whole) is faeco-oral by contaminated food and water, the disease remains a serious problem in the developing world where it is confounded by low socio-economic conditions and overcrowding. Cost-of-illness studies have shown that the burden of disease increases in most countries upon the emergence of multi-drug resistant forms of enteric fever (unpublished data).

Hence, a need for prevention and control has gained enormous importance in recent years. As humans are the only reservoir of this faeco-orally transmitted disease, preventive measures include improvement of water supply and sanitation facilities.

However, instituting these measures requires a huge investment, making it an almost unachievable task, especially in resource-poor countries where they are needed most. For comprehensive control measures, cases need to be diagnosed early followed by provision of prompt and appropriate treatment. Carriers need to be identified efficiently and early treatment instituted. Additionally, a strong surveillance system should be in

place for early detection of both cases and carriers. Most policy makers in developing countries resort to a comprehensive approach to prevent typhoid through immunisation, thus combining a short-term measure with long-term solutions. An effective vaccine against *S. Para A* is not available to date.

Vaccines

Vaccination of high-risk populations is considered the most promising strategy for the control of typhoid fever. The concept of vaccination against typhoid began in the 1960s when field trials showed the effectiveness of a killed vaccine, reporting a protection rate of approximately 70% after two doses [39]. It was a heat-inactivated, phenol preserved, whole cell typhoid and paratyphoid vaccine constituting *S. Typhi*, *S. Paratyphi A* and *S. Paratyphi B*. The vaccine had a reasonable protection level but severe reactogenicity due to the presence of extra protein components from *S. Paratyphi A* and *B*. The World Health Organization (WHO) recommended discontinuation of this vaccine as it evoked unacceptable adverse effects; it was thereafter abandoned as a public health tool.

In the 1980s, two licensed, newer generation, well-tolerated typhoid vaccines were available, which promised protection without significant adverse effects: the live, attenuated oral vaccine, Ty21a, and the injectable subunit Vi polysaccharide vaccine. Studies conducted in Chile showed that 3 doses of Ty21a conferred a protection of around 62% over a 7-year period and almost 80% protection against typhoid fever over a surveillance span of 5 years. [40]. The same trial showed that the vaccine conferred significant protection against paratyphoid B fever using pool data from two different sites [41]. Both the Ty21a and Vi polysaccharide (PS) vaccine provide significant protection against typhoid by distinctly different immune mechanisms. Vi stimulates the IgG antibody while Ty21a induces humoral and cell-mediated immune responses but not the Vi antibody [42].

The Vi vaccine has been targeted for accelerated introduction into public health programs, due to several advantages it has over Ty21a, including consistent efficacy results (64-77%) even in areas of high typhoid incidence [43]; a single-dose regimen; the lack of patent protection; and less strict cold chain requirements. A review article showed that both the Ty21a and Vi vaccines are less toxic and equally effective than the conventional vaccine [40]. In South Africa, Vi provided a protection coverage of 55% over a 3-year period [44]. A study done in Vietnam to elicit

the efficacy of the Vi vaccine bound to nontoxic recombinant *Pseudomonas aeruginosa* exotoxin A (rEPA) among children 2 to 5 years of age showed that it is safe and immunogenic and has more than 90% efficacy in this age group [42]. A large-scale, community-based demonstration trial of the Vi vaccine has recently been concluded in Kolkata, India, among a population of 60,000 with a coverage of 69%. The results are awaited. If proven effective, this vaccine can be incorporated in India's public health program.

Despite the availability of these vaccines and the WHO's recommendation for the use of vaccines among school children in endemic areas, the use is quite limited because of cost, lack of proper data, and the vaccine's ineffectiveness in children under 2 years of age. In view of the increasing number of infections with *S. Paratyphi A*, development of a suitable vaccine against *S. Paratyphi A* is urgently needed.

Conclusion

The existence of multidrug-resistant bacteria is a serious and growing problem in the treatment of typhoid, especially in the developing world. This situation has been further complicated by the emergence of quinolone resistant strains with reduced susceptibility to FQs, which is a major concern of clinicians who treat enteric fever. When bacteria prove to be resistant to standard antibiotics, morbidity and mortality rates increase. Failure to treat an infection properly leads to prolonged illness, thus increasing the chance of developing a carrier state in which persons are contagious and able to spread the resistant strain to others. As plasmid-mediated mutagenesis among circulating strains occurs much more quickly than the development of new drugs, there is always a fear that highly lethal strains of resistant bacteria will evolve, leaving physicians with no effective way to combat them. Therefore, vaccination has been proven to be an effective way of controlling typhoid in resource-poor countries, especially in vulnerable age groups, mainly children under 15 years of age.

However, the proportion of prevalence of typhoid and paratyphoid around the globe is changing due to altered urbanisation and food habits. As the risk factors for both diseases may not coincide, the typhoid vaccine is not found to be protective against paratyphoid. Some other strategy, such as the development of a suitable conjugate vaccine against both serovars, is required to control the endemicity of the disease in developing countries such as India.

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