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## Global trends in typhoid and paratyphoid fever

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### Abstract

Typhoid and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and southeast Asia where enteric fever is associated with poor sanitation and unsafe food and water. High quality incidence data from Asia are underpinning efforts to expand access to typhoid vaccines. Efforts are underway to develop vaccines that are immunogenic in infants following a single dose and that can be produced locally in endemic countries. The growing importance of *S. Paratyphi A* in Asia is concerning. Antimicrobial resistance has sequentially emerged to traditional first-line drugs, fluoroquinolones, and now to third generation cephalosporins, posing patient management challenges. Azithromycin has proven to be effective alternatives for uncomplicated typhoid fever. The availability of full genome sequences for *S. Typhi* and *S. Paratyphi A* confirms their place as monomorphic, human-adapted pathogens vulnerable to control measures if international efforts can be redoubled.

### Keywords

Antimicrobial drug resistance; epidemiology; paratyphoid fever; prevention and control; typhoid fever

### INTRODUCTION

Enteric fever is a systemic infection caused by the human adapted pathogens *Salmonella enterica* serotype Typhi (*S. Typhi*) and *S. Paratyphi A*, B, and C. These organisms are important causes of febrile illness among crowded and impoverished populations with inadequate sanitation who are exposed to unsafe water and food, and also pose a risk to travelers visiting endemic countries [1]. This review addresses recent trends in global epidemiology, approaches

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to prevention and control, antimicrobial resistance and patient management, and the genomics of these organisms.

## EPIDEMIOLOGY

### Burden of illness and death

In the year 2000 it was estimated that typhoid fever caused 21.7 million illnesses and 217,000 deaths and paratyphoid fever 5.4 million illnesses worldwide [2]. Infants, children, and adolescents in south-central and south-eastern Asia experience the greatest burden of illness [2]. Typhoid and paratyphoid fever most often present as clinically similar acute febrile illnesses and accurate diagnosis relies on laboratory confirmation [3]. Bone marrow culture remains the gold standard diagnostic test for enteric fever [4]. Efforts to develop serologic methods for the diagnosis of typhoid fever that improve on the poor performance of the Widal test still suffer from substantial limitations of both sensitivity and specificity [5]. Serological approaches to the diagnosis of *S. Paratyphi* A, B, and C have been developed but have not been evaluated or adapted for field use [6]. Consequently blood culture, a less sensitive method than bone marrow culture, is often the practical first choice test for both patient diagnosis and for epidemiologic evaluation of *S. Typhi* and *S. Paratyphi* burden. However, most enteric fever occurs in low- and middle-income countries where blood culture capacity is often unavailable, unaffordable, or inconsistently applied [7]. The most robust approach to the measurement of typhoid and paratyphoid fever incidence is by regular, community-wide household visits to identify persons with febrile illness from whom blood for culture confirmation may be obtained. Alternatively, the results of surveys of health seeking behavior and sentinel healthcare facility-based surveillance may be combined to estimate incidence [3]. Because of the limited availability of blood culture services and the logistic challenges of enteric fever surveillance techniques capable of measuring disease incidence, the burden of typhoid and paratyphoid fever is poorly characterized in much of the world, particularly in sub-Saharan Africa. Furthermore, accurate estimates of rates of complications and death at the population level are not available. To reduce gaps in the current understanding of typhoid fever incidence, complications, and case-fatality rate, large population-based studies using blood culture confirmation of cases are needed in representative sites, especially in low and medium human development index countries outside Asia [8].

### Epidemiologic trends

Despite the limitations of currently available epidemiologic data, a number of recent trends in enteric disease epidemiology have emerged in the African, Asian, and Latin American regions. In sub-Saharan Africa where the burden of enteric fever is the least well characterized, hospital-based studies indicate that non-Typhi serotypes of *Salmonella*, particularly *S. Enteritidis* and *S. Typhimurium*, greatly outnumber *S. Typhi* and *S. Paratyphi* as causes of bloodstream infection [9,10]. Nonetheless, outbreaks of typhoid fever are frequently reported from sub-Saharan Africa often with large numbers of patients presenting with intestinal perforations leaving open important questions about the epidemiology of enteric fever in the region [11]. In Asia, a large population-based prospective study using standardized surveillance methods has estimated typhoid fever incidence in China, India, Indonesia, Pakistan, and Vietnam in order to inform typhoid fever vaccine policy. This study confirmed the high incidence of typhoid fever in the region, particularly among children and adolescents, but also demonstrated that substantial variation in incidence occurs between surveillance sites in the same region [12]. Simultaneously, *S. Paratyphi* A appears to be responsible for a growing proportion of enteric fever in a number of Asian countries, sometimes accounting for 50% of *Salmonella* bloodstream isolates among enteric fever patients. This trend raises important concerns about the impact of typhoid fever vaccine on enteric fever rates [13,14]. In Latin America, there is evidence that typhoid fever incidence has declined in parallel with both economic transition

and with water and sanitation measures introduced to control cholera during the last pandemic [2]. While enteric fever remains a public health problem in the region, it does provide a model for what can be accomplished for high incidence countries elsewhere.

## PREVENTION AND CONTROL STRATEGIES

Contaminated water and food are important vehicles for transmission of typhoid fever. Historical surveillance data suggest that enteric fever was endemic in Western Europe and North America and that rates declined in parallel with the introduction of treatment of municipal water, pasteurization of dairy products, and the exclusion of human feces from food production [15]. Today enteric fever prevention focuses on improving sanitation, ensuring the safety of food and water supplies, identification and management of chronic carriers of *S. Typhi*, and the use of typhoid vaccines to reduce the susceptibility of hosts to infection.

### Non-vaccine measures

Extending the benefits of improved sanitation and the availability of safe water and food achieved in industrialized countries a century ago to low- and middle-income countries has proved to be a challenge. United Nations Millennium Development Goal (MDG) 7 sets a target to halve by 2015 the proportion of the population without sustainable access to safe drinking water and basic sanitation.

Recent evidence suggests that interventions to improve the quality of drinking water may be relatively more important for the prevention of enteric infection relative to sanitation measures than was previously thought [16]. While centrally-treated reticulated water for all is an important goal, a growing body of research suggests that improving water quality at the household level as well as at the source can significantly reduce diarrhea [16]. Although not formally evaluated with enteric fever as an outcome, it is likely that interventions that reduce diarrheal diseases transmitted through contaminated water and food, and poor hygiene, would have similar effects on rates of enteric fever.

The identification and management of *S. Typhi* carriers, particularly those involved with food production, has proven to be an important strategy for the control of typhoid fever in low-incidence settings. While carriers can be identified by serial culture of stool specimens, this approach is labor intensive. Anti-Vi antibody assays have proven to be a useful alternative to stool culture for identifying carriers in outbreak settings [17]. However, when testing at the community level in a typhoid endemic area the high background levels of anti-Vi antibody appear to render the method impractical [18] and the method would also have limitations in settings where Vi-based vaccine use is widespread.

### Vaccines

Currently there are two vaccines available in the United States for the prevention of typhoid fever. The Ty21a vaccine (Vivotif Berna®) is a live attenuated oral vaccine containing the *S. Typhi* strain Ty21a, while the parenteral Vi vaccine (Typhim-Vi®), is based on the *S. Typhi* Vi antigen (Table). Ty21a is available as enteric capsules and is licensed in the United States for use for children  $\geq 6$  years of age and elsewhere for children as young as 2 years of age. The Vi-based vaccine is licensed in the United States for children aged  $\geq 2$  years. The effectiveness of parenteral Vi vaccine has recently been confirmed in young children and the protection of unvaccinated neighbors of Vi vaccinees has been demonstrated [19]. A new conjugate vaccine under development, Vi-rEPA, includes Vi antigen bound to a nontoxic recombinant protein that is antigenically identical to *Pseudomonas aeruginosa* exotoxin. It has been shown to be safe and immunogenic in Vietnamese children aged 2 to 5 years, providing protective efficacy of 91.5% [20] and is undergoing evaluation in younger age groups. In addition, efforts are

underway to develop and evaluate improved live attenuated oral vaccines with the goals of maintaining safety while improving efficacy and reducing the number of doses required [21].

Since *S. Paratyphi* lack the Vi antigen, Vi-based vaccines are unlikely to provide protection against paratyphoid fever. There is evidence from pooled analyses of randomized controlled field trials done in Chile that Ty21a provides some limited protection against *S. Paratyphi* B [22] and a descriptive analysis of national enteric fever surveillance data among Israeli travelers suggests that Ty21a may offer protection against *S. Paratyphi* A [23]. Despite some preliminary efforts [24], there are currently no licensed vaccines against *S. Paratyphi* [25], a matter for great concern given the evidence for the emergence of this pathogen [14].

Despite having been evaluated among populations in endemic middle- and low-income countries, typhoid fever vaccines have been used predominantly among travelers from high-income countries [1] and only occasionally used in endemic settings [26]. However, this situation is changing thanks to the availability of high quality burden of disease data from endemic countries [12], the experience of typhoid vaccination programs in Thailand, China, Vietnam, and India [27], and of vaccine demonstration projects in five Asian countries [28]. Furthermore, a 2008 World Health Organization position paper on the use of typhoid vaccines provides a mandate to member states by suggesting that countries should consider the programmatic use of Ty21a and Vi vaccines for controlling endemic disease. The position paper indicates that the use of vaccine should be based on an understanding of the local epidemiology of typhoid fever in order to target vaccine to high risk groups, such as pre-school or school-age children and that vaccine should be implemented in the context of broad disease control efforts [29]. Ultimately, the adoption of typhoid vaccine in endemic settings would be greatly aided by the availability of vaccines that are efficacious in infants to facilitate integration with Expanded Programs of Immunization (EPI), that can be administered as a single dose, and that are produced locally to reduce cost [28].

Opinion on the use of typhoid vaccines to curtail epidemics has developed over time. Historically, expert groups have recommended to the WHO that epidemic typhoid control focus on the antimicrobial treatment of acute cases and on improvements in water and sanitation. The conservative approach to the use of vaccine was based on the requirement for multiple doses, the risk for adverse reactions, and concern that vaccination campaigns would divert resources away from attention to the source, usually sanitation and water problems. The effect of antimicrobial resistance on patient management [12], the availability of safe vaccines with simpler dosing regimens [1], the logistic challenges of rapidly addressing major water and sanitation infrastructure problems, combined with the success of mass vaccination programs in typhoid endemic countries have led to vaccine being more widely considered for epidemic control [30].

## ANTIMICROBIAL RESISTANCE AND PATIENT MANAGEMENT

Antimicrobial resistance is a major public health problem in both *S. Typhi* and *S. Paratyphi* and timely treatment with appropriate antimicrobial agents is important for reducing the mortality of enteric fever [31].

### Multiple drug resistance

Resistance to the traditional first-line antimicrobial agents ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole defines multiple drug resistance (MDR) in *Salmonella*. The MDR phenotype has been shown to be widespread among *S. Typhi* for many years [32] and is present, albeit at lower rates, among *S. Paratyphi* [33,34]. Surveillance studies demonstrate considerable geographic variation in the proportion of *S. Typhi* isolates that are MDR within the same region, with sites in India, Pakistan, and Vietnam having higher rates of MDR than

sites in China and Indonesia [12]. Furthermore, longitudinal studies at the same site demonstrate marked changes in the proportion of *S. Typhi* and *S. Paratyphi A* with MDR over time, including reductions in the proportion of isolates with MDR [35].

### Fluoroquinolone resistance

The wide distribution and high prevalence of MDR among *Salmonella* has led to fluoroquinolones assuming a primary role in the therapy for invasive salmonellosis. Some investigators have noted increases in the prevalence of more susceptible *S. Typhi* and *S. Paratyphi* strains coinciding with a switch from traditional first-line antimicrobials to fluoroquinolones for the management of enteric fever [35,36]. However, the widespread use of fluoroquinolones has also been associated with decreased susceptibility [37] and documented resistance to this class of drugs [38]. A single chromosomal mutation in the quinolone resistance determining region (QRDR) of the *gyrA* gene may be sufficient to result in decreased ciprofloxacin susceptibility (DCS). Nalidixic acid resistance in the presence of ciprofloxacin susceptibility had been thought to be a reliable indicator of DCS, but this is now known not to be the case and many have suggested that DCS is most reliably determined by measurement of the ciprofloxacin minimum inhibitory concentration [39,40]. Patients with enteric fever due to isolates with DCS are more likely to have prolonged fever clearance times and higher rates of treatment failure [41]. In the United States MDR and DCS *S. Typhi*, are associated with travel to the Indian subcontinent [37]. In addition to DCS, ciprofloxacin resistance has been reported among both *S. Typhi* [42] and *S. Paratyphi A* [35].

### Future concerns in antimicrobial resistance

As fluoroquinolone use continues to expand and as DCS and fluoroquinolone resistance drives the use of third generation cephalosporins and other agents for the management of enteric fever, new patterns of antimicrobial resistance can be anticipated. Patterns of antimicrobial resistance seen in non-Typhi *Salmonella* and Enterobacteriaceae may emerge in *S. Typhi* and *S. Paratyphi*. Although quinolone resistance among Enterobacteriaceae usually arises due to mutations in the QRDR of *gyrA*, plasmid-mediated resistance is increasingly recognized. Plasmid-mediated quinolone resistance is associated with *qnr* genes that encode a protein that protects DNA gyrase from ciprofloxacin and by *aac(6′)-Ib-cr*, an aminoglycoside-modifying enzyme with activity against ciprofloxacin [34]. Plasmids bearing *qnr* or *aac(6′)-Ib-cr* may also contain an extended-spectrum cephalosporin resistance gene, which would pose a threat to the success of two major antimicrobial classes for the management of invasive salmonellosis. Indeed, an *S. Typhi* isolate producing an SHV-12 extended-spectrum beta-lactamase (ESBL) [43] and ESBL-producing *S. Paratyphi A* have recently been reported [44]. Of further concern, rare non-Typhi *Salmonella* isolates have been described containing the carbapenemase, *bla*<sub>IMP-4</sub> as well as *qnrB4* conferring both meropenem resistance and DCS [45].

### Antimicrobial management of enteric fever

Optimal antimicrobial management of patients with enteric fever depends on an understanding of local patterns of antimicrobial resistance and is enhanced by the results of antimicrobial susceptibility testing of the *Salmonella* isolated from the individual patient. Ciprofloxacin continues to be widely used, but clinicians need to be aware that patients with *Salmonella* with DCS may not respond adequately [41]. In this circumstance, third generation cephalosporins such as ceftriaxone may be used. However, the cost and route of administration make ceftriaxone less suitable for patient management in some low- and middle-income countries and the oral third generation cephalosporin cefixime appears to be inferior to other oral agents both in terms of fever clearance time and treatment failure [46]. In these circumstances, recent clinical trials suggest that azithromycin 500mg once daily for 7 days in adults or azithromycin 20mg/kg/day up to a maximum of 1,000mg/day for 7 days in children is useful for the

management of uncomplicated typhoid fever [47]. Due to its pharmacokinetic profile, gatifloxacin has potential as a new agent for managing patients infected with DCS isolates [48] but carries risk for dysglycemia which may limit its widespread use.

## GENOMICS

The complete genome sequence has been determined for *S. Typhi* strains CT18 [49] and Ty2 [50] and for *S. Paratyphi A* strain ATCC9150 [51]. The availability of these genome sequences and of newer sequencing technologies that make draft genome sequence simpler and more cost effective provide new opportunities to understand the evolution of *S. Typhi* and *S. Paratyphi A*. Sequenced based molecular subtyping also brings more resolution to the molecular epidemiology of these pathogens than is afforded by more traditional methods such as pulsed field gel electrophoresis (PFGE).

### Evolution of *S. Typhi* and *S. Paratyphi A*

Comparing the sequence diversity at multiple, conserved housekeeping genes by multilocus sequence typing (MLST) suggests that *S. Typhi* has a relatively recent origin 15,000 to 150,000 years ago during the human hunter-gatherer phase [52]. Full sequence analysis suggests that *S. Typhi* and *S. Paratyphi A* are much more closely related to each other than they are to other *S. enterica* serotypes [51]. Furthermore, the genomes of both *S. Typhi* and *S. Paratyphi A* show little sequence diversity and considerable loss of gene function through pseudogene formation and gene deletion. These features are found in many host-restricted pathogenic bacteria compared to their host-generalist relatives and are likely to be the result of selection by the host and genetic drift associated with population bottlenecks during or following adaptation to the new niche [53,54].

## CONCLUSIONS

Enteric fever remains a major public health challenge. Economic development and progress towards the achievement of MDG 7 will assist low- and middle-income countries experience similar reductions in enteric fever as were seen in industrialized countries a century ago. The occurrence of enteric fever in poor populations with limited access to diagnostic services means that disease burden is poorly quantified and policy makers have lacked the data needed to make decisions about the deployment of enteric fever prevention measures and vaccines. However, recent studies and vaccine demonstration projects are beginning to change this situation in Asia. Such data are not yet available for other regions, particularly sub-Saharan Africa. While Ty21a and Vi polysaccharide vaccines are effective, the development of cheap, safe vaccines with efficacy among infants that can provide protective immunity after a single dose and that could be easily adapted for EPI would facilitate adoption into national programs. The growing importance of *S. Paratyphi A* as a cause of enteric fever is of great concern, particularly due to the lack of availability of an effective vaccine.

Antimicrobial resistance continues to emerge in *S. Typhi* and *S. Paratyphi* resulting in loss over time of the value of traditional first-line drugs and fluoroquinolones. DCS and more recently fluoroquinolone resistance have led to greater use of third generation cephalosporins. Azithromycin and the newer fluoroquinolone gatifloxacin show some promise for the management of uncomplicated typhoid fever and provide a useful alternative to ceftriaxone for settings where a cheaper oral regimen is needed. The historical adaptation of *Salmonella* to patterns of antimicrobial use suggests that vigilance for the emergence of ceftriaxone-resistant strains is warranted.

Recent insights into the evolution of *S. Typhi* and *S. Paratyphi A* from genomics confirm that the organisms are genetically monomorphic and show other features of highly host-adapted

pathogens. These features remind us of the organisms' vulnerabilities and the potential for major gains in disease control. Added to the increasing complexity of managing enteric fever due to antimicrobial resistance, there is a strong case for much greater effort in disease control through improvements in sanitation, greater access to safe water and food, identification and treatment of *S. Typhi* carriers, and the more widespread use of currently available vaccines in high-risk populations.

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## References

- Whitaker JA, Franco-Paredes C, del Rio C, Edupuganti S. Rethinking typhoid fever vaccines: implications for travelers and people living in highly endemic areas. *J Travel Med* 2009;16:46–52. [PubMed: 19192128]
- Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. *Bull World Health Organ* 2004;82:346–53. [PubMed: 15298225]
- Crump JA, Youssef FG, Luby SP, et al. Estimating the incidence of typhoid fever and other febrile illnesses in developing countries. *Emerg Infect Dis* 2003;9:539–44. [PubMed: 12737736]
- Gilman RH, Terminel M, Levine MM, Hernandez-Mendoza P, Hornick RB. Relative efficacy of blood, urine, rectal swab, bone-marrow, and rose-spot cultures for recovery of *Salmonella* Typhi in typhoid fever. *Lancet* 1975;1:1211–3. [PubMed: 48834]
- Olsen SJ, Pruckler J, Bibb W, et al. Evaluation of rapid diagnostic tests for typhoid fever. *J Clin Microbiol* 2004;42:1885–9. [PubMed: 15131144]
- Chart H, Cheasty T, De Pinna E, et al. Serodiagnosis of *Salmonella enterica* serovar Typhi and *S. enterica* serovars Paratyphi A, B and C human infections. *J Med Microbiol* 2007;56:1161–6. [PubMed: 17761477]
- Archibald LK, Reller LB. Clinical microbiology in developing countries. *Emerg Infect Dis* 2001;7:302–5. [PubMed: 11294729]
- Crump JA, Ram PK, Gupta SK, Miller MA, Mintz ED. Part 1. Analysis of data gaps pertaining to *Salmonella enterica* serotype Typhi infections in low and medium human development index countries, 1984–2005. *Epidemiol Infect* 2008;136:436–48. [PubMed: 17686194]
- Shaw, AV.; Reddy, EA.; Crump, JA. Etiology of community-acquired bloodstream infections in Africa. 46th Annual Meeting of the Infectious Diseases Society of America; Washington, DC: Infectious Diseases Society of America; 2008.
- Mweu E, English M. Typhoid fever in children in Africa. *Trop Med Int Health* 2008;13:1–9. [PubMed: 18578806]
- Muyembe-Tamfum JJ, Veyi J, Kaswa M, Lunguya O, Verhaegen J, Boelaert M. An outbreak of peritonitis caused by multidrug-resistant *Salmonella* Typhi in Kinshasa, Democratic Republic of Congo. *Travel Med Infect Dis* 2009;7:40–3. [PubMed: 19174300]
- Ochiai RL, Acosta CJ, Danovaro-Holliday MC, et al. A study of typhoid fever in five Asian countries: disease burden and implications for control. *Bull World Health Organ* 2008;86:260–8. [PubMed: 18438514]
- Woods CW, Murdoch DR, Zimmerman MD, et al. Emergence of *Salmonella enterica* serotype Paratyphi A as a major cause of enteric fever in Kathmandu, Nepal. *Trans R Soc Trop Med Hyg* 2006;100:1063–7. [PubMed: 16714040]
- Ochiai RL, Wang XY, von Seidlein L, et al. *Salmonella* Paratyphi A rates, Asia. *Emerg Infect Dis* 2005;11:1764–6. [PubMed: 16318734]
- Anonymous. Typhoid in the large cities of the United States in 1919: eighth annual report. *JAMA* 1920;74:672–5.

16. Clasen T, Schmidt W-P, Rabie T, Roberts I, Cairncross S. Interventions to improve water quality for preventing diarrhoea: systematic review and meta-analysis. *Brit Med J* 2007;334:782. [PubMed: 17353208]
17. Engleberg NC, Barrett TJ, Fisher H, Porter B, Hurtado E, Hughes JM. Identification of a carrier by using Vi enzyme-linked immunosorbent assay serology in an outbreak of typhoid fever in an Indian reservation. *Journal of Clinical Microbiology* 1983;18:1320–2. [PubMed: 6655039]
18. Gupta A, My Thanh NT, Olsen SJ, et al. Evaluation of community-based serologic screening for identification of chronic *Salmonella* Typhi carriers in Vietnam. *Int J Infect Dis* 2006;10:309–14. [PubMed: 16412678]
19. Sur D, Ochiai RL, Bhattacharya SK, et al. A cluster-randomized effectiveness trial of Vi typhoid vaccine in India. *N Eng J Med* 2009;361:335–44.
20. Lin FY, Ho VA, Kheim HB, et al. The efficacy of a *Salmonella* Typhi Vi conjugate vaccine in two-to-five-year-old children. *N Engl J Med* 2001;344:1263–9. [PubMed: 11320385]
21. Tacket CO, Levine MM. CVD 908, CVD 908-*htrA*, and CVD 909 live oral typhoid vaccines: a logical progression. *Clin Infect Dis* 2007;45:S20–3. [PubMed: 17582563]
22. Levine MM, Ferreccio C, Black RE, Lagos R, Martin OS, Blackwelder WC. Ty21a live oral typhoid vaccine and prevention of paratyphoid fever caused by *Salmonella enterica* serovar Paratyphi B. *Clin Infect Dis* 2007;45:S24–8. [PubMed: 17582564]
23. Meltzer E, Sadik C, Schwartz E. Enteric fever in Israeli travelers: a nationwide study. *J Travel Med* 2005;12:275–81. [PubMed: 16256052]
24. Ruan P, Xia X-P, Sun D, et al. Recombinant SpaO and H1a as immunogens for protection of mice from lethal infections with *Salmonella* Paratyphi A: implications for rational design of typhoid fever vaccines. *Vaccine* 2008;26:6639–44. [PubMed: 18834913]
25. Arya SC, Sharma KB. Urgent need for effective vaccine against *Salmonella* Paratyphi A, B and C. *Vaccine* 1995;13:1727–8. [PubMed: 8719526]
26. Levine MM. Mass vaccination to control epidemic and endemic typhoid fever. *Curr Top Microbiol Immunol* 2006;304:231–46. [PubMed: 16989273]
27. deRoeck D, Ochiai RL, Yang J, Anh DD, Alag V, Clemens JD. Typhoid vaccination: the Asian experience. *Expert Rev Vaccines* 2008;7:547–60. [PubMed: 18564010]
28. Ochiai RL, Acosta CJ, Agtini M, et al. The use of typhoid vaccines in Asia: the DOMI experience. *Clin Infect Dis* 2007;45:S34–8. [PubMed: 17582567]
29. World Health Organization. Typhoid vaccines: WHO position paper. *Wkly Epidemiol Record* 2008;83:49–60.
30. Yang HH, Kilgore PE, Yang LH, et al. An outbreak of typhoid fever, Xing-An county, People's Republic of China, 1999: estimation of the field effectiveness of Vi polysaccharide typhoid vaccine. *J Infect Dis* 2001;183:1775–80. [PubMed: 11372030]
31. Edelman R, Levine MM. Summary of an international workshop on typhoid fever. *Rev Infect Dis* 1986;8:329–49. [PubMed: 3726393]
32. Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant *Salmonella* Typhi: a worldwide epidemic. *Clin Infect Dis* 1997;24:S106–9. [PubMed: 8994789]
33. Gupta SK, Medalla F, Omondi MW, et al. Laboratory-based surveillance of paratyphoid fever in the United States: travel and antimicrobial resistance. *Clin Infect Dis* 2008;46:1656–63. [PubMed: 18422453]
34. Parry CM, Threlfall EJ. Antimicrobial resistance in typhoidal and nontyphoidal salmonellae. *Curr Opin Infect Dis* 2008;21:531–8. [PubMed: 18725804]
35. Maskey AP, Basnyat B, Thwaites GE, Campbell JI, Farrar JJ, Zimmerman MD. Emerging trends in enteric fever in Nepal: 9124 cases confirmed by blood culture 1993–2003. *Trans Royal Soc Trop Med Hyg* 2008;102:91–5.
36. Sood S, Kapil A, Das B, Jain Y, Kabra SK. Re-emergence of chloramphenicol-sensitive *Salmonella* Typhi. *Lancet* 1999;353:1241–2. [PubMed: 10217089]
37. Lynch MF, Blanton EM, Bulens S, et al. Typhoid fever in the United States, 1999–2006. *JAMA* 2009;302:859–65. [PubMed: 19706859]



38. Brown JC, Thomson CJ, Amyes SGB. Mutations of the *gyrA* gene of clinical isolates of *Salmonella* Typhimurium and three other *Salmonella* species leading to decreased susceptibilities to 4-quinolone drugs. *J Antimicrob Chemother* 1996;37:351–6. [PubMed: 8707746]
39. Crump JA, Barrett TJ, Nelson JT, Angulo FJ. Reevaluating fluoroquinolone breakpoints for *Salmonella enterica* serotype Typhi and for non-Typhi salmonellae. *Clin Infect Dis* 2003;37:75–81. [PubMed: 12830411]
40. Threlfall EJ, Ward LR, Skinner JA, Smith HR, Lacey S. Ciprofloxacin-resistant *Salmonella* Typhi and treatment failure. *Lancet* 1999;353:1590–1. [PubMed: 10334265]
41. Crump JA, Kretsinger K, Gay K, et al. Clinical response and outcome of infection with *Salmonella enterica* serotype Typhi with decreased susceptibility to fluoroquinolones: a United States FoodNet multicenter retrospective cohort study. *Antimicrob Agents Chemother* 2008;52:1278–84. [PubMed: 18212096]
42. Chuang C-H, Su LH, Perera J, et al. Surveillance of antimicrobial resistance in *Salmonella enterica* serotype Typhi in seven Asian countries. *Epidemiol Infect* 2009;137:266–9. [PubMed: 18474127]
43. Al Naiemi N, Zwart B, Rijnsburger MC, et al. Extended-spectrum-beta-lactamase production in a *Salmonella enterica* serotype Typhi strain from the Philippines. *J Clin Microbiol* 2008;46:2794–5. [PubMed: 18550740]
44. Pokharel BM, Koirala J, Dahal RK, Mishra SK, Khadga PK, Tuladhar NR. Multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing *Salmonella enterica* (serotypes Typhi and Paratyphi A) from blood isolates in Nepal: surveillance of resistance and a search for newer alternatives. *Int J Infect Dis* 2006;10:434–8. [PubMed: 16978898]
45. Nordmann P, Poirel L, Mak JK, White PA, McIver CJ, Taylor P. Multidrug-resistant *Salmonella* strains expressing emerging antibiotic resistance determinants. *Clin Infect Dis* 2008;46:324–5. [PubMed: 18171274]
46. Pandit A, Arjyal A, Day JN, et al. An open randomised comparison of gatifloxacin versus cefixime for the treatment of uncomplicated enteric fever. *PLoS ONE* 2007;2:e524. [PubMed: 17565377]
47. Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). *Cochrane Database of Systematic Reviews* 2008;4 Art. No.: CD006083.
48. Dolecek C, La TTP, Rang NN, et al. A multi-center randomised controlled trial of gatifloxacin versus azithromycin for the treatment of uncomplicated typhoid fever in children and adults in Vietnam. *PLoS ONE* 2008;3:e2188. [PubMed: 18493312]
49. Parkhill J, Dougan G, James KD, et al. Complete genome sequence of a multidrug resistant *Salmonella enterica* serovar Typhi CT18. *Nature* 2001;413:848–52. [PubMed: 11677608]
50. Deng W, Liou SR, Plunkett G, et al. Comparative genomics of *Salmonella enterica* serovar Typhi strains Ty2 and CT18. *J Bacteriol* 2003;185:2330–7. [PubMed: 12644504]
51. McClelland M, Sanderson KE, Clifton SW, et al. Comparison of genome degradation in Paratyphi A and Typhi, human-restricted serovars of *Salmonella enterica* that cause typhoid. *Nature Genetics* 2004;36:1268–74. [PubMed: 15531882]
52. Kidgell C, Reichard U, Wain J, et al. *Salmonella* Typhi, the causative agent of typhoid fever is approximately 50,000 years old. *Infect Genet Evol* 2002;2:39–45. [PubMed: 12797999]
53. Holt KE, Thomson NR, Wain J, et al. Pseudogene accumulation in the evolutionary histories of *Salmonella enterica* serovars Paratyphi A and Typhi. *BMC Genomics* 2009;10:36. [PubMed: 19159446]
54. Achtman M. Evolution, population structure, and phylogeography of genetically monomorphic bacterial pathogens. *Annu Rev Microbiol* 2008;62:53–70. [PubMed: 18785837]
55. Centers for Disease Control and Prevention. US Department of Health and Human Services. CDC Health Information for International Travel 2010; Atlanta, GA: 2009. Typhoid and paratyphoid fever.

Table

Dosage and schedule for typhoid fever vaccination\*

Vaccination	Age (yrs)	Dose (mode of administration)	No. of doses	Dosing interval	Boosting interval
<b>Oral live attenuated Ty21a vaccine (Vivotif)</b>					
Primary series	≥6	1 capsule (oral)	4	48 hrs	NA
Booster	≥6	1 capsule (oral)	4	48 hrs	Every 5 yrs
<b>Vi capsular polysaccharide vaccine (Typhim Vi)</b>					
Primary series	≥2	0.50 mL (intramuscular)	1	NA	NA
Booster	≥2	0.50 mL (intramuscular)	1	NA	Every 2 yrs

\* Adapted from CDC Health Information for International Travel 2010 [55].

NA = Not applicable