Global Trends in Typhoid and Paratyphoid Fever

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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 after a single dose and that can be produced locally in countries of endemicity. The growing importance of *Salmonella enterica* serotype Paratyphi A in Asia is concerning. Antimicrobial resistance has sequentially emerged to traditional first-line drugs, fluoroquinolones, and third-generation cephalosporins, posing patient treatment challenges. Azithromycin has proven to be an effective alternative for treatment of uncomplicated typhoid fever. The availability of full genome sequences for *S. enterica* serotype Typhi and *S. enterica* serotype Paratyphi A confirms their place as monomorphic, human-adapted pathogens vulnerable to control measures if international efforts can be redoubled.

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

EPIDEMIOLOGY

Burden of illness and death. In 2000, typhoid fever caused an estimated 21.7 million illnesses and 217,000 deaths, and paratyphoid fever caused an estimated 5.4 million illnesses worldwide [2]. Infants, children, and adolescents in south-central and Southeastern 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 epidemiologic evaluation of *S.* Typhi and *S.* Paratyphi burden. However, most enteric fever occurs in low- and middle-income countries where blood cultures are often unavailable, unaffordable, or inconsistently applied [7]. The most robust approach to the measurement of incidence of typhoid and paratyphoid fever is by regular, community-wide household visits to identify persons with febrile illness from whom blood samples for culture confirmation may be obtained. Alternatively, the results of surveys of health-seeking behavior and sentinel health care 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

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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. enterica* serotype Enteritidis and *S. enterica* serotype 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 estimated typhoid fever incidence in China, India, Indonesia, Pakistan, and Vietnam, 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 was responsible for a growing proportion of enteric fever in a number of Asian countries, sometimes accounting for 50% of *Salmonella* bloodstream isolates among patients with enteric fever. 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 decreased in parallel with both economic transition and with water and sanitation measures introduced to control cholera during the last pandemic [2]. Although enteric fever remains a public health problem in the region, it does provide a model for what can be accomplished for countries with a high incidence of enteric fever.

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 decreased in parallel with the introduction of treatment of municipal water, pasteurization of dairy products, and the exclusion of human feces from food production [15]. At present, enteric fever prevention focuses on improving sanitation, ensuring the safety of food and water supplies, identification and treatment of chronic carriers of *S.* Typhi, and use of typhoid vaccines to reduce the susceptibility of hosts to infection.

Nonvaccine measures. Extending the benefits of improved sanitation and the availability of safe water and food that was achieved in industrialized countries a century ago to low- and middle-income countries has proved to be a challenge. United Nations Millennium Development Goal 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]. Although 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 the rate of diarrheal diseases transmitted through contaminated water, food, and poor hygiene would have similar effects on rates of enteric fever.

The identification and treatment 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. Although 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 used at the community level in an area where typhoid is endemic, the high background levels of anti-Vi antibody appear to render the method impractical [18]. Furthermore, the method would also have limitations in settings where Vi-based vaccine use is widespread.

Vaccines. Currently, there are 2 vaccines available in the United States for the prevention of typhoid fever. The Ty21a vaccine is a live, attenuated, oral vaccine containing the *S.* Typhi strain Ty21a, and the parenteral Vi vaccine is based on the *S.* Typhi Vi antigen (Table 1). Ty21a is available as enteric capsules and is licensed in the United States for use in children ⩾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 ⩾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 2–5 years, providing protective efficacy of 91.5% [20], and is undergoing evaluation in younger age groups. In addition, efforts are underway to

Table 1 Dosage and Schedule for Typhoid Fever Vaccination

Vaccination	Age, years	Dose (mode of administration)	No. of doses	Dosing interval	Boosting interval
Oral, live, attenuated Ty21a vaccine					
Primary series	≥6	1 capsule (oral)	4	48 h	NA
Booster	≥6	1 capsule (oral)	4	48 h	Every 5 years
Vi capsular polysaccharide vaccine					
Primary series	≥2	0.50 mL (intramuscular)	1	NA	NA
Booster	≥2	0.50 mL (intramuscular)	1	NA	Every 2 years

NOTE. Adapted from the Centers for Disease Control and Prevention Health Information for International Travel (2010) [55]. NA, not applicable.

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].

Because *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], which is a matter for concern, given the evidence for the emergence of this pathogen [14].

Despite having been evaluated in populations in middle- and low-income countries of endemicity, typhoid fever vaccines have historically been used predominantly among travelers from high-income countries [1] and have been only occasionally used in settings of endemicity [26]. However, this situation is changing because of the availability of high-quality burden of disease data from countries of endemicity [12]; the experience of typhoid vaccination programs in Thailand, China, Vietnam, and India [27]; and vaccine demonstration projects in 5 Asian countries [28]. Furthermore, a 2008 World Health Organization (WHO) 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 to target vaccine to groups at high risk of disease, such as preschool- 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 settings of endemicity would be greatly aided by the availability of vaccines that are efficacious in infants to facilitate integration with Expanded Programs of Immunization, that can be administered as a single dose, and that are produced locally to reduce cost [28].

Opinion about 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 from attention to the source, usually sanitation and water problems. The effect of antimicrobial resistance on patient treatment [12], the availability of safe vaccines with simpler dosing regimens [1], the logistic challenges of rapidly addressing major water and sanitation infrastructure problems, and the success of mass vaccination programs in countries where typhoid fever is endemic 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 associated with enteric fever [31].

Multidrug resistance. Resistance to the traditional first-line antimicrobial agents ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole defines multidrug resistance (MDR) in *S. enterica.* 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 in the same region, with sites in India, Pakistan, and Vietnam having higher rates of MDR isolates than sites in China and Indonesia [12]. Furthermore, longitudinal studies at the same site showed 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* species has led to fluoroquinolones assuming a primary role in the therapy for invasive salmonellosis. Some investigators have noted increases in the prevalence of *S.* Typhi and *S.* Paratyphi strains susceptible to traditional first-line antimicrobials coinciding with a switch 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 of the *gyrA* gene may be sufficient to result in decreased ciprofloxacin susceptibility. Nalidixic acid resistance in the presence of ciprofloxacin susceptibility had been thought to be a reliable indicator of decreased ciprofloxacin susceptibility; however, this is now known not to be the case, and many have suggested that decreased ciprofloxacin susceptibility is most reliably determined by measurement of the ciprofloxacin minimum inhibitory concentration [39, 40]. Patients with enteric fever due to isolates with decreased ciprofloxacin susceptibility are more likely to have prolonged fever clearance times and higher rates of treatment failure [41]. In the United States, *S.* Typhi with MDR and decreased ciprofloxacin susceptibility are associated with travel to the Indian subcontinent [37]. In addition to decreased ciprofloxacin susceptibility, 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 decreased ciprofloxacin susceptibility 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* species and Enterobactericeae may emerge in *S.* Typhi and *S.* Paratyphi. Although quinolone resistance among Enterobactericeae usually arises as the result of mutations in the quinolone resistance determining region 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 2 major antimicrobial classes for the management of invasive salmonellosis. Indeed, an *S.* Typhi isolate producing an SHV-12 extended-spectrum β-lactamase [43] and extended-spectrum β-lactamase–producing *S.* Paratyphi A have recently been reported [44]. Of further concern, rare non-Typhi *Salmonella* isolates have been described that contain the carbapenemase $bla_{\text{IMP-4}}$ and *qnrB4* conferring both meropenem resistance and decreased ciprofloxacin susceptibility [45].

Antimicrobial management of enteric fever. Optimal antimicrobial treatment 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 infected with *Salmonella* with decreased ciprofloxacin susceptibility 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 treatment 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 treatment (500 mg once daily for 7 days for adults or 20 mg/kg/day up to a maximum of 1000 mg/day for 7 days for children) is useful for the management of uncomplicated typhoid fever [47]. Because of its pharmacokinetic profile, gatifloxacin has potential as a new agent for treating patients infected with isolates with decreased ciprofloxacin susceptibility [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. Sequence-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.

Comparison of the sequence diversity at multiple, conserved housekeeping genes by multilocus sequence typing suggests that *S.* Typhi has a relatively recent origin (15,000–150,000 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 with 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 after adaptation to the new niche [53, 54].

CONCLUSIONS

Enteric fever remains a major public health challenge. Economic development and progress toward the achievement of Millennium Development Goal 7 will assist low- and middle-income countries with experiencing reductions in the rate of enteric fever that are similar to those that 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. Although 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 Expanded Programs of Immunization would facilitate adoption into national programs. The growing importance of *S.* Paratyphi A as a cause of enteric fever is of great concern, particularly because of 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. Decreased ciprofloxacin susceptibility and, more recently, fluoroquinolone resistance have led to greater use of third-generation cephalosporins. Azithromycin shows 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 because of 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 populations at high risk of infection.

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