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Review

Persistent Threat Of Typhoid Fever: Challenges In Endemic Regions And The Role Of Vaccination

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Abstract

Typhoid fever, caused by salmonella typhi (s.typhi) is a life-threatening disease, usually food-borne and commonly associated with international travel. the disease transmission remains endemic in many low- and middle-income countries, representing further hotspots for seeding new global outbreaks. china has historically. been affected by typhoid fever, but the respective roles of local transmission and importation remain unknown while typhoid fever has largely been eliminated in high-income regions which have developed modern water, sanitation, and hygiene facilities it remains a significant public health burden resulting in morbidity and mortality among millions of individuals in resource-constrained settings. prevention and control efforts are needed that integrate several high-impact interventions targeting facilities and infrastructure, including those addressing improvements in sanitation, access to safe water, and planned urbanization, together with parallel efforts directed at effective strategies for use of typhoid conjugate vaccines (tcv). the use of tcvs is a critical tool with the potential of having a rapid impact on typhoid fever disease burden; their introduction will also serve as an important strategy to combat evolving antimicrobial resistance to currently available typhoid fever treatments.

Keywords: salmonella typhi, typhoidal fever, transmission, exploiting genomics, pandemic clone

INTRODUCTION

Enteric fever, primarily caused by *Salmonella enterica* serovar Typhi (*S. Typhi*), remains one of the most prevalent bacterial infections in low- and middle-income countries (LMICs), with *Salmonella* Paratyphi (*S. Paratyphi*) as a secondary causative agent (Aljanaby & Medhat, 2017; Teferi et al., 2021). Humans serve as the exclusive reservoir for these pathogens, facilitating sustained transmission in endemic regions through fecal-oral contamination (Galgallo et al., 2018). The disease burden is staggering, with an estimated 25 million annual

cases and over 200,000 deaths, predominantly in Asia and Africa, where poor sanitation and limited access to clean water perpetuate outbreaks (Shahid et al., 2021; Awol et al., 2001).

Diagnostically, *S. Typhi* is identified by its characteristic Gram-negative, H_2S-positive, motile colonies with peritrichous flagella when cultured on Salmonella-Shigella (SS) agar (Masuet-Aumatell & Atouguia, 2021). Contaminated food and water are the primary transmission vehicles, with infection severity influenced by bacterial virulence factors and inoculum dose (Brockett et al., 2020; Milligan et al., 2018; Im et al., 2020). The Indian subcontinent reports the highest incidence, driven by overcrowding, inadequate WASH (water, sanitation, hygiene) infrastructure, and delayed medical intervention (Manesh et al., 2021).

Clinically, typhoid manifests with prolonged fever, headache, nausea, abdominal pain, and leukopenia, though symptom variability often complicates early diagnosis (Moser-Van der Geest et al., 2019). Blood and stool cultures remain the gold-standard diagnostic methods, despite challenges in resource-limited settings where rapid serological tests are often unreliable (Kumar & Kumar, 2017).

A critical emerging concern is antibiotic resistance, particularly in India, where >80% of *S. Typhi* isolates exhibit fluoroquinolone resistance, undermining first-line treatment (Crump, 2019). This resistance crisis is exacerbated by unregulated antibiotic use and inadequate surveillance, necessitating urgent adoption of Typhoid Conjugate Vaccines (TCVs) alongside improved WASH measures (Milligan et al., 2018).

Disease transmission dynamics are further shaped by socio-cultural practices, population density, and healthcare access (Crump, 2019). For instance, traditional food handling in endemic regions and reliance on untreated groundwater amplify outbreaks (Brockett et al., 2020). Meanwhile, urbanization without proper sanitation planning in LMICs creates high-risk environments (Galgallo et al., 2018).

Efforts to curb typhoid must integrate multicomponent strategies: (1) vaccination campaigns (TCVs have shown 80–90% efficacy in trials), (2) sanitation reforms, and (3) antimicrobial stewardship to preserve treatment efficacy (Teferi et al., 2021). Without such interventions, the cyclical burden of enteric fever fueled by climate change, migration, and drug resistance—will persist as a global health threat (Shahid et al., 2021).

Typhoid Fever: Etiology, Transmission Routes, and Risk Factors

Typhoid fever is caused by Salmonella enterica serovars Typhi (S. Typhi) and Paratyphi (S. Paratyphi A, B, C), both members of the Enterobacteriaceae family (Huang et al., 2020). These pathogens are distinguished from non-typhoidal Salmonella (NTS), which primarily cause gastroenteritis, particularly in children, whereas typhoidal strains lead to systemic infection (Crump & Mintz, 2010). Advanced molecular techniques, such as multiplex quantitative PCR, have enabled precise serotyping, confirming that S. Typhi corresponds to serotype D, while S. Paratyphi A, B, and C correspond to serotypes A, B, and C, respectively (Wirth et al., 2022).

Transmission occurs predominantly via the fecal-oral route, with contaminated water and food serving as primary vehicles (WHO, 2019). S. Typhi can survive for weeks in water and months in sewage, making poor sanitation infrastructure a major driver of outbreaks (Connor & Schwartz, 2005). In overcrowded urban slums and disaster-stricken regions, open defecation and inadequate waste disposal amplify transmission (Baker et al., 2018). Additionally, undercooked poultry, eggs, and unpasteurized dairy products are common foodborne sources, with studies detecting Salmonella in 57% of samples from Chinese poultry slaughterhouses using whole-genome sequencing (Li et al., 2021).

A unique feature of typhoidal Salmonella is its strict human-specific host adaptation, meaning no animal reservoirs exist unlike NTS, which infects livestock (Dougan & Baker, 2014). This restricts transmission to person-to-person contact or ingestion of food/water contaminated by human carriers (Parry et al., 2002). Asymptomatic carriers, particularly those with chronic gallbladder colonization, play a key role in long-term persistence (Gonzalez-Escobedo et al., 2011).

Dietary habits significantly influence infection risk. In Turkey, consumption of raw foods like çiğ köfte (spiced raw meat) and unwashed lettuce was linked to outbreaks (Hosoglu et al., 2003). Similarly, cut papaya, with its neutral pH, supports bacterial growth when left unrefrigerated, posing a major hazard in tropical regions (Aung et al., 2018).

Host susceptibility is modulated by gut microbiota composition. Broad-spectrum antibiotics (e.g., streptomycin) disrupt protective intestinal flora, facilitating S. Typhi invasion (Stecher et al., 2007). Malnutrition exacerbates this vulnerability by reducing commensal bacterial diversity, increasing typhoid risk (Monack et al., 2004). Thus, populations with poor diets and frequent antibiotic exposure face higher infection rates (Roumagnac et al., 2006).

Water contamination remains the most critical transmission pathway. In South Asia, reliance on groundwater contaminated by sewage seepage perpetuates endemicity (Gaffga et al., 2007). A single infected individual can pollute an entire water supply, as S. Typhi persists in freshwater for 7–14 days (Vollaard et al., 2004). Public defecation further compounds this issue, especially where sanitation coverage is low (Mogasale et al., 2014).

Climate and urbanization also contribute. Flooding disperses pathogens into drinking sources, while high population density facilitates rapid spread (Deen et al., 2014). In India and sub-Saharan Africa, monsoon seasons correlate with spikes in typhoid cases due to water contamination (John et al., 2016). Preventive strategies must address multiple transmission routes:

1. Vaccination: Typhoid Conjugate Vaccines (TCVs) show 81% efficacy in endemic areas (Patel et al., 2021).
2. Water Sanitation: Chlorination and piped water systems reduce outbreaks (Clasen et al., 2015).
3. Food Safety: Avoiding raw produce and proper cooking mitigate risk (Havelaar et al., 2015).
4. Antibiotic Stewardship: Preventing fluoroquinolone overuse curbs resistance (Klemm et al., 2018).

Without integrated interventions, typhoid will persist as a poverty-related disease, disproportionately affecting LMICs with weak health systems (Stanaway et al., 2019).

Epidemiology

Typhoid and paratyphoid fevers, collectively termed enteric fever, remain significant global health concerns despite being preventable diseases. According to Yash Srivastav and Aditya Srivastav (2023), the United States reports fewer than 100 culture-confirmed cases of paratyphoid fever and only about 350 cases of typhoid fever annually. However, these numbers starkly contrast with the global burden, where an estimated 26 million typhoid cases and 5 million paratyphoid infections occur each year, resulting in approximately 215,000 deaths (Antillón et al., 2017). The disparity highlights how enteric fever predominantly affects low- and middle-income countries (LMICs), particularly in South-Central Asia and sub-Saharan Africa, where inadequate water sanitation and poor hygiene infrastructure perpetuate transmission (Stanaway et al., 2019).

In industrialized nations, most cases are imported by travelers visiting friends and relatives (VFR travelers) in endemic regions (Angelo et al., 2018). These individuals pose particular risks as they are less likely to seek pre-travel medical advice, obtain typhoid vaccinations, or adhere to food safety precautions during their journeys (Heywood et al., 2021). The seasonal patterns of typhoid also show higher incidence in tropical and temperate climates, with outbreaks frequently linked to heavy rainfall, flooding, and contaminated groundwater (Baker et al., 2011). Salmonella Typhi accounts for most enteric fever cases globally, while Salmonella Paratyphi A infections outnumber Paratyphi B, though regional variations exist (Connor et al., 2020).

Recent surveillance data from South Asia indicates that S. Typhi may cause over 80% of enteric fever cases in this high-burden region (Saha et al., 2022). In India, where the Surveillance of Enteric Fever (SEF) study is ongoing, preliminary findings suggest the country bears the world's highest typhoid burden, though precise estimates await publication (John et al., 2023). Urban slums with overcrowded living conditions and open sewage systems serve as hotspots for transmission, with children aged 2–15 years being disproportionately affected (Mogasale et al., 2014). Alarmingly, the combination of rapid urbanization, population growth, and climate change has contributed to rising case numbers in many endemic areas (Pitzer et al., 2015).

Clinically, typhoid fever presentation has evolved in the antibiotic era. Classic signs like rose spots (observed in just 1.5% of U.S. cases) and splenomegaly (present in 10%) have become uncommon (Yousaf et al., 2020). Instead, nonspecific symptoms prolonged fever, headache, and constipation often delay diagnosis (Parry et al., 2002). Approximately 4% of patients become chronic carriers, maintaining S. Typhi in their biliary systems for months to years post-recovery (Gonzalez-Escobedo et al., 2011). Carrier states predominantly affect middle-aged women and individuals with gallstones or biliary abnormalities, with blood group antigens potentially influencing susceptibility (Näsström et al., 2014).

Antimicrobial resistance (AMR) has emerged as a critical challenge. Multidrug-resistant (MDR) strains resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole now circulate globally, while fluoroquinolone resistance exceeds 80% in some Asian regions (Klemm et al., 2018). Despite these trends, mortality rates have declined from historical estimates of 600,000 annual deaths to ~200,000, attributable to improved diagnostics, revised treatment protocols (e.g., azithromycin for uncomplicated cases), and better supportive care (GBD 2017 Typhoid and Paratyphoid Collaborators, 2019).

Prevention strategies show promise. Typhoid conjugate vaccines (TCVs) demonstrated 81–95% efficacy in trials, prompting WHO prequalification and Gavi-supported introductions in endemic countries (Patel et al., 2021). When combined with water, sanitation, and hygiene (WASH) interventions, TCVs could significantly reduce transmission (Andrews et al., 2020). However, persistent gaps exist: paratyphoid vaccines remain under development, chronic carriers require identification/treatment, and antimicrobial stewardship programs need expansion to curb resistance (Jin et al., 2017).

Ongoing research aims to refine burden estimates through blood culture surveillance while exploring novel interventions like phage therapy and Vi-tetanus toxoid conjugate vaccines (Darton et al., 2022). As urbanization and climate variability intensify, a One Health approach integrating human, animal, and environmental health will be essential to control enteric fever in vulnerable populations (Marks et al., 2022).

Pathophysiology

Pathogenesis, Diagnosis, and Management of Typhoid Fever: Current Perspectives

The natural history of *Salmonella enterica* serovar Typhi (*S. Typhi*) infection has been elucidated through pioneering work by Gordon Dougan, Paul Everest, John Wain, Mark Roberts, and Graham Rook, combining human volunteer studies with animal models (Dougan et al., 2021). The most validated animal model employs *Salmonella Typhimurium* in mice, which mirrors key aspects of human typhoid despite species-specific differences (Tsolis et al., 2011). Following ingestion, *S. Typhi* traverses the small intestinal mucosa via M-cells overlying Peyer's patches (PPs), subsequently invading mesenteric lymph nodes where primary replication occurs (Raffatellu et al., 2006). Transient primary bacteremia disseminates bacteria to the liver, spleen, and bone marrow, where macrophages phagocytose but fail to kill the pathogen, enabling intracellular multiplication (Nix et al., 2007). Clinical disease manifests during secondary bacteremia, when bacteria re-enter circulation 7–14 days post-infection (Keestra-Gounder et al., 2015). Hepatobiliary reinfection establishes a reservoir in the gallbladder, particularly in individuals with pre-existing biliary pathology (Gonzalez-Escobedo et al., 2011). Subsequent reinvasion of distal ileal PPs triggers a TH1-mediated immune response, causing PP hypertrophy, necrosis, and characteristic "typhoid ulcers" that may perforate during the third week of illness (Mills et al., 2018). Perforation complications occurring in <5% of cases but with 40–83% mortality if delayed >96 hours typically involve the terminal ileum (75% single perforation) and precipitate life-threatening peritonitis (Edelman et al., 2020).

Clinically, typhoid presents with a 1–14 day incubation period followed by nonspecific prodromal symptoms: sustained fever (step-ladder pattern in 40%), headache, abdominal pain, and either constipation (60%) or diarrhea (20–40%) in adults (Parry et al., 2002). The classic "rose spots" (blanching erythematous macules) now appear in <2% of cases due to early antibiotic use (Connor et al., 2020). Histopathologically, PP hyperplasia progresses to ulceration with neutrophilic infiltrates, while "typhoid nodules" granuloma-like macrophage aggregates with central necrosis develop in hepatic and splenic parenchyma (Mills et al., 2018). Intestinal hemorrhage arises from necrotic venule erosion, typically during the third week (Edelman et al., 2020).

Diagnostic challenges persist despite technological advances. As emphasized by Crump, Sjölund-Karlsson, Gordon, and Parry (2015), optimal diagnosis integrates clinical evaluation with microbiological and serological testing. Blood culture remains the gold standard, detecting 40–80% of cases pre-treatment, while bone marrow culture achieves >80% sensitivity but is rarely feasible in endemic settings (Wain et al., 2018). Automated systems like VITEK2® improve isolate identification (Aljanaby & Aljanaby, 2018), though pretreatment antibiotic use often necessitates molecular methods. PCR assays targeting *fliC* (flagellin) or *viaB* (Vi antigen) genes demonstrate 85–95% sensitivity in blood but require technical resources (Zhou et al., 2022). The century-old Widal test, despite poor specificity (50–70%) from cross-reactivity with other *Salmonellae*, persists in resource-limited areas due to low cost (Keddy et al., 2017). Rapid IgM lateral flow assays (e.g., Typhidot®, Tubex®) offer 75–90% sensitivity but variable specificity (60–95%) (Hendriksen et al., 2019). Emerging urine antigen tests for Vi polysaccharide show promise (75% sensitivity) but require validation (Andrews et al., 2020).

Therapeutic strategies confront escalating antimicrobial resistance (AMR). While chloramphenicol revolutionized care in 1948, multidrug-resistant (MDR) strains resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole now dominate in South Asia (Klemm et al., 2018). Fluoroquinolones (ciprofloxacin 500mg BD for 5–7 days) became first-line, but *gyrA* mutations confer resistance in >80% of Indian isolates (Yousaf et al., 2020). Azithromycin (1g daily for 5 days) and third-generation cephalosporins (ceftriaxone 2g IV daily for 7–10 days) are now preferred for uncomplicated and MDR cases respectively, achieving 90–95% cure rates with <3% fecal carriage (Arjyal et al., 2021). Combination therapy (azithromycin + ceftriaxone) reduces treatment failure to <5% in high-resistance settings (Dolecek et al., 2022). Severe cases require ICU monitoring for intestinal perforation, with surgical intervention mortality dropping to 15–25% with prompt laparotomy (Edelman et al., 2020).

Vaccination represents the most sustainable control measure. Three WHO-prequalified vaccines exist: (1) oral live-attenuated Ty21a (67% efficacy for 5 years), (2) Vi polysaccharide (Vi-PS; 55–70% efficacy for 2–3 years), and (3) Vi-conjugate (Vi-TT; Typbar-TCV®; 81–95% efficacy for ≥4 years) (Patel et al., 2021). TCVs overcome limitations of earlier vaccines by inducing T-cell memory (permitting use in children ≥6 months) and reducing asymptomatic carriage (Jin et al., 2017). Pakistan's 2019 TCV campaign during an XDR typhoid outbreak demonstrated 97% effectiveness in children (Qamar et al., 2022). The WHO's 2017 recommendation for TCV introduction in endemic countries has seen rollout in Liberia, Nepal, and Zimbabwe, though vaccine costs ($1.50/dose) remain prohibitive for some LMICs (Meiring et al., 2023).

Epidemiologically, typhoid disproportionately affects children 2–15 years old in South Asia (incidence >500/100,000), sub-Saharan Africa (>100/100,000), and Southeast Asia (>50/100,000) (GBD 2019 Typhoid Collaborators, 2022). While global mortality has declined from 600,000 (1990) to ~200,000 annually due to improved care, rising AMR threatens progress (Antillón et al., 2017). Climate modeling predicts a 5–10% incidence increase by 2030 from warming temperatures and flooding (Carlton et al., 2022). Elimination will require integrated strategies: (1) TCV mass vaccination in endemic zones, (2) WASH infrastructure investment (chlorination, sewage systems), and (3) AMR surveillance networks (Andrews et al., 2020). Novel approaches

like phage therapy (targeting XDR strains) and Vi-diphtheria toxoid conjugate vaccines (in Phase III trials) may soon expand the toolkit (Darton et al., 2022).

Table 1: Recommended Antibiotic Treatment for Typhoid Fever

Susceptibility Profile	First-Line Drug	Dosage & Duration	Alternative Options	Special Considerations
Fully Sensitive	Ciprofloxacin (Oral)	500 mg twice daily × 7–10 days	Azithromycin 1 g daily × 5 days	Avoid in pregnancy; monitor for QT prolongation.
MDR Strains	Azithromycin (Oral)	1 g daily × 5–7 days	Ceftriaxone 2 g IV daily × 7–10 days	Preferred for children; no resistance reported in endemic regions.
Fluoroquinolone-Resistant	Ceftriaxone (IV)	2 g once daily × 7–10 days	Cefixime 20 mg/kg/day oral × 7–10 days	Switch to oral cefixime if clinical improvement after 3–5 days.
XDR Strains	Meropenem (IV)	1 g every 8 hours × 7–10 days	Azithromycin + Ceftriaxone combo	Reserved for culture-confirmed XDR cases (resistant to ≥5 drug classes).
Severe/Complicated	Ceftriaxone (IV) + Azithromycin	Ceftriaxone: 2 g/day × 10–14 days + Azithromycin: 1 g/day × 7 days	Tigecycline (last-resort)	Surgical consult if perforation suspected; monitor for biliary carriage post-treatment.
Chronic Carriers	Ciprofloxacin + Amoxicillin	Ciprofloxacin: 750 mg twice daily × 4 weeks + Amoxicillin: 1 g three times daily × 6 weeks	C	

CONCLUSION

Typhoid fever is still a serious health concern in the world, especially in areas with inadequate access to clean water and poor sanitation. it is brought on by the salmonella typhi bacteria and is characterised by a persistent fever, gastrointestinal symptoms, and, if managed, possible consequences. typhoid fever still has a significant negative impact on healthcare systems, local economies, and impacted populations even with improvements in diagnosis and treatment, such as the use of medicines and vaccinations. a multimodal strategy is needed to control and prevent typhoid fever, including vaccine campaigns, infrastructure improvements for sanitation, promotion of hygienic practices, and antimicrobial stewardship. governments, healthcare professionals, international organisations, and communities must work together to lower the prevalence of typhoid fever, lessen its effects, and eventually eradicate it as a hazard to public health. The main tactics for preventing ty"hoid'disease are a clean and safe water source, sufficient sanitary facilities, and good hygiene habits. but these demand long-term political commitment, significant financial outlays, and sustainable investments. the wash situation in india has improved with the implementation of the wash programme, while there is still a large achievement gap. controlling the burden of disease has also been hampered by a number of other problems.

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