TYPHOID FEVER AND MULTIDRUG RESISTANCE: A COMPREHENSIVE REVIEW OF MECHANISMS, EPIDEMIOLOGY, AND THERAPEUTIC CHALLENGE

Abdul latif
Fergana medical institute of Public Health
Correspondence: zainnlateef@gmail.com

ABSTRACT

Background: Typhoid fever, caused by Salmonella enterica serovar Typhi (S. Typhi), remains a major infectious disease burden in low- and middle-income countries, with an estimated 13 million cases and over 130,000 deaths annually. The emergence and global dissemination of multidrug-resistant (MDR), fluoroquinolone-non-susceptible (FQNS), and extensively drug-resistant (XDR) strains has substantially reduced treatment options. Objectives: This review synthesises current evidence on the molecular epidemiology, resistance mechanisms, clinical management, and preventive strategies for MDR typhoid. Methods: A systematic literature search was conducted across PubMed, Embase, and Web of Science covering publications from 2000 to 2024, using the MeSH terms "Salmonella Typhi," "multidrug resistance," "XDR typhoid," "plasmid-mediated resistance," and "typhoid conjugate vaccine." Results: MDR S. Typhi emerged in the 1980s and is predominantly encoded by IncHI1 plasmids. The globally dominant H58 haplotype (genotype 4.3.1) carries chromosomally integrated resistance cassettes conferring resistance to first-line drugs. The XDR clone, first identified in Sindh, Pakistan in November 2016, additionally carries the IncY plasmid harbouring blaCTX-M-15 and qnrS, rendering it resistant to third-generation cephalosporins and fluoroquinolones, leaving only azithromycin and carbapenems as treatment options. Emerging azithromycin resistance, driven by acrB mutations, represents a critical threat. Typhoid conjugate vaccines (TCVs) demonstrate 81–97% efficacy and represent the most promising near-term control strategy. Conclusion: MDR and XDR typhoid fever represent an evolving global health emergency. An integrated approach combining rapid genomic surveillance, rational antimicrobial stewardship, expanded TCV rollout, and sustained WASH investment is essential to prevent an era of untreatable typhoid.

Keywords: *Salmonella Typhi; multidrug resistance; XDR typhoid; IncY plasmid; blaCTX-M-15; typhoid conjugate vaccine; antimicrobial stewardship; H58 haplotype*

1. INTRODUCTION

Typhoid fever, an acute systemic febrile illness caused by the Gram-negative facultative intracellular bacterium Salmonella enterica subsp. enterica serovar Typhi (S. Typhi), continues to impose a disproportionate burden on populations in South Asia, sub-Saharan Africa, and parts of Southeast Asia. Unlike most Salmonella serovars, S. Typhi is exclusively adapted to the human host, exploiting the gastrointestinal tract as its primary portal of entry before disseminating haematogenously to the liver, spleen, bone marrow, and gallbladder [1]. The global burden of typhoid remains substantial: estimates from the Global Burden of Disease 2021 study indicate approximately 7–13 million cases per year, with 128,000 to 161,000 deaths attributable to the disease annually [2,3].

Antimicrobial therapy has been the mainstay of typhoid treatment since the introduction of chloramphenicol in 1948. However, the decades-long empirical and often unsupervised use of antibiotics has exerted profound selection pressure on S. Typhi, driving sequential waves of resistance. The first wave, emerging in the late 1970s, produced strains resistant to first-line drugs – chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole (co-trimoxazole) – collectively labelled multidrug-resistant (MDR) S. Typhi [4]. The second wave, developing from the 1990s, produced strains with fluoroquinolone non-susceptibility (FQNS) resulting from point mutations in the quinolone resistance-determining regions (QRDRs) of DNA gyrase (gyrA) and topoisomerase IV (parC) [5]. The most alarming development occurred in November 2016, when Sindh Province, Pakistan witnessed an outbreak of extensively drug-resistant (XDR) S. Typhi, defined as resistance to all first-line drugs, fluoroquinolones, and third-generation cephalosporins simultaneously, with treatment options effectively reduced to azithromycin and carbapenems [6].

The H58 haplotype (now reclassified as genotype 4.3.1 under the Pathogenwatch nomenclature) has emerged as the globally dominant MDR lineage, identified across Asia, sub-Saharan Africa, and beyond through whole-genome sequencing (WGS) studies [7]. The XDR variant within the H58 lineage (4.3.1.1P) acquired an IncY plasmid carrying blaCTX-M-15 and qnrS resistance genes, representing a sentinel event in the evolutionary trajectory of S. Typhi resistance [6,8]. More recently, the detection of azithromycin-resistant strains driven by mutations in the acrB efflux pump gene has raised the spectre of pan-drug-resistant typhoid – a scenario that would render infections essentially untreatable [9].

This review provides a comprehensive synthesis of the current understanding of MDR and XDR typhoid, covering molecular epidemiology, mechanisms of resistance, clinical presentation and management, vaccine-based prevention, and global surveillance frameworks. Our objective is to consolidate available evidence and highlight key research and policy priorities for the global health community.

2. GLOBAL EPIDEMIOLOGY AND DISEASE BURDEN

Typhoid fever is predominantly endemic in regions characterised by inadequate access to safe water, poor sanitation infrastructure, and limited healthcare resources. South Asia bears the greatest burden: Pakistan, India, Bangladesh, and Nepal collectively account for the majority of global cases. The Surveillance for Enteric Fever in Asia Project (SEAP) documented significant heterogeneity in incidence across study sites in Bangladesh, Nepal, and Pakistan, with the highest rates observed in urban slum settings, reaching 450 or more cases per 100,000 persons annually [10]. Sub-Saharan Africa, and particularly East Africa, contributes a growing share of the disease burden, with estimates revised upward following improved blood-culture surveillance [3].

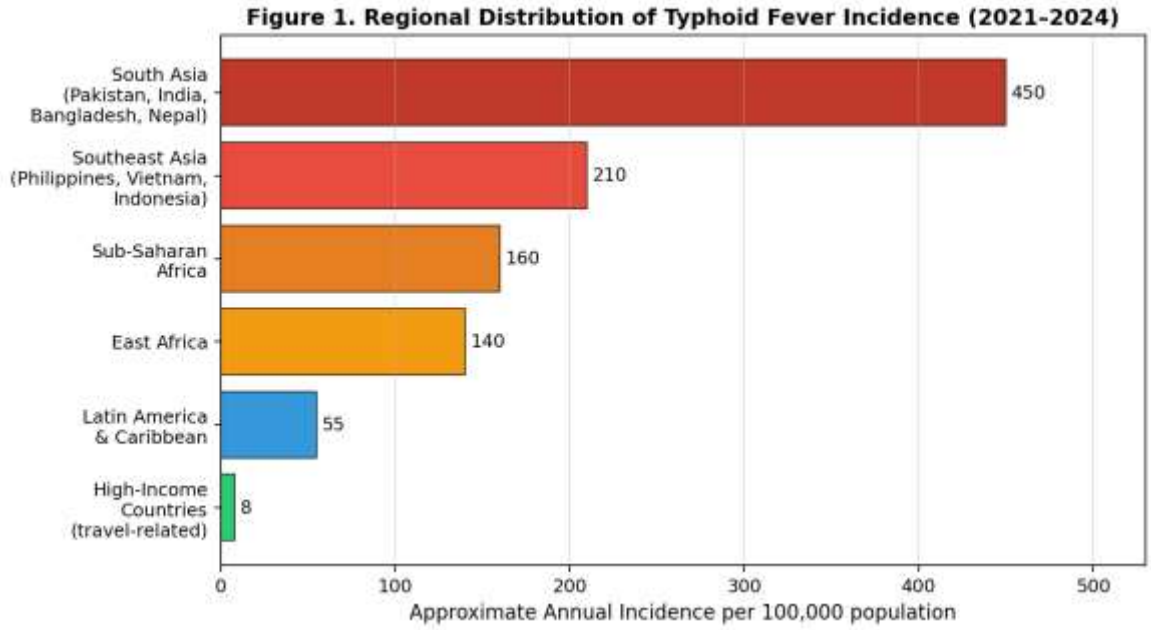

Figure 1. Regional distribution of estimated typhoid fever incidence per 100,000 population (2021–2024). Data synthesised from GBD 2021 and SEAP surveillance programmes. South Asia carries the highest absolute burden, followed by Southeast Asia and sub-Saharan Africa.

Children aged 2 to 14 years are disproportionately affected in high-burden settings, representing up to 60% of cases in some cohort studies. However, the epidemiology differs in areas where adults have not yet accumulated immunity through repeated exposure, reflecting the intersection of host immunological status, infecting dose, and strain virulence. The case-fatality rate ranges from less than 1% in treated patients with susceptible strains to up to 10–20% in untreated severe disease or when therapy is delayed by diagnostic uncertainty or drug resistance [11].

Globally, MDR strains are most prevalent in Asia, where they have constituted 20–60% of isolates across different surveillance periods. The 24-year retrospective cohort from Dhaka, Bangladesh documented a peak MDR prevalence of 80% in 2002, declining to 17% by 2022, concomitant with reduced co-trimoxazole consumption, demonstrating that selection pressure reduction can drive observable resistance declines [12]. Conversely, fluoroquinolone non-susceptibility has remained persistently above 90% across South Asian sites, driven by continued ciprofloxacin use [12]. India’s 2023 modelling analysis estimated 4.9 million typhoid cases, with fluoroquinolone-resistant infections accounting for approximately 600,000 hospitalisations annually [13].

3. PATHOGENESIS AND VIRULENCE DETERMINANTS

3.1 Infection Biology and Intracellular Survival

S. Typhi establishes infection through ingestion of contaminated food or water, with an infecting dose as low as 10^3 colony-forming units in susceptible individuals. Upon reaching the small intestine, the bacterium traverses the intestinal epithelium preferentially through M cells overlying Peyer's patches. Within the lamina propria, S. Typhi is engulfed by macrophages but actively evades intracellular killing by modulating phagosome maturation through the activity of effector proteins secreted by two critical Type III Secretion Systems (T3SS), encoded within Salmonella Pathogenicity Islands 1 and 2 (SPI-1 and SPI-2) [1].

The Vi capsular polysaccharide antigen, encoded by the viaB locus on a 134-kb pathogenicity island, serves as a critical virulence determinant unique to S. Typhi. Vi polysaccharide shields the bacterium from complement-mediated killing and inhibits TLR5 recognition by masking flagellin, thereby dampening early innate immune responses [14]. Recent studies have shown that single missense mutations in Vi capsule synthesis genes can confer hypervirulence, further complicating the host-pathogen dynamic [15].

3.2 Chronic Carriage and Gallbladder Colonisation

Approximately 2–5% of individuals infected with S. Typhi become chronic carriers, defined as persistent faecal or urinary shedding for more than one year after acute illness. Chronic carriage is strongly associated with the presence of gallstones, which provide a hydrophobic surface conducive to S. Typhi biofilm formation [16]. Within the gallbladder biofilm, bacteria exhibit markedly reduced susceptibility to antibiotics and can form persister cells that survive antibiotic exposure through metabolic quiescence rather than genetically encoded resistance mechanisms. This chronic reservoir sustains S. Typhi transmission within communities and is a critical impediment to eradication, particularly in regions with high gallstone prevalence [16].

4. MOLECULAR MECHANISMS OF ANTIMICROBIAL RESISTANCE

4.1 First-Line Drug Resistance and the IncHI1 Plasmid

The emergence of MDR S. Typhi in the 1970s and 1980s was principally mediated by the acquisition of the IncHI1 plasmid, a large conjugative plasmid that carries multiple resistance determinants: catA1 conferring chloramphenicol resistance, blaTEM-1 conferring ampicillin resistance, and sul1 and dfrA genes conferring resistance to sulphonamides and trimethoprim respectively [4,17]. The first large MDR outbreak was documented in Mexico City in 1972, involving S. Typhi harbouring an IncHI1 plasmid. Subsequent decades saw rapid global spread of MDR S. Typhi, with high-income countries reporting cases primarily in returning travellers.

Importantly, chromosomally integrated resistance determinants subsequently replaced plasmid-borne resistance in the dominant H58 lineage, providing a more stable mechanism of MDR inheritance not subject to plasmid curing. The chromosomally integrated composite transposon within H58 S. Typhi encodes resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole simultaneously, representing the “MDR core” of the lineage [7].

4.2 Fluoroquinolone Non-Susceptibility: QRDR Mutations and PMQR

Fluoroquinolone resistance in S. Typhi arises through two principal mechanisms: (1) chromosomal point mutations within the quinolone resistance-determining regions (QRDRs) of gyrA (encoding the GyrA subunit of DNA gyrase) and parC (encoding the ParC subunit of topoisomerase IV), and (2) plasmid-mediated quinolone resistance (PMQR) genes, principally qnrS. The most clinically significant QRDR mutation is gyrA Ser83Phe (S83F), which confers reduced ciprofloxacin susceptibility (MIC 0.25–1.0 μg/mL) and predicts clinical treatment failure [5,18]. Double mutations in gyrA (S83F + D87N) or combined gyrA-parC mutations result in higher-level resistance. Whole-genome sequencing of 29 MDR and XDR S. Typhi isolates from Pakistani paediatric patients confirmed gyrA-S83F and qnrS1 in all isolates, underscoring their central role in fluoroquinolone resistance [18].

4.3 The XDR Determinant: IncY Plasmid and blaCTX-M-15

Figure 3. Molecular Mechanisms of Antimicrobial Resistance in Salmonella Typhi

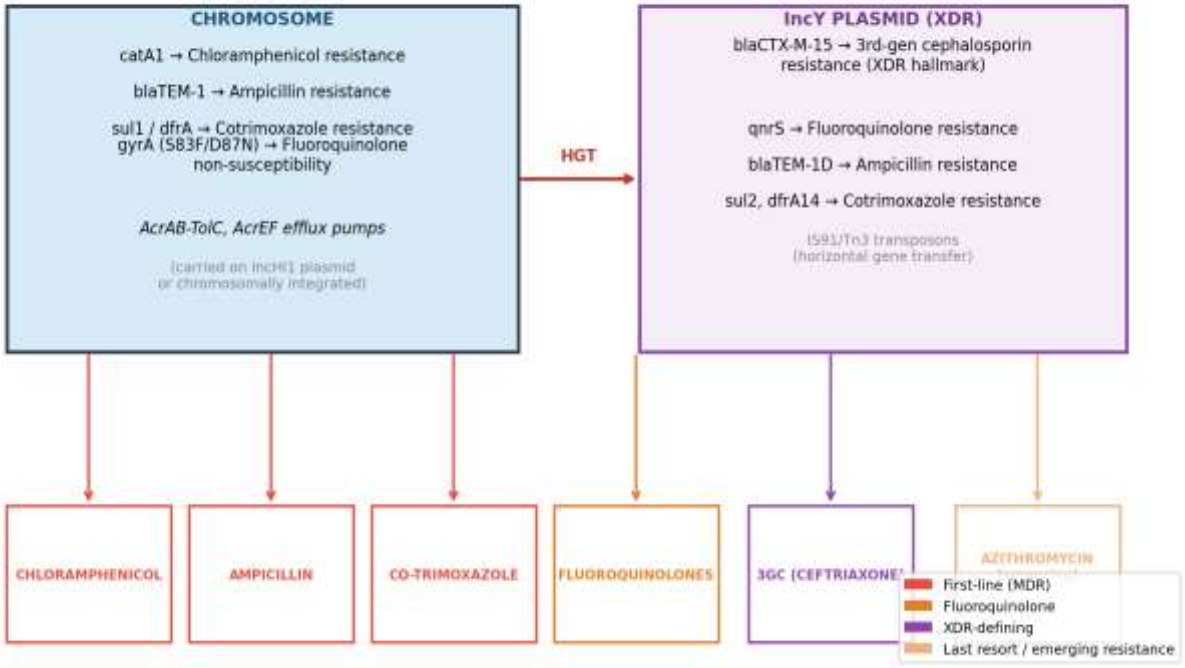

Figure 3. Schematic representation of molecular mechanisms underlying multidrug resistance in Salmonella Typhi. Chromosomally integrated cassettes and the IncY plasmid together encode resistance to all first-line agents, fluoroquinolones, and third-generation cephalosporins in XDR strains. HGT: horizontal gene transfer; 3GC: third-generation cephalosporins.

The 2016 Sindh XDR outbreak strain (4.3.1.1P) marked the first large-scale emergence of S. Typhi with simultaneous resistance to five antibiotic classes: chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones, and third-generation cephalosporins [6]. The XDR phenotype is conferred by a promiscuous IncY plasmid (p60006, approximately 45 kb) that carries: blaCTX-M-15 encoding an extended-spectrum β-lactamase (ESBL) capable of hydrolysing third-generation cephalosporins; qnrS providing fluoroquinolone resistance via target protection; and blaTEM-1D encoding a narrow-spectrum β-lactamase [6,8,19]. The IncY plasmid demonstrates high sequence identity to plasmids found in Escherichia coli and other Enterobacteriaceae from geographically diverse locations, suggesting acquisition via horizontal gene transfer (HGT) from the broader enteric bacterial gene pool [6].

Genomic analyses from Pakistan demonstrate that IncY (together with IncQ1 and IncC replicons) accounts for the majority of cephalosporin resistance in XDR isolates, with the IncY plasmid found in 14–38% of sequenced clinical isolates depending on the study population [11,18,19]. In India, where XDR S. Typhi has emerged sporadically rather than as a large outbreak, the ceftriaxone resistance is mediated by different plasmids (IncX3 carrying blaSHV-12, or IncN carrying blaTEM-1B + blaDHA-1), reflecting independent acquisition events [20].

4.4 Efflux Pumps and Emerging Azithromycin Resistance

Azithromycin has emerged as a last-resort oral therapy for uncomplicated XDR typhoid. Resistance to azithromycin in S. Typhi is primarily mediated by mutations in the acrB gene, encoding the inner membrane component of the AcrAB-TolC efflux pump, a tripartite efflux system in the resistance-nodulation-division (RND) superfamily. Specific acrB mutations (R717Q/L) confer high-level azithromycin resistance by increasing drug efflux capacity [9]. A landmark genomic surveillance study of 3,489 S. Typhi strains from South Asia (2014–2019) found that azithromycin-resistance-associated mutations, while not yet present in XDR strains, are independently spreading in multiple genotypes, creating a molecular trajectory toward pan-drug resistance [9]. Should azithromycin resistance be acquired by XDR S. Typhi, treatment options would be effectively limited to carbapenems alone, requiring intravenous administration in hospital settings.

5. TEMPORAL TRENDS IN RESISTANCE AND PHYLOGENOMICS

Figure 2. Temporal Trends in Antimicrobial Resistance of Salmonella Typhi (1972-2024)

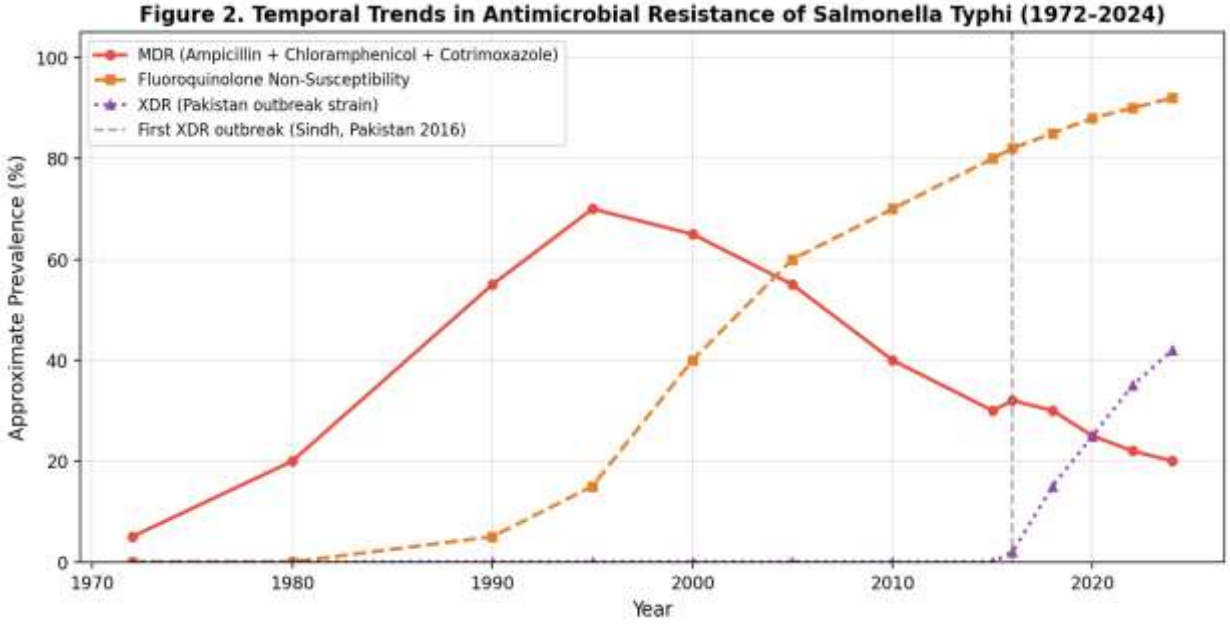

Figure 2. Temporal trends in antimicrobial resistance prevalence among Salmonella Typhi (1972–2024). MDR (multidrug resistance) peaked in the early 1990s and has gradually declined. Fluoroquinolone non-susceptibility (FQNS) has risen progressively since the 1990s and now exceeds 90% in South Asia. XDR emerged abruptly in 2016 and has continued to increase. Data synthesised from published surveillance studies and GBD 2021 modelling.

The H58 haplotype (Pathogenwatch genotype 4.3.1), which carries the chromosomally integrated MDR resistance cassette, has been designated the globally dominant lineage since its first description. Phylogenomic analysis of thousands of S. Typhi genomes has traced the intercontinental spread of H58 from South Asia to sub-Saharan Africa, the Middle East, and high-income countries through international travel and trade networks. Within H58, the XDR subclade 4.3.1.1P is genetically highly clonal, with remarkable conservation of the IncY plasmid across hundreds of isolates, suggesting a single acquisition event followed by rapid clonal expansion in Sindh [6,7].

Genomic surveillance data from Bangladesh over 24 years (1999–2022; 12,435 culture-confirmed cases) demonstrated that MDR prevalence correlated inversely with cotrimoxazole antibiotic consumption at the national level, declining from 38% in 1999 to 17% in 2022 as cotrimoxazole use fell from 0.8 to 0.1 defined daily doses per 1,000 population per day [12]. This observation provides strong epidemiological evidence that reducing antibiotic selection pressure can drive meaningful reductions in resistance prevalence, underscoring the importance of antimicrobial stewardship.

India's burden modelling estimated 4.9 million typhoid cases in 2023, of which 600,000 hospitalisations were attributable to fluoroquinolone-resistant strains. Deaths specifically linked to fluoroquinolone resistance were estimated at 4,700, with those due to MDR at 122, reflecting the current differential mortality burden imposed by FQNS strains [13]. Third-generation cephalosporin resistance and azithromycin resistance each contributed an estimated 183 deaths in 2023, figures that are expected to increase substantially if current resistance trajectories continue [13].

6. CLINICAL FEATURES AND MANAGEMENT OF MDR/XDR TYPHOID

6.1 Clinical Presentation

The clinical presentation of MDR and XDR typhoid fever is not pathognomically distinct from susceptible strains at onset. The characteristic features include a sustained febrile illness exceeding 39°C lasting more than one week, relative bradycardia (Faget sign), headache, anorexia, malaise, and a “step-ladder” fever pattern with progressive toxaemia. Abdominal manifestations – including hepatosplenomegaly, abdominal distension, and constipation in adults (diarrhoea more common in children) – are prominent. Rose spots, a maculopapular

rash appearing on the trunk in the first week, are pathognomonic but observed in fewer than 30% of patients and rarely in darker-skinned individuals [4]. Complications, occurring in approximately 10–15% of untreated or delayed-treatment cases, include intestinal haemorrhage, intestinal perforation (3–3%), hepatitis, myocarditis, and typhoid encephalopathy. MDR and XDR strains are associated with a two-fold higher risk of complications and mortality compared to susceptible strains [2].

6.2 Antimicrobial Treatment Options

Resistance Profile	First-Line Drug	Alternative	Route	Duration
Susceptible S. Typhi	Chloramphenicol / Ampicillin / Cotrimoxazole	Ciprofloxacin	Oral / IV	14 days
FQNS (reduced susceptibility)	Ceftriaxone (IV) or Cefixime (oral)	Azithromycin	IV or Oral	10–14 days
MDR (resistant to 3 first-line drugs)	Ceftriaxone or Azithromycin	Cefixime (oral) if susceptible	IV or Oral	14 days
XDR (MDR + FQ + 3GC resistant)	Azithromycin (oral, uncomplicated) Meropenem (IV, complicated)	Imipenem / Ertapenem	Oral / IV	10–14 days
Pan-drug resistant (theoretical)	Meropenem + Azithromycin combination Fosfomycin (investigational)	None currently approved	IV	Extended

Table 1. Current Antimicrobial Treatment Options for Typhoid Fever Stratified by Resistance Profile (WHO 2018 Updated Guidance). FQNS: fluoroquinolone non-susceptibility; MDR: multidrug resistant; XDR: extensively drug resistant; 3GC: third-generation cephalosporins; FQ: fluoroquinolones.

Azithromycin has proven efficacious for uncomplicated XDR typhoid owing to its high intracellular concentrations, extensive tissue distribution, and activity against intracellular S. Typhi. However, for severe or complicated XDR typhoid, intravenous meropenem is the agent of choice. The cost (US$30–80 per day) and requirement for intravenous administration make carbapenem therapy inaccessible in many resource-limited settings where typhoid is most prevalent, risking a return to pre-antibiotic era mortality [21]. Cases of reduced azithromycin susceptibility (MIC ≥ 16 μg/mL) have been increasingly documented, and combination therapy with azithromycin plus a carbapenem is being explored for such cases [9]. The WHO has listed carbapenems as “Watch” class antibiotics under the AWaRe framework, emphasising the need to preserve their efficacy through stewardship.

7. PREVENTIVE STRATEGIES: TYPHOID CONJUGATE VACCINES

Vaccination represents the most scalable and cost-effective near-term strategy to control typhoid fever and reduce the circulation of drug-resistant strains. Three generations of typhoid vaccines have been developed: whole-cell killed vaccines (no longer recommended), the oral live-attenuated Ty21a vaccine, the unconjugated Vi polysaccharide vaccine (ViPS), and the

newer Vi-conjugate vaccines (TCVs). The WHO recommended the preferential use of TCVs over older vaccines in 2018, citing their superior immunogenicity in children under two years of age, T-cell-dependent immune responses enabling immune memory, and suitability for administration from six months of age [22].

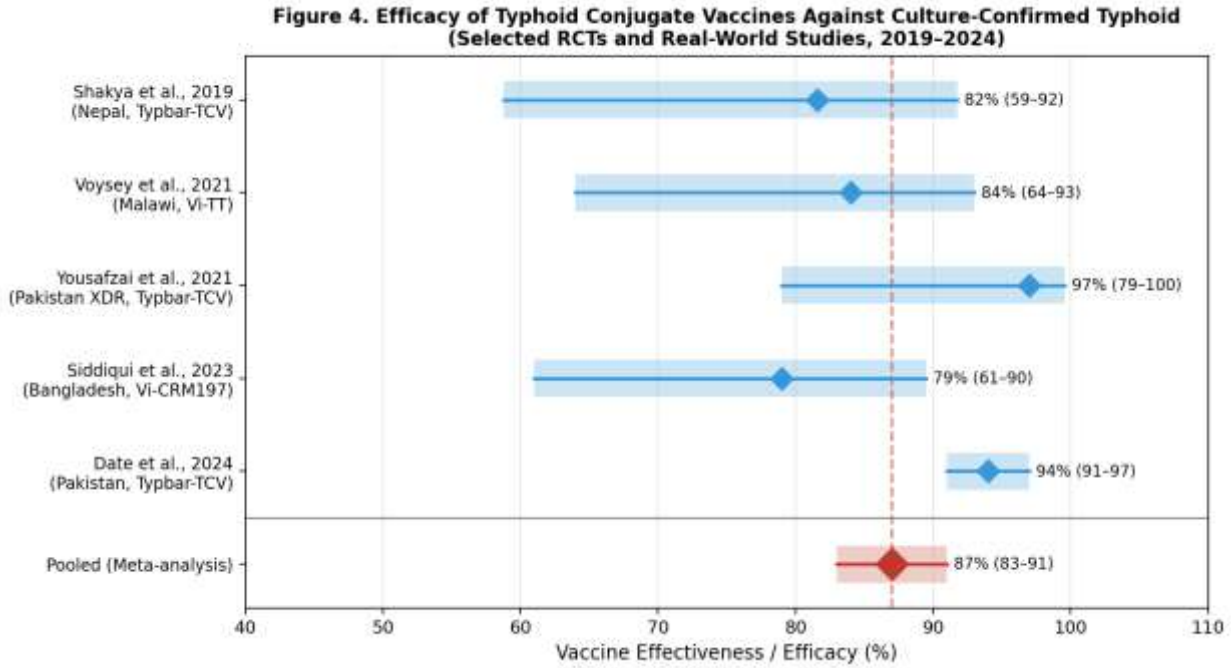

Figure 4. Vaccine efficacy and effectiveness of typhoid conjugate vaccines (TCVs) from key randomised controlled trials and real-world effectiveness studies (2019–2024). The pooled meta-analytic estimate demonstrates approximately 87% effectiveness against culture-confirmed typhoid. Studies in XDR outbreak settings (Yousafzai et al., 2021; Date et al., 2024) demonstrate particularly high effectiveness (≥94%) against XDR S. Typhi. CI: confidence interval; OR: odds ratio; XDR: extensively drug resistant. [Adapted from meta-analyses; see text for details.]

Currently, four WHO-prequalified TCVs are available: Typbar-TCV® (Bharat Biotech, India; prequalified 2017), TYPHIBEV® (Biological E, India; prequalified 2020), SKYTyphoid™ (SK bioscience, Korea; prequalified 2024), and ZyVac® TCV (Zydus Lifesciences; prequalified 2024). Typbar-TCV consists of 25 µg Vi polysaccharide conjugated to tetanus toxoid and has the largest clinical evidence base.

Key trial data demonstrate: (1) Nepal: Phase 3 RCT (Shakya et al., 2019) demonstrated 81.6% protective efficacy (95% CI: 58.8–91.8%) against culture-confirmed typhoid in children 9 months to 16 years [23]; (2) Malawi: Phase 3 RCT showed 84% efficacy (95% CI:

64–93%) in children 9 months to 12 years with sustained protection; (3) Pakistan XDR Setting: A real-world cohort study in Hyderabad during the XDR outbreak demonstrated 97% effectiveness of Typbar-TCV against XDR S. Typhi [29]; (4) Meta-analysis: A pooled analysis of four real-world effectiveness studies calculated an overall VE of 87% (OR 0.13) against culture-confirmed typhoid, with VE of 94% in children under five years and 95% in children five years and older [29]. These data collectively represent among the strongest vaccine effectiveness evidence for any infectious disease in low-income settings.

Despite strong evidence for TCV efficacy, only 10 countries had incorporated TCV into national immunisation programmes by 2025: Pakistan (2019), Liberia, Zimbabwe, and Samoa (2021), Nepal (2022), Malawi, Fiji (2023), Tuvalu (2024), Burkina Faso, and Kenya (2025). Modelling studies predict that TCV introduction with catch-up campaigns in Gavi-eligible countries could avert 46–74% of typhoid cases and reduce the prevalence of drug-resistant typhoid by at least 16% over ten years [28]. Pakistan's programme, the first in the world, has demonstrated operational feasibility in resource-limited urban settings.

8. SURVEILLANCE, GENOMICS, AND ANTIMICROBIAL STEWARDSHIP

Effective control of MDR typhoid requires robust and integrated surveillance systems capable of detecting emerging resistance in near-real time. Blood culture, the gold standard for diagnosing typhoid fever, concurrently provides the isolate required for antimicrobial susceptibility testing (AST) and genomic analysis. Whole-genome sequencing (WGS) has revolutionised typhoid surveillance by enabling precise phylogenetic characterisation, resistance gene identification, and plasmid typing that phenotypic AST alone cannot provide [7,18,19]. Platforms such as Pathogenwatch provide user-friendly web-based phylogenetic tools for genotyping S. Typhi sequences, facilitating both clinical and epidemiological applications.

International networks – including the Surveillance for Enteric Fever in Asia Project (SEAP), the International Typhoid Consortium, and WHO’s Global Antimicrobial Resistance Surveillance System (GLASS) – coordinate multi-site prospective surveillance, providing harmonised incidence and resistance data essential for policy decisions, including vaccine targeting and treatment guideline updates [10].

Antimicrobial stewardship (AMS) programmes represent a critical complementary intervention. The epidemiological evidence from Bangladesh convincingly demonstrates that reducing antibiotic consumption can diminish selection pressure and slow resistance accumulation [12]. Key AMS principles applicable to typhoid-endemic settings include: empirical treatment only with nationally endorsed agents matched to current local resistance data; mandatory blood culture before initiating antibiotics in febrile patients with suspected enteric fever; pharmacy-level controls on over-the-counter fluoroquinolone sales (particularly

relevant in Pakistan and India where illicit antibiotic sales drive resistance); and regular updating of national treatment guidelines in response to evolving surveillance data [20]. The WHO AWaRe framework, which classifies antibiotics as “Access,” “Watch,” and “Reserve,” provides a policy scaffold for national AMS programmes.

WASH (Water, Sanitation, and Hygiene) interventions remain the foundation of sustainable typhoid control. Historically, the decline of typhoid in high-income countries was driven by municipal water chlorination and sewage treatment infrastructure rather than vaccines or antibiotics. However, the scale of investment required for WASH improvements in low-income urban settings means that TCVs and stewardship must serve as bridging strategies in the interim [3].

9. EMERGING THREATS AND FUTURE DIRECTIONS

The convergence of several resistance trajectories presents a deeply concerning prognosis. First, the spread of azithromycin resistance genes (acrB mutations) across multiple S. Typhi genotypes independently of XDR strains creates a molecular framework for pan-drug-resistant typhoid if horizontal gene transfer links these mutations with the XDR clone [9]. Second, the demonstrated ability of S. Typhi to acquire diverse resistance plasmids from other Enterobacteriaceae – as seen with IncX3 and IncN plasmids in India – means that the XDR resistance repertoire could be augmented by acquisition of additional ESBL or carbapenemase genes from co-colonising bacteria in the gut [20]. Third, international travel facilitates rapid global dissemination of resistance clones; nearly 200 instances of international XDR typhoid spread have been documented since 1990, including cases in the UK, USA, Canada, Australia, and multiple European countries [7].

Novel therapeutic approaches under investigation include: (1) phage therapy targeting S. Typhi, capitalising on the specificity of bacteriophages for host strains; (2) antivirulence strategies targeting the Vi polysaccharide capsule or T3SS effectors; (3) gut microbiota-derived antimicrobial compounds with activity against S. Typhi, facilitated by AI-assisted multi-omics discovery platforms [15]; (4) repurposed agents such as fosfomycin and tigecycline, which retain activity against XDR strains in vitro, although clinical evidence remains sparse; and (5) novel β-lactam/β-lactamase inhibitor combinations active against CTX-M-15-producing strains [7].

From a vaccine perspective, the development of bivalent conjugate vaccines targeting both S. Typhi and S. Paratyphi A – the two principal causes of enteric fever – is a key research priority. Additionally, longer-term follow-up of TCV recipients is needed to characterise the duration of protection, determine the requirement for booster doses, and evaluate herd immunity effects in high-coverage populations. Rapid diagnostic tests that provide pathogen identification and resistance profiling at the point of care, without requiring laboratory blood

culture infrastructure, would substantially improve both clinical management and surveillance capacity in resource-limited settings.

10. CONCLUSION

Multidrug-resistant and extensively drug-resistant typhoid fever represent one of the most pressing antimicrobial resistance crises in infectious disease, driven by the convergent forces of inappropriate antibiotic use, inadequate sanitation, and the extraordinary adaptive capacity of S. Typhi. The emergence of XDR typhoid in Pakistan and its progressive geographic spread, combined with the independent emergence of azithromycin resistance across multiple lineages, threatens to render typhoid fever untreatable in the near future unless decisive action is taken.

A comprehensive, multi-pronged response is urgently required: (1) rapid scale-up of typhoid conjugate vaccines, particularly in South Asian and African high-burden settings, supported by Gavi financing and strong national political commitment; (2) implementation of rigorous antimicrobial stewardship programmes that restrict empirical fluoroquinolone use and regulate over-the-counter antibiotic access; (3) investment in whole-genome sequencing-based surveillance networks to detect and characterise emerging resistance in real time; (4) long-term commitment to WASH infrastructure investment as the foundational public health strategy for sustainable typhoid control; and (5) prioritisation of research into novel therapeutics, diagnostics, and next-generation vaccines against enteric fever. Without coordinated global action across these domains, the world faces a foreseeable return to the pre-antibiotic era for typhoid fever – a scenario measured in preventable deaths, disproportionately among children in the world’s most disadvantaged communities.

DECLARATIONS

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REFERENCES

[1] Han J, et al. Infection biology of Salmonella enterica. EcoSal Plus. 2024;12(1). https://doi.org/10.1128/ecosalplus.esp-0001-2023

[2] Diwaker A, et al. Enteric fever and the diagnostic tools: defining the accuracy. Front Bacteriol. 2024;3. https://doi.org/10.3389/fbrio.2024.1332180

[3] Piovani D, Figlioli G, Nikolopoulos GK, Bonovas S. The global burden of enteric fever, 2017–2021: a systematic analysis from the Global Burden of Disease Study 2021. EClinicalMedicine. 2024;77:102883.

[4] Zaki SA, Karande S. Multidrug-resistant typhoid fever: a review. J Infect Dev Ctries. 2011;5(5):324–337.

[5] Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. N Engl J Med. 2002;347(22):1770–1782.

[6] Klemm EJ, Shakoor S, Page AJ, et al. Emergence of an Extensively Drug-Resistant Salmonella enterica Serovar Typhi Clone Harboring a Promiscuous Plasmid Encoding Resistance to Fluoroquinolones and Third-Generation Cephalosporins. mBio. 2018;9(1):e00105-18.

[7] Dyson ZA, Klemm EJ, Palmer S, Dougan G. Antibiotic resistance and typhoid. Clin Infect Dis. 2019;68(Suppl 2):S165–S170.

[8] Andrews JR, Qamar FN, Charles RC, Ryan ET. Extensively drug-resistant typhoid — are conjugate vaccines arriving just in time? N Engl J Med. 2018;379:1493–1495.

[9] Sajib MSI, Tanmoy AM, Hooda Y, et al. Tracking the emergence of azithromycin resistance in multiple genotypes of typhoidal Salmonella. Lancet Microbe. 202 2;3:e567–577.

[10] Garrett DO, et al. Incidence of typhoid and paratyphoid fever in Bangladesh, Nepal, and Pakistan: results of the SEAP study. Lancet Glob Health. 2022;10(7):e978–e988.

[11] Asghar M, et al. Exploring the antimicrobial resistance profile of Salmonella Typhi and its clinical burden. Antibiotics. 2024;13(8):765.

[12] Tanmoy AM, Hooda Y, Sajib MSI, et al. Trends in antimicrobial resistance amongst Salmonella Typhi in Bangladesh: a 24-year retrospective observational study (1999–2022). PLoS Negl Trop Dis. 2024;18(10):e0012558.

[13] Pitzer VE, et al. Burden of typhoid fever and antimicrobial resistance in India (2023): a modelling study. ScienceDirect. 2026. https://doi.org/10.1016/S2772-3682(25)00185-4

[14] de Jong HK, Parry CM, van der Poll T, Wiersinga WJ. Host-pathogen interaction in invasive salmonellosis. PLoS Pathog. 2012;8(10):e1002933.

[15] Lee GY, Song J. Single missense mutations in Vi capsule synthesis genes confer hypervirulence to Salmonella Typhi. Nat Commun. 2024;15:5258.

[16] Diwaker A, et al. Chronic carriers and multidrug resistance in typhoid fever: pathogenesis, challenges, and integrated control strategies. Infection. 2025. https://doi.org/10.1007/s15010-025-02703-9

[17] Rowe B, Ward LR, Threlfall EJ. Multidrug-resistant Salmonella typhi: a worldwide epidemic. Clin Infect Dis. 1997;24(Suppl 1):S106–S109.

[18] Rasheed F, et al. Whole-Genome Sequencing Analysis of Drug-Resistant Salmonella Typhi in Children. Pathogens. 2025;14(10):967.

[19] Satheesh R, et al. Salmonella Typhi acquires diverse plasmids from other Enterobacteriaceae to develop cephalosporin resistance. J Infect Dev Ctries. 2021. PMC8276774.

[20] Shaikh OA, Asghar Z, Aftab RM, et al. Antimicrobial resistant strains of Salmonella typhi: the role of illicit antibiotics sales, misuse, and self-medication practices in Pakistan. J Infect Public Health. 2023;16(10):1591–1597.

[21] Pustake M, Giri P, Tambolkar S, Nayak S. Extensively drug-resistant typhoid fever: a call to action. Indian J Community Med. 2022;47(1):153–154.

[22] World Health Organization. Typhoid vaccines: WHO position paper — March 2018. Wkly Epidemiol Rec. 2018;93(13):153–172.

[23] Shakya M, et al. Phase 3 efficacy analysis of a typhoid conjugate vaccine trial in Nepal. N Engl J Med. 2019;381:2209–2218.

[24] Voysey M, et al. The TyVac trial: typhoid conjugate vaccine safety and efficacy in Malawian children. Lancet. 2021. (Trial results).

[25] Gloeck NR, et al. Typhoid conjugate vaccines for preventing typhoid fever (enteric fever). Cochrane Database Syst Rev. 2023. https://doi.org/10.1002/14651858.CD015746

[26] Nampota-Nkomba N, Carey ME, et al. Using typhoid conjugate vaccines to prevent disease, promote health equity, and counter drug-resistant typhoid fever. Open Forum Infect Dis. 2023;10(Suppl 1):S6–S12.

[27] Shakya M, et al. Efficacy of typhoid vaccines against culture-confirmed Salmonella Typhi in typhoid endemic countries: systematic review and meta-analysis. Lancet Glob Health. 2024. https://doi.org/10.1016/S2214-109X(23)00606-X

[28] Kaufhold S, et al. Modelling the impact of typhoid conjugate vaccines on AMR typhoid burden in Gavi-eligible countries. Vaccine. 2023.

[29] Tanveer A, et al. Real-world vaccine effectiveness of typhoid conjugate vaccine in children and adolescents: systematic review and meta-analysis. Vaccine. 2025. https://doi.org/10.1016/j.vaccine.2025.11697

[30] Deng L, Wang S. Colonization resistance: the role of gut microbiota in preventing Salmonella invasion and infection. Gut Microbes. 2024. https://doi.org/10.1080/19490976.2024.2424914