

Review Article

The Evolving Panorama of Typhoid Fever: International Burden, Antimicrobial Resistance, and the Tactical Integration of Conjugate Vaccines

Piyush Kumar¹, Snehil Niharika², Advocate Anupama³

1. Health Department, Government of Bihar, India; 2. Noida, Amity University, India; 3. Patna, Bihar, Bar Council, India

Typhoid fever, caused by *S. Typhi*, is a public health threat in LMICs. Emergence of resistant strains has severely compromised antimicrobial regimens. This paper systematically synthesizes latest epidemiological data, mechanisms of resistance, diagnostic limitations, and preventative paradigms—specifically Typhoid Conjugate Vaccines (TCVs). Globally, an estimated 9–14 million typhoid fever cases occur annually, leading to roughly 110,000 deaths, tilted heavily toward children less than five years in South Asia and Sub-Saharan Africa. The attainment of the *bla*CTX-M-15 gene alongside plasmid-mediated resistance has rendered 3rd-generation cephalosporins useless in multiple endemic clusters, leaving azithromycin as one of the few feasible oral therapies. Medical management of typhoid in an era of drug resistance demands a structural shift. Relying only on antibiotics is no longer sustainable; global strategies must combine mass immunization campaigns with TCV as well as targeted infrastructure investment in water, sanitation, and hygiene (WASH) systems.

Corresponding author: Piyush Kumar, drpiyush003@gmail.com

1. Introduction

Typhoid fever is a systemic, occasionally life-threatening febrile illness caused by the obligate human pathogen *Salmonella enterica* serovar Typhi (*S. Typhi*) [1]. It is transmitted via the faeco-oral route through infected food or water, the disease has traditionally tracked alongside rapid urbanization, overcrowding, and ineffective wastewater treatment [2]. While almost eradicated in high-income settings,

it remains exceedingly endemic in some parts of Southern Asia, Southeast Asia, and Sub-Saharan Africa ^[3].

The clinical treatment of typhoid is facing a critical inflection point. For past few decades, the disease was treated with affordable, first-line oral antimicrobials ^[4]. However, injudicious use of antibiotics and genomic plasticity has enabled *S. Typhi* to incessantly evolve defense mechanisms against varying antibiotic drugs ^[5]. This paper reviews the contemporary global burden of the disease, the genetic structural design compelling its resistance, and the real-world effectiveness of updated vaccine initiatives.

2. Global Epidemiology and Burden

According to estimates made by the World Health Organization (WHO), annually typhoid fever causes approximately 9-14 million illnesses and 1,10,000 deaths globally ^[6].

2.1. Geographic Disparities

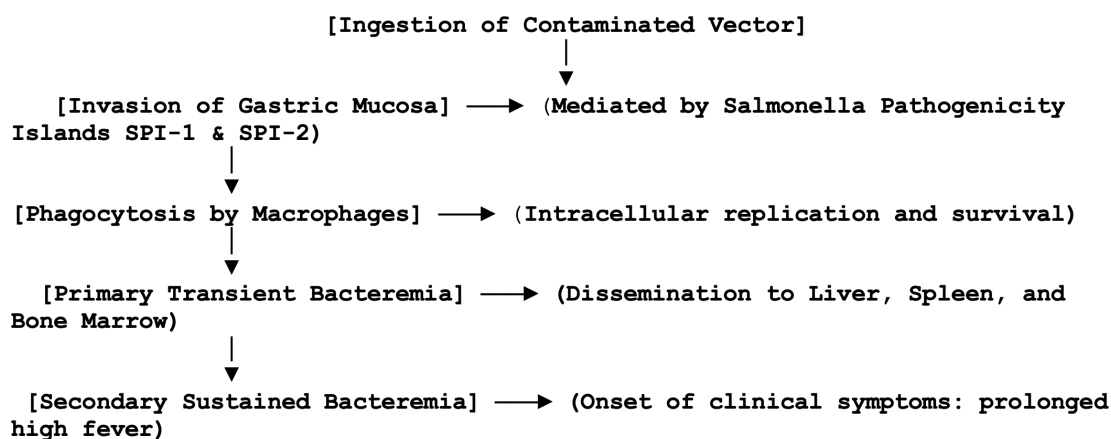
The burden of typhoid is extremely heterogeneous. **High-incidence zones** (defined as more than 100 cases per 100,000 person-years) are situated in south-central and southeast Asia ^[7]. **Medium-incidence zones** (10 to 100 cases per 100,000 person-years) are concentrated across broader territories in Africa, Latin America, and Oceania ^[8].

2.2. Demographic Vulnerability

Seroincidence data revealed that child under the age of five face disproportionately high infection rates and elevated bacterial loads ^[9]. This finding challenges previous diagnostic assumptions that suggested typhoid primarily as a disease of school-aged children and young adults ^[10].

3. Pathogenesis and Clinical Manifestations

Following ingestion, *S. Typhi* survives the gastric acid barrier and invades the intestinal mucosa via M (microfold cell) cells in Peyer's patches ^[11].



The clinical presentation is similar to other tropical febrile illnesses, such as malaria, dengue, and un-typed rickettsial infections ^[12].

- **Early Stage:** Insidious onset of a low-grade fever that steadily climbs (step ladder pyrexia) to a high, sustained plateau (39°C to 40°C), accompanied by a dry cough, profound malaise, and headache ^[13].
- **Advanced Stage (Weeks 2-3):** Relative bradycardia (**Faget's sign**), hepatosplenomegaly, and abdominal upset (constipation in adults, diarrhea in children) ^[14]. In critical, untreated cases, profound ulceration of Peyer's patches can lead to life-threatening intestinal perforation or serious hemorrhage ^[15].

4. The Emergence of Antimicrobial Resistance (AMR)

The defining challenge of modern typhoid management is the fall down of standard therapeutic options. The evolution of drug resistance in *S. Typhi* can be categorized into three succeeding waves ^[16], see table -1 below:

Resistance Era	Defining Resistant Classes	Genetic Determinants / Plasmids	Clinical Impact
MDR Typhi (1070s–1990s)	Chloramphenicol, Ampicillin, Co-trimoxazole	IncHI1 Plasmid composite transposons	Forced global shift to Fluoroquinolones as first-line therapy.
Fluoroquinolones Resistance (2000s)	Ciprofloxacin, Ofloxacin,	Point mutations in quinolone resistance–determining regions (<i>gyrA</i> , <i>gyrB</i> , <i>parC</i>)	Led to widespread clinical failures and delayed fever clearance times.
XDR Typhi (2016–Present)	MDR baseline + Fluoroquinolones+ Third-generation Cephalosporins (e.g., Ceftriaxone)	H58 haplotype baseline; acquisition of blaCTX-M-15 resistance gene	Leaves Azithromycin as the sole reliable oral option; pushes treatment toward expensive IV carbapenems.

Table-1. The Emergence of Antimicrobial Resistance (AMR) in *S. Typhi*

Note on Azithromycin: Latest surveillance has revealed sporadic resistance to azithromycin attributable to mutations in the *acrB* efflux pump gene ^[17]. If these strains spread globally, outpatient oral treatment of typhoid fever could become unaffordable as well as unviable in high-burden regions ^[18].

Note that the attainment of the blaCTX-M-15resistance gene is no longer limited to the classic Pakistani outbreaks ^[19]. Recent tracking shows that the **H58 lineage II (genotype 4.3.1.2)** has developed the potential to acquire multidrug-resistant plasmids (such as IncFIB(K)} plasmid backbone) directly from other *Enterobacteriales*, fueling a new wave of Ceftriaxone-resistant *S. Typhi* in South Asian countries like India ^[20].

5. Diagnostic Horizons and Limitations

Accurate diagnosis is essential for global surveillance and effective clinical management.

- **Blood Culture:** The **diagnostic gold standard**, however it possesses a sensitivity of 40% to 60% due to low bacterial concentration in peripheral blood (often less than 1 CFU/mL) and widespread injudicious pre-hospital antibiotic self-administration ^[21].
- **Bone Marrow Culture:** **Highly sensitive (~90%)** and less impacted by prior antibiotic use, but highly invasive and impractical for routine use or field clinics ^[22].
- **Serology (The Widal test):** Although affordable and widely used across rural/urban clinics, it has **poor specificity** and elevated cross-reactivity with non-typhoidal *Salmonella* and other enterics, often leading to wrong-diagnosis and inappropriate antibiotic usage ^[23].
- **Emerging Tools:** Present focus is on loop-mediated isothermal amplification (LAMP) assays and tracking specific IgA/IgM antibodies against hemolysin E (HlyE) via rapid diagnostic tests (RDTs) ^[24].

6. Prevention: The Strategic Pivot to Typhoid Conjugate Vaccines (TCVs)

Traditionally, typhoid control leaned profoundly on clean water infrastructure. Although water, sanitation, and hygiene (WASH) programs still remain the ultimate goal, updating civil infrastructure requires long-term investment. In reaction to the AMR threat, the WHO Strategic Advisory Group of Experts (SAGE) on Immunization has prioritized the incorporation of TCVs ^[25].

6.1. TCV vs. Older Generation Vaccines

Typhoid Vaccine Acceleration Consortium (TyVAC) funded by the Bill & Melinda Gates Foundation pioneered the individually randomized Phase 3 trials in Malawi and Nepal, along with the cluster-randomized trial in Bangladesh, providing the foundational clinical endpoint validation (blood culture-confirmed cases) that drove SAGE's routine rollout recommendations ^[26].

Unlike previous unconjugated Vi polysaccharide vaccines (which cannot be given to infants and offer brief protection) or oral live-attenuated Ty21a vaccines (which require complex multi-dose schedules), TCVs link the Vi capsular polysaccharide to a carrier protein (such as tetanus toxoid) ^[27]. This alteration induces a T-cell-dependent immune response, yielding:

- Long-term immunologic memory.

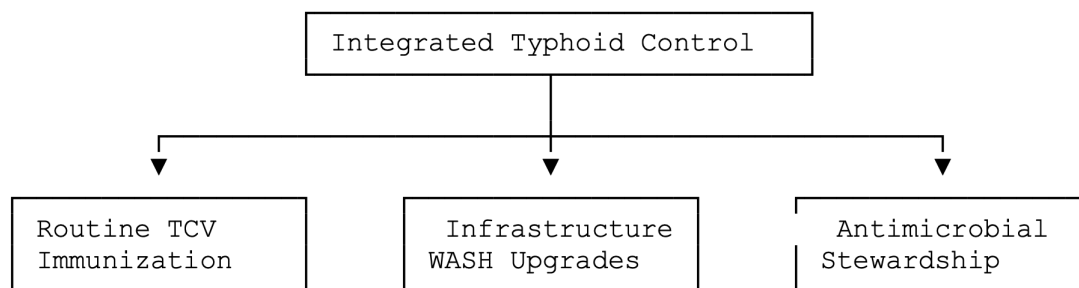
- High efficacy (>80% protection based on large-scale field data from Malawi, Bangladesh, and Nepal) [28].
- Safety profiles suitable for infants as young as 6 months.

6.2. Updated WHO/SAGE Policy Guidance

Recent guidelines highlight introducing TCV into routine childhood immunization program in nations with high or very high endemic typhoid burdens or where AMR rates are steep [29]. Moreover, real-world data showing long-term antibody decline has prompted an advice to consider a booster dose around age 5 for children who received their first dose during infancy.

7. Discussion and Comprehensive Control Strategies

The global health community cannot medicate its way out of the coming future typhoid crisis. An effective response needs an incorporated approach across multiple sectors:



1. **Aggressive Vaccine Deployment:** Increasing Gavi (Global Alliance for Vaccines and Immunization) supported TCV introduction into routine national immunization programs can protect vulnerable infant demographics and decreases the selection pressure driving further antibiotic resistance.
2. **Targeted WASH Investments:** Urban/rural sanitation, pipeline security, and rapid response to drinking water contamination (as seen in point-source outbreaks) are indispensable to permanently break transmission loops.
3. **Antimicrobial Stewardship:** Implementing rapid molecular diagnostic screening in hospitals can control the empirical injudicious overuse of third-generation cephalosporins and safeguard left over choices like azithromycin.

7.1. Future Directions and Research Priorities

Despite substantial progress in comprehension and controlling typhoid fever, several significant challenges remain. The rapid surfacing and international dissemination of AMR *Salmonella* Typhi strains threaten to challenge decades of clinical and public health gains. Future control efforts must therefore incorporate advances in vaccination, surveillance, diagnostics, and environmental health.

Genomic Surveillance

Whole-genome sequencing has emerged as an influential tool for tracking the evolution and transmission of AMR *S. Typhi* strains [30]. The extensive circulation of the H58 genotype and its association with multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes emphasize the need for routine genomic surveillance in endemic countries. Real-time genomic monitoring can facilitate early outbreak detection, identify emerging resistance mechanisms, and inform treatment guidelines.

Next-Generation Vaccines

Current Typhoid Conjugate Vaccines (TCVs) demonstrate excellent efficacy and safety; however, questions remain regarding long-term protection, booster requirements, and effectiveness against evolving bacterial strains. Research is ongoing to develop multivalent enteric fever vaccines capable of providing protection against both *S. Typhi* and *Salmonella* Paratyphi A. Such vaccines may significantly reduce the global burden of enteric fever.

Artificial Intelligence and Digital Health

Artificial intelligence (AI) and machine learning technologies offer promising opportunities for disease prediction and surveillance [31]. Integration of climate data, population density, sanitation indicators, and healthcare utilization patterns may enable early identification of high-risk areas and support targeted vaccination campaigns. AI-assisted analysis of antimicrobial resistance trends could further improve stewardship programs.

Environmental and Wastewater Surveillance

Environmental surveillance through wastewater monitoring has gained considerable attention following its successful application during the COVID-19 pandemic [32]. Detection of *S. Typhi* genetic material in

wastewater systems may provide early warning signals of community transmission, particularly in densely populated urban settings where traditional surveillance systems are limited.

One Health Approach

Typhoid control requires teamwork across multiple sectors including healthcare, environmental engineering, education, urban/rural planning, and public policy. Adoption of a One Health framework can strengthen integrated responses by addressing environmental contamination, antimicrobial stewardship, and community-level prevention simultaneously.

Future research should prioritize longitudinal vaccine effectiveness studies, improved point-of-care diagnostics, genomic surveillance networks, and cost-effectiveness analyses of integrated vaccination and WASH interventions in endemic settings.

8. Conclusion

Typhoid fever has transformed from an uncomplicated bacterial infection into a multifaceted global health security hazard driven by antimicrobial resistance. The augmentation of XDR *S. Typhi* strains demonstrates the restrictions of an exclusively reactive, antibiotic-dependent management strategy. Effectively mitigating this disease needs combining the rapid deployment of tremendously protective Typhoid Conjugate Vaccines with uninterrupted improvements in clean water infrastructure and diagnostics.

Strength and Limitations

This is a novel review study. The key limitation is availability of data.

About the Authors

The key author is currently working as Senior General Medical Officer for the government of Bihar.

Notes

This is the first version of this work and more versions will evolve in future with more information and analysis.

Abbreviation

low- and middle-income countries (LMICs); multidrug-resistant (MDR); extensively drug-resistant (XDR); Typhoid Conjugate Vaccines (TCVs); water, sanitation, and hygiene (WASH); *Salmonella enterica* serovar Typhi (S. Typhi; World Health Organization (WHO); M (microfold cells) cells; loop-mediated isothermal amplification (LAMP); hemolysin E (HlyE); rapid diagnostic tests (RDTs); Strategic Advisory Group of Experts (SAGE); Gavi (Global Alliance for Vaccines and Immunization); Typhoid Vaccine Acceleration Consortium (TyVAC).

Statements and Declarations

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Potential Competing Interests

No potential competing interests to declare.

Ethics

Not applicable. This study has not involved any human or animals in real or for experiments. The submitted work does not contain any identifiable patient/participant information.

Author Contributions

The whole work is done by the Author - Dr Piyush Kumar, M.B.B.S., E.M.O.C., P.G.D.P.H.M., -Senior General Medical Officer- Bihar Health Services- Health Department- Government of Bihar, India and others mentioned above.

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References

1. [△]Crump JA, Mintz ED (2010). "Global Trends in Typhoid and Paratyphoid Fever." *Clin Infect Dis.* **50**(2):241–246.
2. [△]Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, et al. (2014). "Burden of Typhoid Fever in Low-Income and Middle-Income Countries: A Systematic Review." *Lancet Glob Health.* **2**(10):e570–e580.
3. [△]Stanaway JD, Reiner RC Jr, Blacker BF, Goldberg EM, Khalil IA, Troeger CE, et al. (2019). "The Global Burden of Typhoid and Paratyphoid Fevers: A Systematic Analysis." *Lancet Infect Dis.* **19**(4):369–381.
4. [△]Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ (2002). "Typhoid Fever." *N Engl J Med.* **347**(22):1770–1782.
5. [△]Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK, et al. (2018). "Emergence of an Extensively Drug-Resistant *Salmonella* Enterica Serovar Typhi Clone." *mBio.* **9**(1):e00105–18.
6. [△]World Health Organization (2024). "Typhoid Fact Sheet." World Health Organization. Geneva: WHO.
7. [△]GBD 2021 Typhoid and Paratyphoid Collaborators (2024). "Global Burden of Typhoid and Paratyphoid Fever 1990–2021." *Lancet Infect Dis.*
8. [△]Antillón M, Warren JL, Crawford FW, Weinberger DM, Kürüm E, Pak GD, et al. (2017). "The Burden of Typhoid Fever in Low- and Middle-Income Countries." *PLoS Negl Trop Dis.* **11**(2):e0005376.
9. [△]Aiemjoy K, Seidman JC, Saha S, Munira S, Sajib MSI, Sium SMA, et al. (2022). "Estimating Typhoid Incidence from Community-Based Serosurveys." *Sci Transl Med.* **14**(638):eabk3149.
10. [△]Britto CD, Dyson ZA, Duchene S, Carter MJ, Gurung M, Kelly DF, et al. (2018). "Laboratory and Molecular Surveillance of Typhoid Fever." *Clin Infect Dis.* **68**(Suppl 2):S147–S153.
11. [△]Dougan G, Baker S (2014). "*Salmonella* Enterica Serovar Typhi and the Pathogenesis of Typhoid Fever." *Annu Rev Microbiol.* **68**:317–336.
12. [△]Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL (2015). "Typhoid Fever." *Lancet.* **385**(9973):1136–1145.
13. [△]Buckle GC, Walker CLF, Black RE (2012). "Typhoid Fever and Paratyphoid Fever: Systematic Review." *Bull World Health Organ.* **90**:640–650.
14. [△]Crump JA (2019). "Progress in Typhoid Fever Epidemiology." *Clin Infect Dis.* **68**(Suppl 2):S4–S9.
15. [△]Bhutta ZA (2006). "Current Concepts in the Diagnosis and Treatment of Typhoid Fever." *BMJ.* **333**(7558):78–82.

16. [△]Wong VK, Baker S, Connor TR, Pickard D, Page AJ, Dave J, et al. (2016). "An Extended Genotyping Framework for *Salmonella* Typhi." *Nat Commun.* **7**:12827.
17. [△]Hooda Y, Sajib MSI, Rahman H, Luby SP, Bondy-Denomy J, Endtz HP, et al. (2019). "Molecular Mechanism of Azithromycin Resistance in Typhoidal *Salmonella*." *mBio.* **10**(6):e01908-19.
18. [△]Carey ME, Dyson ZA, Ingle DJ, Amir A, Aworh MK, Chattaway MA, et al. (2023). "Global Dissemination of Antimicrobial-Resistant *Salmonella* Typhi." *Lancet Microbe.* **4**(5):e335-e347.
19. [△]Qamar FN, Yousafzai MT, Khalid M, Kazi AM, Lohana H, Karim S, et al. (2018). "Outbreak Investigation of Ceftriaxone-Resistant *Salmonella* Typhi." *Lancet Infect Dis.* **18**(8):826-836.
20. [△]da Silva KE, Tanmoy AM, Pragasam AK, Iqbal J, Sajib MSI, Mutreja A, et al. (2022). "Genomic Evidence for Emergence of Ceftriaxone-Resistant *Salmonella* Typhi in South Asia." *Clin Infect Dis.* **75**(9):1621-1629.
21. [△]Andrews JR, Ryan ET (2015). "Diagnostics for Invasive *Salmonella* Infections." *Clin Infect Dis.* **61**(Suppl 4):S227-S232.
22. [△]Gasem MH, Dolmans WM, Keuter M, Djokomoeljanto R (2003). "Poor Blood Culture Sensitivity in Typhoid Fever." *J Clin Microbiol.* **41**(2):819-821.
23. [△]Olopoenia LA, King AL (2000). "Widal Agglutination Test – 100 Years Later." *Postgrad Med J.* **76**(892):80-84.
24. [△]Darton TC, Meiring JE, Tonks S, et al. (2023). "Rapid Diagnostics and Biomarkers for Enteric Fever." *J Infect.* **86**(4):e89-e97.
25. [△]World Health Organization Strategic Advisory Group of Experts (SAGE) (2018). "Typhoid Vaccines Position Paper." *Wkly Epidemiol Rec.* **93**(13):153-172.
26. [△]Shakya M, Colin-Jones R, Theiss-Nyland K, Voysey M, Pant D, Smith N, et al. (2019). "Efficacy of Typhoid Conjugate Vaccine in Nepal." *N Engl J Med.* **381**(23):2209-2218.
27. [△]Jin C, Gibani MM, Moore M, Juel HB, Jones E, Meiring J, et al. (2017). "Efficacy and Immunogenicity of a Vi-Tetanus Toxoid Conjugate Vaccine." *Lancet.* **390**(10111):2472-2480.
28. [△]Patel PD, Patel P, Liang Y, Meiring J, Misiri T, Mwakiseghile F, et al. (2021). "Effectiveness of Typhoid Conjugate Vaccine in Malawi." *N Engl J Med.* **385**(12):1104-1115.
29. [△]World Health Organization (2024). "Typhoid Vaccines: WHO Position Paper – Update 2024." World Health Organization. Geneva: WHO.
30. [△]Dyson ZA, Klemm EJ, Palmer S, Dougan G (2019). "Antibiotic Resistance and Genomic Surveillance of *Salmonella* Typhi." *Trends Microbiol.* **27**(8):698-710.

31. [△]Bardaweel SK, et al. (2023). "Artificial Intelligence Applications in Infectious Disease Surveillance and Prediction." *Front Public Health*. **11**:1187254.
32. [△]Sikorski MJ, Levine MM (2023). "Environmental Surveillance and Wastewater Monitoring for Enteric Pathogens." *Clin Infect Dis*. **76**(Suppl 5):S487-S494.

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