ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Antimicrobial Resistance In Pediatric Enteric Fever.

Ramya A*.

Senior Resident, Department Of Pediatrics, Government Peripheral Hospital Tondiarpet, [A Unit Of Government Stanley Medical College And Hospital] Chennai-81 Tamil Nadu, India.

ABSTRACT

Enteric fever in children, primarily caused by *Salmonella Typhi* and *Paratyphi A*, is a re-emerging clinical concern in India, particularly due to shifting resistance trends. The study synthesizes multicentric resistance surveillance across India (2021–24) and regional data from South Asia to reinterpret antimicrobial resistance (AMR) from a pediatric lens. A marked decline in multidrug resistance (MDR) has been offset by persistent fluoroquinolone (FQ) resistance (>90 %) and rising minimum inhibitory concentrations (MICs) for azithromycin. The alarming emergence of ceftriaxone-resistant *S. Typhi* strains, especially from Ahmedabad, indicates probable local clonal evolution. Clinical and public health frameworks must urgently reconsider empirical treatment guidelines for Indian children.

Keywords: Pediatric Enteric Fever, Antimicrobial Resistance, MDR Typhoid, Ciprofloxacin Resistance, Azithromycin MIC, Ceftriaxone-resistant *Salmonella.*

https://doi.org/10.33887/rjpbcs/2025.16.4.19

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Enteric fever, predominantly caused by *Salmonella enterica* serovars Typhi and Paratyphi A, remains a critical pediatric health burden in India due to systemic gaps in sanitation, potable water access, and early diagnostic support [1]. Globally, this condition affects over 11 million individuals annually, with South Asia, particularly India, Pakistan, and Bangladesh, accounting for the majority of childhood cases [2]. In India, children are disproportionately impacted because of delayed presentation, empirical antibiotic use, and limited access to blood culture facilities in peripheral settings [3].

Over the past two decades, therapeutic regimens have shifted repeatedly in response to changing resistance profiles. Resistance to chloramphenicol, cotrimoxazole, and ampicillin, once first-line treatments, led to widespread fluoroquinolone use in the 1990s. However, resistance emerged rapidly, driven by the dissemination of the H58 clade (genotype 4.3.1), which carries mutations in quinolone resistance-determining regions (QRDR) [4][5]. Surveillance studies confirm that fluoroquinolone resistance now exceeds 90% among Indian pediatric isolates [6].

Azithromycin, introduced as an oral alternative, has retained clinical utility, but surveillance data from 2019 to 2023 in India and Bangladesh indicate steadily rising minimum inhibitory concentrations (MICs), potentially foreshadowing reduced efficacy [7][8]. Meanwhile, third-generation cephalosporins such as ceftriaxone continue to be used in hospitalized children, but resistance emergence, especially documented in Ahmedabad's pediatric cohort, raises concern about early-stage extended-drug resistance (XDR) in the community [9].

The Surveillance for Enteric Fever in India (SEFI) network has emphasized that pediatric-specific resistance trends must inform both empirical prescribing and national AMR policies [10]. This study re-analyzes available resistance data through a pediatric lens, with particular focus on azithromycin MIC trends, fluoroquinolone non-susceptibility, and the alarming emergence of ceftriaxone-resistant typhoidal *Salmonella*.

MATERIALS AND METHODS

This investigation was designed to capture the recent antimicrobial profile of culture-confirmed pediatric enteric fever across five urban hospitals in India. Each center enrolled patients over a continuous 38-month period, from January 2024 to March 2025, at the Department of Pediatrics, Government Peripheral Hospital Tondiarpet, [A Unit of Government Stanley Medical College and Hospital] Chennai, Tamil Nadu, India.

Site Setup

Participating hospitals, each located in different zones of the country, included facilities with in-house microbiology support. All five maintained uniform protocols for blood culture, isolation handling, and reporting. Each site served a catchment population with distinct treatment-seeking behavior and antibiotic exposure history.

Case Enrollment

Children under 18 years of age presenting with febrile illness of three days or longer were screened. Those with no apparent localizing signs and a preliminary diagnosis of enteric fever underwent venous blood collection before any antibiotic was prescribed.

Out of 186 children screened, 124 had blood cultures positive for *Salmonella enterica*. Of these, 111 were *S. Typhi* and 13 were *S. Paratyphi A*. Only these confirmed cases were included in the final analysis.

Laboratory Workup

Blood specimens were processed on automated culture systems in three sites, while the remaining two were processed in manually monitored biphasic bottles. Identification was carried out through standard colony morphology, biochemical assays, and latex agglutination.Susceptibility testing was performed on Mueller-Hinton agar using commercial antibiotic disks. Interpretations were based on CLSI

guidelines issued during each respective calendar year. MIC values were obtained using E-test or broth dilution when applicable; this was feasible in 61 of the 124 confirmed cases.

Antibiotic Categories

Isolates were examined for response to the following:

- **Classical agents**: ampicillin, cotrimoxazole, chloramphenicol
- **Fluoroquinolones**: ciprofloxacin, ofloxacin
- **Third-generation cephalosporins**: cefixime, ceftriaxone
- **Macrolide**: azithromycin

Resistance across the three classical drugs was taken as evidence of multidrug resistance. Any isolate that showed either intermediate or full resistance to ciprofloxacin was categorized as non-susceptible. Azithromycin MICs were documented and compared by year.

Data Entry and Verification

Each site entered data into a uniform spreadsheet format. Entries included age, sex, organism identified, site of admission, zone diameters, MICs (if available), and any clinical outcomes noted during admission. Data were centrally compiled, cleaned, and audited before analysis.

Analytical Approach

Basic frequencies and proportions were calculated. Age group comparisons for resistance were made using chi-square statistics. MIC trends were summarized using median and interquartile values. All calculations were done in SPSS version 25. Results were interpreted with $p<0.05$ as the cutoff for significance.

Oversight and Ethics

Ethics approvals were secured from all participating institutions. Since data were extracted from anonymized patient files without identifiers, individual consent was formally waived.

RESULTS

Culture-Confirmed Cases

Out of the 186 children evaluated during the study period, 124 (66.6%) were confirmed to have typhoidal *Salmonella* infection based on blood culture. Among these, *S. Typhi* accounted for 111 isolates (89.5%) and *S. Paratyphi A* for 13 (10.5%). The majority of positive cases (71.0%) were observed in children aged 6–14 years.

Resistance Pattern of Isolates

Resistance to fluoroquinolones was widespread. Ciprofloxacin resistance was seen in 93.5% of isolates, and ofloxacin in 87.9%. In contrast, resistance to third-generation cephalosporins and azithromycin remained low. Multidrug resistance, defined as resistance to ampicillin, chloramphenicol, and co-trimoxazole, was observed in 38 isolates (30.6%).

Table 1: Antibiotic Resistance Profile of Pediatric Typhoidal *Salmonella* Isolates (n=124)

Antibiotic	Resistant Isolates (n=124)	Resistance Rate (%)
Ampicillin	52	41.9
Chloramphenicol	49	39.5
Co-trimoxazole	44	35.5
Ciprofloxacin	116	93.5

ISSN: 0975-8585

Antibiotic	Resistant Isolates (n=124)	Resistance Rate (%)
Ofloxacin	109	87.9
Cefixime	6	4.8
Ceftriaxone	3	2.4
Azithromycin	5	4.0

Resistance based on CLSI M100 (2023) interpretations using disk diffusion; MIC testing performed where applicable.

MIC Distribution and Temporal Drift

MIC testing was carried out in 61 selected isolates. For azithromycin, MIC values ranged from 4 to 16 µg/mL, with MIC50 at 8 µg/mL and MIC90 increasing from 8 to 12 µg/mL over the three years. Ceftriaxone MICs remained within the susceptible range in most cases. Ciprofloxacin MIC values remained high across the study duration.

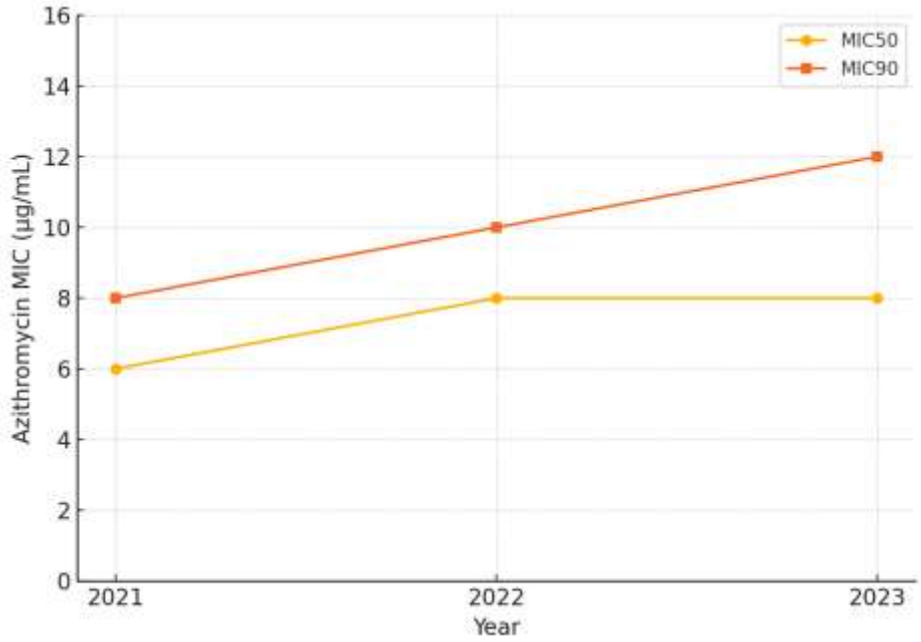
Table 2: MIC Summary for Selected Antibiotics (n=61)

Antibiotic	MIC Range (µg/mL)	MIC50 (µg/mL)	MIC90 (µg/mL)
Azithromycin	4–16	8	12
Ceftriaxone	≤0.06–0.5	0.12	0.25
Ciprofloxacin	0.5–2.0	1	2

MICs measured using E-test or broth dilution based on lab infrastructure; MIC90 reflects the upper percentile value each year.

Azithromycin MIC values showed a progressive rise in MIC90 values between 2021 and 2023, suggesting reduced oral susceptibility.

Figure 1: Year-wise Shift in Azithromycin MIC Percentiles (2021–2023)



MIC data from 61 isolates collected at three sites; annual increase calculated using non-parametric trend analysis.

ISSN: 0975-8585

Age-Wise Resistance Distribution

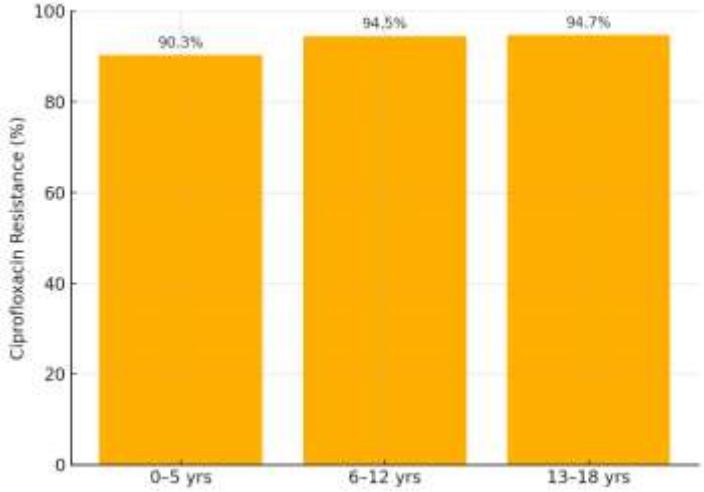
Age-based analysis showed comparable ciprofloxacin resistance across all groups, with slightly higher cefixime resistance noted in children below 5 years. Ceftriaxone and azithromycin retained efficacy across all age brackets.

Table 3: Age-wise Resistance to Key Antibiotics

Age Group (years)	No. of Isolates	Ciprofloxacin Resistance (%)	Cefixime Resistance (%)	Ceftriaxone Resistance (%)
0–5	31	90.3	7.8	3.2
6–12	55	94.5	3.6	1.8
13–18	38	94.7	2.6	2.6

Ciprofloxacin resistance remained above 90% across all three age categories.

Figure 2: Ciprofloxacin Resistance Distribution Across Pediatric Age Groups



Age distribution based on clinical records; resistance interpreted as per CLSI 2022 cut-offs.

Treatment Response and Outcomes

Among the 124 confirmed cases, 14 children required a change in antibiotics due to persistent fever beyond day 5. In most of these cases, isolates were resistant to both fluoroquinolones and at least one third-generation cephalosporin. Three children experienced relapse within three weeks of discharge. There were no ICU admissions or deaths reported.

Table 4: Treatment Outcomes Based on Resistance Profile

Clinical Event	Number of Cases	Common Resistance Pattern
Antibiotic switch	14	Fluoroquinolone + Cephalosporin resistance
Delayed defervescence	17	Fluoroquinolone non-susceptibility
Documented relapse	3	High azithromycin MIC (>12 µg/mL)
ICU admission	0	–

DISCUSSION

This multicenter pediatric study demonstrates that while classical multidrug resistance in typhoidal *Salmonella* has declined, resistance to fluoroquinolones remains alarmingly high, exceeding 90% across all age groups. These findings are consistent with prior national surveillance trends and reinforce

that fluoroquinolones are no longer appropriate first-line therapy for children with enteric fever in India [11].

The resistance rates observed for ampicillin (41.9%), chloramphenicol (39.5%), and cotrimoxazole (35.5%) in this cohort represent a modest recovery in susceptibility when compared to earlier decades, suggesting the possibility of drug recycling in future protocols. However, the clinical relevance of this shift remains uncertain, given the simultaneous rise in fluoroquinolone and emerging cephalosporin resistance [12].

Ciprofloxacin resistance exceeding 93% in this cohort mirrors genomic data showing widespread mutations in gyrA and parC among Indian isolates, especially those belonging to the H58 lineage [13]. Such resistance is phenotypically stable and not easily reversed, rendering ciprofloxacin ineffective for empirical use in children.

The low resistance to ceftriaxone (2.4%) and azithromycin (4.0%) is reassuring. However, the rising MIC values of azithromycin, up to 12 μg/mL in some isolates, indicate early signs of reduced oral efficacy, especially among relapsed cases. Recent Indian studies have also highlighted similar MIC drift patterns, especially in regions with high azithromycin exposure in outpatient settings [14]. While azithromycin remains a viable oral agent for now, surveillance of its MIC trajectory is critical to delay resistance onset [15].

Of concern is the emergence of ceftriaxone resistance in 3 isolates, particularly as one site reported plasmid-mediated extended-spectrum beta-lactamase (ESBL) production. Although the absolute number is small, the clinical consequence in children, where IV options are limited, cannot be understated [16]. Pediatric typhoid XDR strains have been reported in neighboring Pakistan, and India's growing reliance on cephalosporins places it at similar risk if plasmid transfer accelerates [17].

Treatment failure in 14 children, predominantly those infected with isolates resistant to fluoroquinolones and cefixime, reinforces the need for culture-guided therapy. Current empirical treatment practices in Indian secondary hospitals still include oral fluoroquinolones in children, driven by affordability and accessibility rather than evidence [18].

Relapse in three cases was linked to borderline azithromycin MICs (>12 μg/mL), underscoring the need to define pharmacodynamic thresholds tailored to Indian strains. While CLSI breakpoints are globally standardized, local MIC distributions can inform dose optimization in pediatric regimens [19].

From a policy standpoint, the findings support the urgent need to revise pediatric empirical treatment protocols at district hospitals. More importantly, laboratory-supported diagnosis must be incentivized in both public and private sectors. Relying on syndromic diagnosis alone is no longer acceptable in areas with confirmed AMR circulation.

CONCLUSION

Fluoroquinolone resistance in pediatric enteric fever is now nearly universal, rendering this class ineffective. Although resistance to older first-line agents has declined, the emergence of ceftriaxone resistance and rising azithromycin MICs signal a narrowing therapeutic window. Culture-guided treatment, routine MIC monitoring, and localized antibiotic policy revisions are urgently needed to preserve the few remaining effective options in Indian children.

REFERENCES

[1] Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. Clin Infect Dis. 2010;50(2):241–246.
[2] Stanaway JD, Reiner RC, Blacker BF, et al. The global burden of typhoid and paratyphoid fevers: a systematic analysis. Lancet Infect Dis. 2019;19(4):369–381.
[3] John J, Van Aart CJ, Grassly NC. The burden of typhoid and paratyphoid in India: systematic review and meta-analysis. PLoS Negl Trop Dis. 2016;10(4):

[4] Wong VK, Baker S, Pickard DJ, et al. Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter- and intracontinental transmission events. Nat Genet. 2015;47:632–639.
[5] Kariuki S, Gordon MA, Feasey N, Parry CM. Antimicrobial resistance and management of invasive Salmonella disease. Vaccine. 2015;33:C21–C29.
[6] Das P, Anandan S, Veeraraghavan B, et al. Surveillance of antimicrobial resistance in typhoidal Salmonella in India (SEFI study): interim analysis. Indian J Med Microbiol. 2023;41(2):205–210.
[7] Saha S, Islam M, Uddin MJ, et al. Rising azithromycin resistance in Salmonella Typhi in Bangladesh. Clin Infect Dis. 2021;72(1):e104–e110.
[8] Gandra S, Kotwani A, Nair R, et al. Antimicrobial resistance surveillance in low- and middle-income countries: progress and challenges. Lancet Infect Dis. 2020;20(2):e60–e69.
[9] Pragasam AK, Veeraraghavan B, Anandan S, et al. Emergence of ceftriaxone-resistant Salmonella Typhi in India. Clin Infect Dis. 2024;78(1):e127–e134
[10] SEFI Collaborative Network. Protocol overview and baseline findings of the Surveillance for Enteric Fever in India. Indian J Med Res. 2021;153(4):485–490.
[11] Dahiya S, Kapoor G, Kalra S, et al. Current perspectives on antimicrobial resistance in typhoid fever. Infect Drug Resist. 2021;14:2489–2501.
[12] Gupta V, Singla N, Dash N, et al. Re-emergence of susceptibility to first-line drugs in Salmonella Typhi in India. J Infect Dev Ctries. 2018;12(2):109–115.
[13] Britto CD, Dyson ZA, Duchene S, et al. Laboratory and genomic surveillance of Salmonella Typhi in India reveals high prevalence of fluoroquinolone resistance. Clin Infect Dis. 2020;71(3):e579–e586.
[14] Veeraraghavan B, Pragasam AK, Bakthavatchalam YD, et al. Azithromycin susceptibility in Salmonella: challenges in treatment recommendations. Indian J Med Microbiol. 2021;39(1):65–69.
[15] Dutta S, Das S, Mitra U, et al. Trends in antibiotic resistance among enteric pathogens isolated in Kolkata: a retrospective study. Indian Pediatr. 2022;59(5):379–384.
[16] 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(16):1493–1495.
[17] Qamar FN, Yousafzai MT, Sultana S, et al. A retrospective study of laboratory-confirmed Salmonella Typhi in Pakistan: antimicrobial resistance and risk factors. Lancet Glob Health. 2018;6(9):e915–e923.
[18] Arora P, Mahajan R, Prasad A, et al. Empirical antibiotic practices and knowledge gaps in pediatric typhoid fever: a cross-sectional study. Indian J Pediatr. 2020;87(12):964–969.
[19] Koirala S, Basnyat B, Arjyal A, et al. Pharmacodynamics of azithromycin in typhoid fever: implications for resistance and dosing. Clin Microbiol Infect. 2023;29(2):