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Typhoidal *Salmonella* and Emerging Resistance in Outbreak Proportions

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Abstract

Introduction: Typhoidal *Salmonella* causes an invasive infection resulting in 200 000 deaths among 20 million patients annually. Typhoid remains a public health problem in Southeast Asia, the Indian subcontinent, Africa, and South America. Traveler's diarrhea caused by *Salmonella* is common in Asia. Outbreaks of typhoidal *Salmonella* resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole in the 1990s pushed therapy to ciprofloxacin which was replaced by ceftriaxone due to fluoroquinolone resistance.

Methods: This prospective study characterizes demographical, etiological, and resistance patterns in typhoidal *Salmonella* at a 1000-bed teaching hospital in New Delhi, India. Two hundred inpatients in pediatrics, obstetrics-gynecology, medicine, intensive care, and OPD in whom *Salmonella* bacteremia was detected were characterized by routine and automated microbiology techniques.

Results: The mean age of patients in this study was 21.4 years. Overall, 71% of patients suffered from *Salmonella* Typhi followed by 26% from *Salmonella* Paratyphi A. Four cases of *Salmonella* resistance to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol were encountered. A high degree of partial and complete resistance to fluoroquinolones was seen among *Salmonella* Typhi, *Salmonella* Paratyphi A, and *Salmonella* Paratyphi B cases. Resistance to ciprofloxacin was 48% among *Salmonella* Typhi and 100% among *Salmonella* Paratyphi A cases. Only 18% of *Salmonella* Typhi cases were completely resistant to quinolones, while 79% were partially resistant. A total of 92% of *Salmonella* Paratyphi A cases were partially resistant to quinolones. Four *Salmonella* cases were resistant to ceftriaxone.

Conclusion: *Salmonella* Typhi remains the predominant serotype, followed by *Salmonella* Paratyphi A. The high prevalence of quinolone resistance in *Salmonella* Typhi and *Salmonella* Paratyphi A is a serious problem limiting empirical therapy to non-quinolone-based therapy such as ceftriaxone. Multidrug-resistant Salmonella is an emerging problem requiring active surveillance among residents and travelers presenting with tropical fever.

Keywords: *Salmonella*, Typhoid, Multidrug Resistance, Fluoroquinolone Resistance, Traveler's Diarrhea

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Introduction

Salmonella enterica subspecies *enterica* serotypes Typhi, Paratyphi A, Paratyphi B and Paratyphi C cause an acute, invasive and potentially fatal systemic infection known as typhoid fever or enteric fever. Among the 12 to 22 million patients of typhoid fever per annum, the estimated death rate is between 129 000 and 217 000, and 80% of these cases and deaths occur in Asia alone. Due to improved sanitation, most developed countries in Europe and North America are free from enteric fever, but enteric fever is still a disease of concern in Southeast Asia, the Indian subcontinent, Africa, and, to a lesser extent, in South America.[1-3] Regions with the highest incidence of enteric fever are South-Central Asia and Southeast Asia. *Salmonella* has been responsible for numerous outbreaks in the Indian subcontinent, Southeast Asia, and Africa. In Delhi, India, the incidence rate is 9.8 cases/1000 person per year.[4-6]

Salmonella is a common cause of traveler's diarrhea presenting with fever, nausea, vomiting, and abdominal cramps. Up to 70% of travelers from Western countries develop traveler's diarrhea in the first week of travel to tropical destinations in South Asia and Southeast Asia. High-risk regions for traveler's diarrhea are Asia, the Middle East, Africa, Mexico, Central and South America. Intermediate-risk regions are Eastern Europe, South Africa, and some Caribbean islands. Low-risk regions are Northern and Western Europe,

the United States, Canada, Australia, New Zealand, and Japan. A large number of traveler's take empirical ciprofloxacin or azithromycin to reduce the severity and duration of traveler's diarrhea.[7-10]

Effective antimicrobial therapy is required to control morbidity and mortality from typhoid fever. Until the 1960s, all *Salmonella* were susceptible to a wide range of antimicrobials. Ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole were the first line drugs for *Salmonella*. Since 1962, plasmid-mediated resistance has appeared worldwide. Extensive epidemics caused by chloramphenicol resistant *Salmonella* Typhi were first witnessed in India and Mexico in 1972.[11,12] By the late 1980s, multidrug-resistant *Salmonella* resistant to all first line drugs emerged worldwide including in India which is an endemic zone for 50%-80% of multidrug-resistant *Salmonella*. Since 1989, outbreaks by *Salmonella* Typhi resistant to chloramphenicol, ampicillin, trimethoprim, sulfonamides, streptomycin, and tetracyclines have been reported from India and Pakistan. Multidrug-resistant *Salmonella* has no pathogenic clinical features, though it may present with dominant hepatomegaly, toxicity, or complications and is associated with higher mortality.[13-16] Ciprofloxacin became the antibacterial of choice for the treatment of typhoid fever after the emergence of *Salmonella* Typhi strains resistant to chloramphenicol. Ciprofloxacin is also recommended for traveler's diarrhea. However, the minimal inhibitory concentration (MIC) of ciprofloxacin against *Salmonella* Typhi is gradually increasing due to its continuous use. MIC values for *Salmonella* Paratyphi A as high as >126 µg/mL for ampicillin, 256 µg/mL for chloramphenicol, and 64 µg/mL for trimethoprim-sulfamethoxazole have been reported.[17-20]

Ceftriaxone is safe and efficacious against most clinical isolates of *Salmonella* and is now the preferred drug for MDRTF infections.[21,22] Reports of resistance to cephalosporins have been appearing at an increasing rate since 2006. It is pertinent to monitor the resistance characteristics of multidrug-resistant *Salmonella* infections to enable empirical therapy and the treatment of complications. The spread of MDR and fluoroquinolone resistance in *Salmonella* presents increased clinical challenges in countries where enteric fever is imported, requiring enhanced surveillance. This study characterizes demographical trends, etiological and emerging resistance patterns in typhoidal *Salmonella* at a 1000-bed teaching hospital in New Delhi, India.

Methods

This prospective study was conducted among all patients determined to have typhoidal *Salmonella* infections from blood cultures in a 1000-bed tertiary-care hospital over a period of 6 months after approval was obtained from the Institutional Ethics Committee (ICMR STS 2017-01590). All 200 patients with *Salmonella* infections detected in blood cultures were included in the study. Typhoidal *Salmonella* isolated from samples other than blood, patients of non-typhoidal Salmonellosis, and repeat isolates were excluded. Blood samples were collected by skin puncture in Bact/Alert blood culture bottles (Biomerieux, France) following strict aseptic techniques. The quantity of blood drawn was 10 mL for adults and 5 mL for children. Samples were immediately transported to the microbiology laboratory for incubation in the Bact/Alert blood culture system (Biomerieux, France) for 2-120 hours. Subcultures on blood and McConkey agars were incubated for 24-48 hours at 37°C. Inpatients in pediatrics, obstetrics-gynecology, medicine, the intensive care unit (ICU), and OPD were under surveillance. Organism identification and antimicrobial susceptibility were accomplished using standard microbiology techniques and employing routine bacteriological methods, such as colony characteristics, gram staining, motility, carbon-source utilization, and enzymatic activity, and confirmed by the VITEK-2 Compact Automated Microbiology system (Biomerieux, France). Each patient's demographic profile and non-repeat positive cultures with respective antibiograms were taken into account in the profiling of isolates and antimicrobial susceptibility. Descriptive statistics including frequency, percentages, and 95% CIs were worked out using Microsoft Excel.

Results

The age profile revealed mostly young patients up to 40 years of age among both males and females. Mean age was 21.4 years (Figure 1). Most patients (44%, 95% CI: 0.35-0.54) were from OPD followed by the pediatric ward (20%, 95% CI: 0.13-0.29) (Table 1). Most patients (71%, 95% CI: 0.61-0.8) with typhoid fever suffered from *Salmonella* Typhi followed by *Salmonella* Paratyphi A (26%, 95% CI: 0.18-0.35). Most *Salmonella* were susceptible to ampicillin, ceftriaxone, trimethoprim-sulfamethoxazole, chloramphenicol and cefepime. Four MDRTF resistant to ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol were encountered. There was no resistance to cefepime among any *Salmonella* Typhi strains; however, four cases were resistant to ceftriaxone. High degrees of partial and complete resistance to fluoroquinolones were seen among *Salmonella* Typhi, *Salmonella* Paratyphi A, and *Salmonella* Paratyphi B. Resistance to ciprofloxacin was 48% (95% CI 0.37-0.6) among *Salmonella* Typhi and 100% (95% CI: 0.9-1) among *Salmonella* Paratyphi A. Moreover, 18% (95% CI: 0.11-0.3) of *Salmonella* Typhi were completely resistant to quinolones and 79% (95% CI: 0.7-0.9) were partially resistant. Additionally, 92% (95% CI: 0.8-1) of *Salmonella* Paratyphi A were partially resistant to quinolones (Table 1).

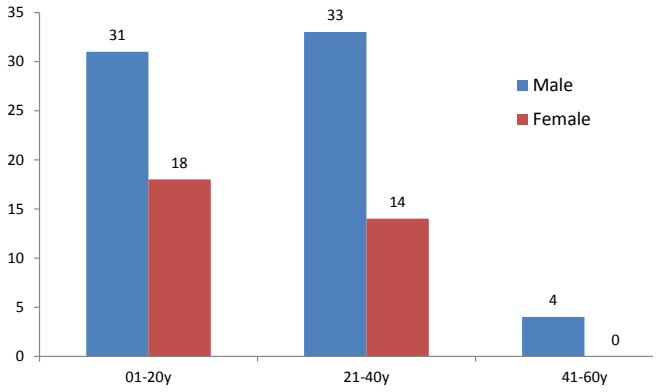

Figure 1. Clinicodemographic Profile of Patients Suffering From Typhoid Fever.

Table 1. Distribution of *Salmonella* Typhi, *Salmonella* Paratyphi A, and *Salmonella* Paratyphi B in Blood Samples From Various Wards

WARD	*Salmonella* Typhi	*Salmonella* Paratyphi A	*Salmonella* Paratyphi B	Total
Pediatrics, No. (%)	16 (80)	4 (20)	0 (0)	20
Obstetrics and gynecology, No. (%)	1 (100)	0 (0)	0 (0)	1
Acute medical ward (females), No. (%)	5 (83.3)	1 (16.7)	0 (0)	6
ICU, No. (%)	0 (0)	0 (0)	1 (100)	1
Acute medical ward (males), No. (%)	11 (64.7)	6 (85.7)	0 (0)	17
Subacute medical ward, No. (%)	8 (72.7)	3 (27.3)	0 (0)	11
OPD, No. (%)	30 (68.2)	12 (27.3)	2 (4.5)	44
Total, No. (%)	71 (71)	26 (26)	3 (3)	100

Table 2. Resistance patterns of *Salmonella* Typhi *and Salmonella* Paratyphi A and B

MIC µg/mL	Ampicillin		Ceftriaxone		Nalidixic Acid		Ciprofloxacin		Cotrimoxazole		Chloramphenicol		Cefepime		Quinolones
	≤8	≥32	≤1	≥4	≤8	≥32	<1	≥1	≤8	≥32	≤8	≥32	≤2	≥16	
Interpretation	S	R	S/I	R	S	R	S/I	R	S	R	S	R	S/I	R	
S. Typhi	69	2	67	4	-	71	37	34	69	2	69	2	69/2	-	PR-56 R-13
S. Paratyphi A	26	-	15/2	9	-	26	-	26	26	-	26	-	19/5	-	PR-24
S. Paratyphi B	3	-	-	-	-	-	3	-	3	-	3	-	3	-	
Total number of isolates	98	2	84	13	-	97	40	60	98	2	98	2	100	-	93

Susceptible – S, Resistant –R, Intermediate- I, Partially resistant – PR.

Discussion

Enteric fever is more common in tropical regions because of flooding of rain water, the distribution of sewage into drinking water sources, and increased bacterial concentrations in rivers and streams in the hot and dry season. The distribution of typhoid fever is not well documented in developing countries, because facilities capable of performing the blood culture tests essential for diagnosis are far and few, or because it remains unknown or unaffordable to many patients from resource-limited communities. The incidence of typhoid fever may be as high as 1000 patients per 100 000 population per year in certain regions. In such regions, the excretion of *Salmonella* Typhi in feces is the main source of infection, and children are predominantly affected. *Salmonella* infections are associated with poverty; therefore, they tend to cause infections in families and communities.[23]

Travelers to tropical destinations are increasingly at risk of *Salmonella* infections when traveling to villages or remote rural areas of the countryside where diagnostic and treatment facilities may be far and few. Special precautions are required for travelers with pre-existing bowel/systemic problems such as irritable bowel syndrome, inflammatory bowel disease, poorly controlled diabetes, hepatic cirrhosis, or renal impairment. Patients with a tendency to severe traveler's diarrhea or patients on antacids need to be vigilant in food and water choices while traveling to tropical countries.[24-27]

The current study revealed a young patient profile suffering from *Salmonella* bacteremia. The high degree of resistance to fluoroquinolones is alarming among all serotypes, viz. *Salmonella* Typhi, *Salmonella* Paratyphi A, and *Salmonella* Paratyphi B. Almost all strains of *Salmonella* Paratyphi A were resistant to quinolones. Four isolates of multidrug-resistant *Salmonella* showed an increasing trend toward the emergence of resistance in uncomplicated typhoid. The *Salmonella* serotypes found in this study were 71% *Salmonella* Typhi, 26% *Salmonella* Paratyphi A, and 3% *Salmonella* Paratyphi B, which was in accordance with a study in Indonesia that showed the predominance of *Salmonella* Typhi over *Salmonella* Paratyphi.[28] In the current study, there appears to be an increasing susceptibility to first line drugs such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole; i.e. *Salmonella* Typhi susceptibility to more than three was 99%. The antimicrobial resistance rates of *Salmonella* Typhi differ among different countries in the world. A study in Pakistan showed that resistance rates of *Salmonella* Typhi and *Salmonella* Paratyphi were 66.1% for ampicillin, 88.2% for fluoroquinolone, and 66.5% for trimethoprim-sulfamethoxazole.[29] A study in Nepal showed resistance rates of *Salmonella* Typhi against ampicillin and *Salmonella* Paratyphi against ciprofloxacin were 1.8% and 3.9%, respectively, while there was no resistance against trimethoprim-sulfamethoxazole.[30] Another study in China showed that resistance rates of *Salmonella* Typhi and Paratyphi were respectively 0.8% and 2.0% for ampicillin, 13.5% and 5.9% for ciprofloxacin, 5.4% and 1.4% for sulfamethoxazole, 5.4% and 0.8% for levofloxacin, 10% and 5.4% for ceftriaxone, and 0% for meropenem and imipenem. A study in Bangladesh showed resistance rates were 68.4% for ampicillin, 39.5% for ciprofloxacin, 57.9% for trimethoprim, and 68.4% for sulfamethoxazole. A study in Vietnam showed 80.4% for ampicillin, trimethoprim, and sulfamethoxazole, and 0% for ciprofloxacin, while in Indonesia they were 1.8% for ampicillin and trimethoprim, 0% for ciprofloxacin, and 3.6% for sulfamethoxazole.[31] Studies from 2001 to 2003 in Indonesia showed that 2.5% of *Salmonella* Typhi was resistant to ampicillin, while there was no or very low resistance

against trimethoprim-sulfamethoxazole, ceftriaxone, or ciprofloxacin[13] A hospital-based study from 2006 to 2010 in Indonesia also showed similar results; *Salmonella* Typhi showed no resistance against trimethoprim-sulfamethoxazole, ciprofloxacin, or meropenem, 1.9% against ampicillin, 0.9% against ceftriaxone, and 1.6% against cefotaxime.[32] A study done in Indonesia on the DNA profiles of *Salmonella* Typhi showed clear differences according to regions, but all the *Salmonella* Typhi isolates showed similar phenotypes which were susceptible to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole.[33]

MDR *Salmonella* is an emerging problem which has led to increased mortality, particularly in infants and children below five years of age and those who are malnourished.[34] Nalidixic acid-resistant *Salmonella* Typhi (NARST) over and above MDR *Salmonella* reduces treatment options for enteric fever. Ciprofloxacin was the most effective prophylactic antimicrobial and the drug of choice for traveler's diarrhea until the emergence and high prevalence of resistance in *Salmonella, Shigella,* and *Campylobacter*. Improvements in public sanitation facilities, the rational use of antibacterials, clean drinking water, safe food handling practices, public-health education, and mass immunization in endemic areas are required for the prevention of *Salmonella* infections. Ongoing hospital-based surveillance programs for MDR infections should include *Salmonella*, which can be traced with epidemiological surveillance.[35-38] Capacity-building for regional laboratory services and outbreak preparedness are mandated for enhancing contingency and resilience capital of community-based health systems.[39-41] Typhoidal Salmonella has high epidemic potential amid the emergence of MDR and NARST, and thus forms an important threat in human congregations such as the Kumbh Mela in India, Hajj pilgrimage in Saudi Arabia, and displaced migrant camps.[42-44] The overlapping epidemicity of *Salmonella* Typhi and *Salmonella* Paratyphi A emphasizes a bivalent vaccine covering both as an apparently better choice than a monovalent vaccine in the control strategy of enteric fever.

Conclusion

Typhoid remains an important public health problem in tropical developing countries threatening both residents and travelers. *Salmonella* Typhi remains the predominant serotype followed by *Salmonella* Paratyphi A. The high prevalence of quinolone resistance in *Salmonella* Typhi and *Salmonella* Paratyphi A is a serious problem limiting empirical therapy to non-quinolone-based therapy such as ceftriaxone. Multidrug-resistant *Salmonella* is an emerging problem requiring active surveillance among residents and travelers presenting with tropical fever in hospitals, communities, and mass-gathering scenarios.

Authors' Contributions

All authors contributed equally to this study.

Conflicts of Interest Disclosures

None.

Research Highlights

What Is Already Known?

Typhoid remains a public-health problem in the tropical world, affecting residents and travelers alike. The emergence of multidrug resistance led to outbreaks of typhoidal *Salmonella* resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole in the 1990s. Ceftriaxone is the current drug of choice, because fluoroquinolone resistance limits empirical therapy in both residents and travelers.

What This Study Adds?

1. High degrees of partial and complete resistance to fluoroquinolones are prevalent among typhoidal Salmonella. Resistance to ceftriaxone is emerging.
2. Multidrug-resistant Salmonella is an emerging problem requiring active surveillance among residents and travelers presenting with tropical fever in hospitals, communities, and mass-gathering scenarios

Ethical Approval

Ethical approval was covered by the Institutional Committee (ICMR STS 2017-01590).

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