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# RESEARCH ARTICLE

## ANTIMICROBIAL SUSCEPTIBILITY OF TYPHOID FEVER CAUSED BY SALMONELLA ENTERICA IN INDIA: A ONE-YEAR LABORATORY-BASED STUDY

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**ABSTRACT**

Enteric fever, commonly referred to as Typhoid fever, remains a significant global health concern, particularly in regions like India. This study aimed to comprehensively investigate the occurrence of enteric fever linked to Salmonella enterica and evaluate its susceptibility to crucial therapeutic antimicrobial agents. A laboratory-based cross-sectional approach was employed, analyzing blood culture samples collected at Healthians Labs Gurugram, India, from March 1, 2022, to March 31, 2023. Out of 2,714 samples tested using the Bactec FX 40 system for aerobic blood culture, 145 (5.34%) were positive for typhoidal salmonellae. Predominantly, S. Typhi (99, 68%) was identified, followed by S. Paratyphi A (46, 33%). Notably, both S. Typhi and S. Paratyphi A infections exhibited higher prevalence among males and within the 0-20 years age group. The peak incidence was observed between June and September, with the highest number of cases reported in September. Remarkably, cefotaxime and azithromycin demonstrated the highest sensitivity against S. Typhi, with a 100% efficacy rate, followed by cefepime and chloramphenicol (99%), and ampicillin (97%). For S. Paratyphi A, ampicillin, cefepime, cefotaxime, trimethoprim-sulfamethoxazole, and chloramphenicol all exhibited 100% effectiveness as antibiotics. These findings highlight the persistent public health significance of enteric fever and underscores the importance of continuous surveillance and the adaptation of treatment approaches in the face of evolving antibiotic resistance patterns within Salmonella strains.



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# INTRODUCTION

Enteric fever, also known as Typhoid fever, is a global health concern and is endemic in India. In India, the incidence of culture-confirmed typhoid cases is approximately 377 per 100,000 population, with an approximate case fatality rate of 1%[1].The disease earned its name, Typhoid fever, due to its clinical resemblance to Typhus [2]. It is a systemic illness characterized by fever and abdominal pain, caused by Salmonella enterica subspecies enteric serovar Typhi (S. Typhi), and a closely related but usually milder disease caused by Salmonella enterica subspecies enterica serovar Paratyphi A (S. Paratyphi A). In Europe, S. Paratyphi B is the predominant strain, while S. Paratyphi C is rare and mostly found in the Far East [3] The definitive diagnosis of enteric fever is achieved through the isolation of the organisms from the blood and bone marrow. Although serological tests like the Widal test can be conducted, they are not entirely reliable due to the potential for false-positive results[4]. Initially, ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole (cotrimoxazole) were commonly used as first-line drugs for treating enteric fever. Salmonella enterica serovars Typhi and Paratyphi resistant to these three first-line antibiotics are referred to as multidrug-resistant (MDR) strains[5]. With the rise in MDR strains, fluoroquinolones (such as ofloxacin, nalidixic acid, ciprofloxacin, etc.) became the preferred choice for treating enteric fever. However, a significant increase in fluoroquinolone-resistant strains has been observed since the year 2000 [6]. As a result, third-generation cephalosporins (like cefixime, cefalexin, ceftazidime, etc.) and azithromycin have been more recently employed for the treatment of MDR and fluoroquinolone-resistant Salmonella strains. Nonetheless, sporadic cases of resistance have been noted for ceftriaxone and azithromycin [7,8].

**Objective:** The principal focus of this study is to delve into the prevalence of enteric fever attributed to Salmonella enterica and to determine its susceptibility to commonly used therapeutic antimicrobial agents.

# METHODOLOGY

In this study, we conducted a laboratory-based cross-sectional approach, where we examined blood culture samples tested at the Healthians Labs in Gurugram, India. The study spanned from March 1, 2022, to March 31, 2023, and a total of 2,714 samples were analyzed. The processing of aerobic blood culture bottles was carried out using the Bactec FX 40 system which lasted for 5 days with continuous monitoring. This methodology formed the basis of our investigation, allowing us to assess and gather valuable data during

the specified time frame. When a culture bottle flagged positive, it was removed from the instrument and transferred to a biological safety cabinet. The contents of the bottle were thoroughly mixed by inversion, subsequently, the positive bottles were sub-cultured onto suitable agar plates and gram stain preparation was followed for the examination of colony morphology, identification, and antibiotic susceptibility testing. Serotyping was conducted using slide agglutination tests following the Kauffmann-White scheme, with polyvalent O antisera used for serogrouping. Confirmation of S. Typhimurium, S. Paratyphi A, and S. Typhi was achieved using serovar-specific O2, O4, and O9 antisera. For bacterial identification, and antibiotic susceptibility testing (AST)panels were conducted using the BD Phoenix M50 system and the gram-negative panel N55. The antimicrobial agents tested included ampicillin, cefepime, cefotaxime, chloramphenicol, ciprofloxacin, trimethoprim-sulfamethoxazole, and azithromycin. The minimal inhibitory concentration (MIC) of each antibiotic was determined, and susceptibility was categorized as susceptible, intermediate, or resistant based on the Clinical and Laboratory Standards Institute (CLSI) breakpoints.

# RESULTS

In our study, we made several noteworthy observations. Over the course of the one-year study period, our laboratory received a total of 2,714 blood cultures. Among these, 145 cultures (5.34%) were found to be positive for typhoidal salmonellae. It's worth highlighting that the prevailing serotype identified as S. Typhi, constituting 99 cases (68% of the positive cultures). Following closely, S. Paratyphi A was responsible for 46 cases (32% of the positive cultures), as depicted in Figure 1.1. These findings highlight the prevalence of S. Typhi and S. Paratyphi A in our study population, offering valuable insights into the epidemiology of enteric fever within our region.

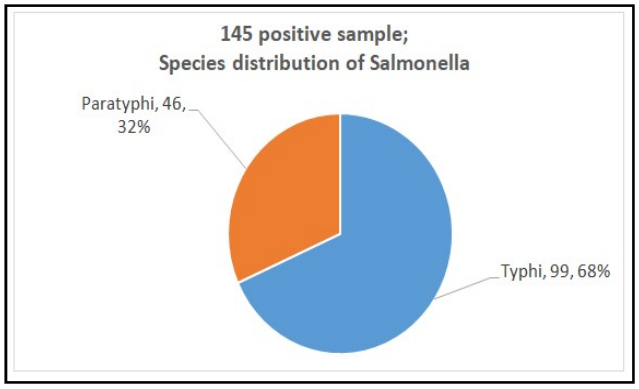


**Figure 1.1.**

The male-to-female ratio for culture-positive S. Typhi cases was 57:42 (57 males to 42 females), and for S. Paratyphi A, it was 5:2 (5 males to 2 females), as demonstrated in Figure 1.2. These ratios indicate the proportion of male-to-female cases in our study and offer insights into the gender distribution of enteric fever.

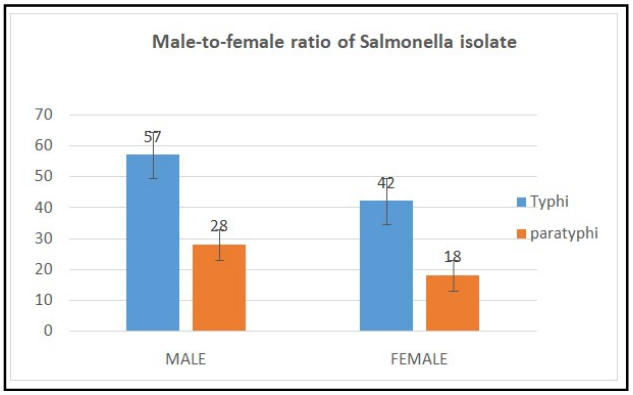


**Figure 1.2**

The highest number of S. Typhi cases were observed within the age group of 0-20 years, totaling 53 cases, while the lowest number of cases, 2 in total, were found in the age group of 61-80 years. Additionally, there were 39 cases in the age group of 21-40 years and 5 cases in the age group of 41-60 years. For S. Paratyphi, the maximum number of cases was found in the age group of 0-20 years, with a total of 28 cases, while the minimum number of cases, also 2 in total, were identified in the age group of 61-80 years. Furthermore, there were 13 cases in the age group of 21-40 years and 3 cases in the age group of 41-60 years, as illustrated in Figure 1.3. These age-specific trends provide valuable insights into the distribution of S. Typhi and S. Paratyphi cases across different age groups in our study.

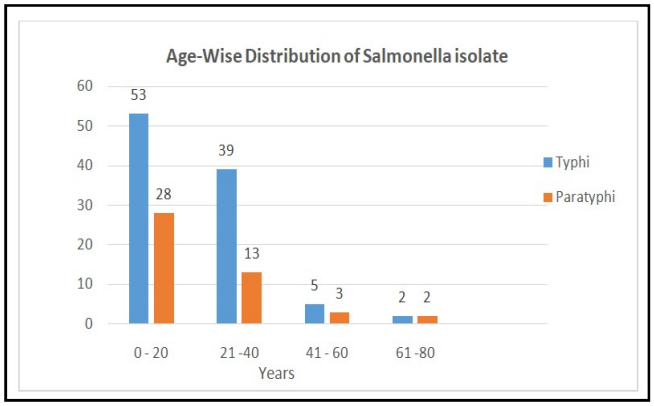


**Figure1.3.**

Typhoid fever cases were recorded in all months of the year, but there was a noticeable peak in cases during September, as illustrated in Figure 1.4. This suggests a seasonal pattern with a higher incidence of typhoid fever cases in September compared to other months. Understanding such seasonal variations can be important for public health planning and disease prevention strategies.

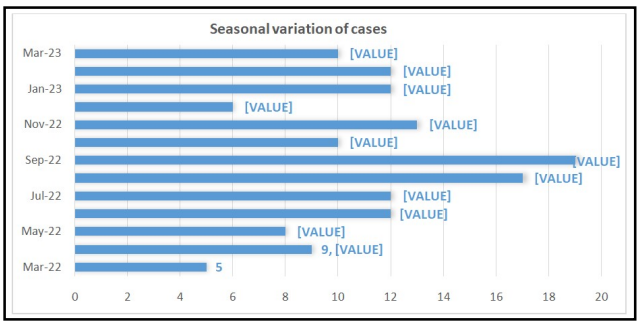


**Figure 1.4**

In our current study, we observed that cefotaxime and azithromycin were the most effective antibiotics against S. Typhi, displaying an impressive sensitivity rate of 100%. Close behind, cefepime and chloramphenicol demonstrated a sensitivity rate of 99%, followed by ampicillin with a sensitivity of 97%, and Trimethoprim-sulfamethoxazole with a sensitivity rate of 94%.

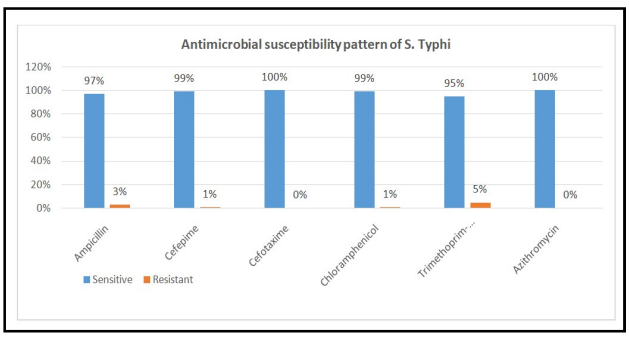


**Figure 1.5**

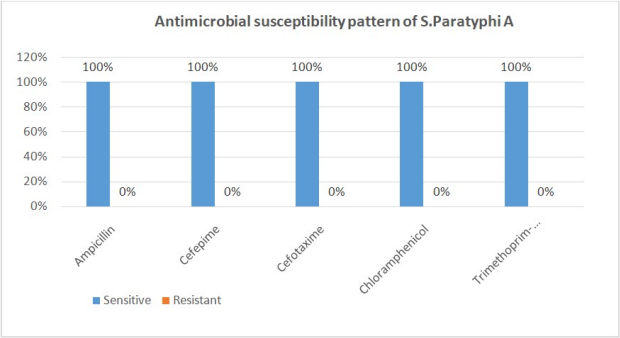


**Figure 1.6**

These findings, graphically represented in Figure 1.5, underscore the suitability of cefotaxime and azithromycin as first-line treatment options for S. Typhi infections in our study population. Ampicillin, cefepime, cefotaxime,trimethoprim-sulfamethoxazole, and chloramphenicol all demonstrated 100% effectiveness against S. Paratyphi A. The antimicrobial susceptibility testing (AST) pattern of S.Paratyphi A is illustrated in Figure 1.6.

# DISCUSSION

During our year-long study, we collected a total of 2,714 blood cultures. Among these, a total of 145 cultures, equivalent to 5.34%, tested positive for typhoidal salmonellae. Notably, the dominant serotype identified as S. Typhi, accounting for 99 cases (68%), followed by S. Paratyphi A with 46 cases (32%). This prevalence of Salmonella Typhi and Salmonella Paratyphi A in our study mirrors findings reported by Dhirendra et al. [4] and Petersiel et al. [9] A relatively low rate of isolation from blood cultures can be attributed to factors such as delays in seeking medical attention for diagnosis, widespread antibiotic use, and the challenges associated with obtaining sufficiently large blood volumes[2] Furthermore, our study revealed that both S. Typhi and S. Paratyphi A cases were more common in males compared to females [10,11] and the highest incidence occurred in the age group of 0-20 years. The peak in cases was observed from June through September, with a notable spike in September [12.13]. These findings align with previous research and emphasize the need for increased awareness, timely diagnosis, and targeted interventions, especially during the peak months, to effectively combat enteric fever caused by Salmonella Typhi and Salmonella Paratyphi A in our region. We have observed that cephalosporins, specifically cefotaxime and cefepime, have demonstrated excellent efficacy against the isolated Salmonella serovars in our study. To prevent clinical failures, third-generation cephalosporins have become the preferred choice for treating multidrug-resistant (MDR) and nalidixic acid-resistant isolates, primarily due to the emergence of decreased ciprofloxacin susceptibility (DCS) phenomenon. While the current incidence of resistance to cephalosporins remains low, at 1%, there is a gradual emergence of sporadic resistance with their increased use [20,21] This underscores the critical role of a specific group of antibiotics as reserve drugs for managing cases of multi-drug resistance (MDR) and ciprofloxacin-resistant infections. Clinicians must exercise extreme caution because the increased use of cephalosporin or azithromycin in treating fluoroquinolone-resistant S. Typhi may lead to the development of cephalosporin resistance or result in azithromycin treatment failures. In the era of multi-drug resistance, combination therapy might be the most effective approach for successfully treating cases of enteric fever. Notably, in the current study, cefotaxime demonstrated the highest sensitivity, exhibiting 100% effectiveness against both S. Typhi and S. Paratyphi A[2].

Third-generation cephalosporins, such as cefotaxime, proved to be highly effective against both S. Typhi and S. Paratyphi A, given their notably high susceptibility rates[4]. Ampicillin also exhibited significant efficacy, with 97% effectiveness against most S. Typhi strains and 100% effectiveness against S. Paratyphi A strains. Amoxicillin,cotrimoxazole, and chloramphenicol had been used previously as the first-line drug against the Salmonella infection. However, resistance to these first-line drugs has been reported (Ochiai et al. 2008)[18]. Chloramphenicol, in particular, was historically considered a gold standard for treating enteric fever since the 1940s. Still, its utility has declined due to the emergence of resistance [Mandal et al., 2004[19]. Interestingly, our study revealed that both Salmonella serovars, S. Typhi and S. Paratyphi A, exhibited high susceptibility to chloramphenicol (S. Typhi - 99%, S. Paratyphi A - 100%). These findings align with another similar study conducted in Nepal [Amatya et al., 2007][14], reinforcing the notion that chloramphenicol can still be effective in treating enteric fever caused by these Salmonella serovars in specific regions. It's essential to consider regional variations in antibiotic susceptibility patterns and carefully evaluate the effectiveness of antibiotics to inform treatment strategies in the face of evolving drug resistance. Additionally, our study demonstrated that S. Typhi displayed a high susceptibility rate of 100% to the antibiotic azithromycin. This finding aligns with previous research, where Kumar et al. found a susceptibility rate of 93.6% for S. Typhi to azithromycin [Kumar et al., 2008][15]. Similarly, another study reported an antibiotic susceptibility rate of 81.25% for S. Typhi to azithromycin [Hasan et al., 2011][16]

Furthermore, there is evidence suggesting that azithromycin may offer advantages in terms of fever clearance and relapse rates for the treatment of enteric fever caused by multidrug-resistant (MDR) and fluoroquinolone-resistant (FQR) Salmonella isolates [Shah, 2009][17]. Therefore, our study underscores the potential of azithromycin as an alternative treatment option for managing MDR and FQR Salmonella isolates. This highlights the importance of considering azithromycin in the context of evolving antibiotic resistance patterns.

# CONCLUSION

Enteric fever presents a significant diagnostic challenge, often resembling symptoms of various other febrile illnesses. While rapid diagnostic methods have advanced, clinical diagnosis should be complemented by blood culture confirmation to ensure accurate identification and treatment of enteric fever cases. We highlight the need for regular in-vitro tests of antimicrobial sensitivity for enteric fever patients to ensure timely and effective treatment. This strategy reduces the misuse of antibiotics and the emergence of drug resistance, which can lower the costs and complications in healthcare settings.We also acknowledge the global spread of antimicrobial susceptibility and resistance profiles, and the emergence of diverse antibiotic resistance patterns among Salmonella strains, which may be related to pathogenic and virulence factors. Constant and careful monitoring of these trends is crucial to improve the treatment of salmonellosis and to address the challenges of antibiotic resistance in advance. In our study, the rate of classical MDR S. Typhi has kept decreasing, the reintroduction of conventional first-line antibiotics could be considered to increase the number of effective antibiotics for typhoid fever treatment.

In conclusion, many challenges persist for the successful control and management of typhoid in endemic countries. This issue would require various measures, such as adequate investments in safe water and sanitation services, community education, control over antimicrobial prescribing and over-the-counter sales, and large-scale vaccination strategies. Two typhoid vaccines are available (Oral Ty21a vaccine& Vi polysaccharide vaccine), both with proven efficacy of 60-80%, and should be taken at least two weeks before travel[22]. continuous AMR surveillance and constant re-evaluation of empiric antimicrobial therapy need to be done to facilitate evidence-based national policy decisions and practice. Moreover, we must recognize the global expansion of antimicrobial susceptibility and resistance profiles, along with the emergence of diverse antibiotic resistance patterns within Salmonella strains, potentially linked to pathogenic and virulence factors. Continuous and vigilant monitoring of these trends is essential to enhance the treatment of salmonellosis and proactively address the challenges posed by antibiotic resistance in the future.

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