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# Antimicrobial Resistance Patterns of Salmonella Typhi Isolates Among Paediatric Patients: A Single-Center Study

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**ABSTRACT**

**Objective:** To determine the pattern of Salmonella Typhi isolates among paediatric patients diagnosed with Enteric fever at a tertiary care hospital in Islamabad, Pakistan.

**Methodology:** This cross-sectional study was conducted in paediatric department. Dr Akbar Niazi Teaching Hospital Islamabad from January 2023-December 2023. Analysis of blood culture and sensitivity data from paediatric patients (2-12 years) diagnosed with enteric fever at a tertiary care hospital in Islamabad, Pakistan, over one-year period. Blood samples were processed using Standard microbiological techniques to confirm Salmonella Typhi and determine antimicrobial susceptibility.

**Results:** A total of 61 Salmonella Typhi isolates from paediatric patients were analysed with high resistance rates to first-line antibiotics, including Ampicillin (83.1%), Chloramphenicol (75.6%), and Co-trimoxazole (56.1%). Alarmingly,32% of isolates exhibited multi-drug resistance (MDR) and 27% showed extensive-drug resistance (XDR). However, Carbapenems (Imipenem and Meropenem) exhibited high efficacy with sensitivity rates of 98.2% and 98.3%, respectively.

**Conclusion:** The increasing prevalence of antibiotic resistant Salmonella Typhi strains in paediatric patients necessitates immediate attention and action. Our study emphasizes the urgent need for rational antibiotic use, enhance disease surveillance and develop effective control and prevention strategies to combat the spread of antibiotic-resistant Enteric fever.

**Keywords:** Antimicrobial resistance, Enteric fever, Typhoid fever, Paediatric typhoid, Salmonella typhi, MDR and XDR typhoid.

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## Introduction

Salmonella enterica serovar Typhi, a Gram-negative pathogen is the primary cause of typhoid fever, contributing significantly to the global disease burden.[1] In 2017, there were over 14 million cases of both typhoid and paratyphoid fever combined, resulting in over 130,000 fatalities, with South Asia accounting for approximately 70% of these cases.[2,3] High income countries have largely conquered enteric fever through sanitation advancements, while low and middle income countries rely heavily on antibiotics for disease management.[4,5] Pakistan reports the highest rate of typhoid fever cases with an estimated 493.5 cases per 100,000 populations per year.[6] The ingestion of a faeces containing food or drink leads to the ingestion of a pathogenic organism, causing enteric fever. Incubation period range from 9.7 to 21.2 days, contingent on the amount of the pathogen. The clinical presentation varies from mild symptoms with low grade fever, malaise, gastrointestinal symptoms and headache to severe complications gastrointestinal bleeding, peritonitis, perforation or CNS involvement.[7] The length of the illness prior to the start of appropriate therapy, the choice

of antimicrobial treatment, age, prior exposure or immunization history, the virulence of the bacterial strain, the amount of inoculum ingested, and the hosts immune status all have an impact on the severity and clinical prognosis.[8] Antimicrobials are the only answer to these organisms and many have been used at different eras. Previously, first-line antimicrobial drugs for the treatment of typhoid included chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole. However, in the 1980s, the first line treatment which included ampicillin, chloramphenicol and trimethoprim were all declared null as multidrug-resistant(MDR) S. Typhi strains infected the concerned patients due to the widespread injudicious use of these agents.[5]

Fluoroquinolones were the next in line, but they were only effective until 1992, and currently, third-generation cephalosporins and macrolides are being used until November 2016, after a large outbreak of S. Typhi rendered them useless in Hyderabad and Karachi, Sindh Pakistan, for XDR strains, which are resistant to these two drugs; the only option left is carbapenems.[9,10]

Salmonellae are considered high-risk pathogens by the WHO due to their increasing resistance to antimicrobials.[11] Our country lacks sufficient data on the prevalence of XDR S. Typhi, with existing reports predominantly coming from Sindh.[12] Because of the illness load and the potential underreporting caused by inadequate facilities for microbiological testing, it is anticipated that the case fatality rate of enteric fever will continue to grow. Patients identified with the XDR strain of enteric fever are gradually presenting their clinical paradigms, which include more complications, a longer clinical course, and higher mortality rates.[13] Children are especially vulnerable to the disease, experiencing more severe symptoms and complications than adults. As antibiotic-resistant strains become more prevalent, the standard therapies used to combat typhoid fever are often ineffective, leading to prolonged illness and increased risk of severe complications. Clinicians will quickly run out of antibiotics and suitable diagnostic tools, making it difficult to treat this condition.[14] There is an urgent need for improved surveillance and better antibiotic stewardship, especially when selecting antibiotics for empirical treatment. Also financial constraints and socioeconomic disparities complicate the treatment of typhoid, especially for XDR cases.[15] In the following study children who have been identified with MDR and XDR have been reported in a tertiary hospital of Islamabad, Pakistan.

# Methodology

This study was reviewed and approved by the Institutional Review Board (IRB approval number: 98/IMDC/IRB-2022) on 7th November, 2022. This was a cross sectional study conducted at the Paediatrics department of Dr. Akbar Niazi Teaching Hospital Islamabad, Pakistan. Written informed consent taken from parents or guardians of participants before blood collection and completion of Questionnaire. This study included children between 2-12 years of age diagnosed with Enteric fever and admitted to the hospital between January 2023-December 2023, with laboratory-confirmed Salmonella Typhi infection. Patients with other co morbidities like Asthma, Pneumonia or other systemic infections as well as those having congenital anomalies were excluded from the study as mentioned in exclusion criteria.

Data from culture sensitivity tests were taken from diagnosed patients having age between 2-12 years of enteric fever over a period of one year in Dr. Akbar Niazi Teaching Hospital Islamabad. Culture sensitivity test were done via collection and culturing of blood samples. 3-5ml of peripheral blood was obtained from each child by an experienced phlebotomist after taking informed consent. All samples were promptly inoculated into tryptic soya broth and incubated at 35°C for 72 hours. Bottles were evaluated daily for visible signs of growth. Those showing growth were then sub-cultured onto MacConkey's agar, chocolate agar and blood agar for further characterization. If the culture showed NLF (Non-lactose fermenter) growth it was then gram stained. Then oxidase test was performed to confirm Salmonella Typhi. At last API (analytic profile index) test was performed to identify the specific stain of S. Typhi.

Antimicrobial susceptibility was evaluated using the Kirby-Bauer disc diffusion technique. A panel of 7 antibiotics was used consisting of ampicillin, ciprofloxacin, ceftriaxone, chloramphenicol, azithromycin, imipenem, meropenem, and trimethoprim-sulfamethoxazole. Isolates that showed resistant to at least three different classes of antimicrobials were classified as MDR *S*. Typhi, while those demonstrating resistance to all with susceptibility limited to two or more antimicrobials were termed XDR *S*. Typhi.

The statistical analysis was performed by using The Statistical Package for the Social Sciences (SPSS) version 27. Pie charts were plotted for each antibiotic and the trends of resistance and sensitivity were recorded.

The results were then cumulated in a single bar chart showing sensitivity patterns of all individual antibiotics.

Sample was also divided on basis of age and gender. Two age group were labelled as A and B having children with between age of 2-9 years in 1 group and 10-16 in another group. Chi-square test was done for both age and gender to get a p-value.

# Results

Out of 100 patients, 46 were male and 54 were female. Regarding individual first line antibiotics as shown in Figure 1, 49 (83.1%) of the isolates were resistant to Ampicillin, 34(75.6%) to Chloramphenicol and 32(56.1%) to Co-trimoxazole. From the second line antibiotics the resistance to Ciprofloxacin came out to be 45(83.3%) and it was 41 (68.3%) to Ceftriaxone. In case of Azithromycin 7.1% of the isolates showed resistance.

Out of the total isolates the percentage of MDR strains were (32%) and XDR strains were (27%).

No resistant isolate was found for Imipenem showing 55(98.2%) of the isolates completely sensitive and 1.8% intermediately sensitive. For Meropenem the sensitive isolates were 59 (98.3%) and 1.7% were intermediately sensitive.

Then difference of antibiotic sensitivity and resistance based on gender and age was analysed using Chi-square test. None of the strains showed any significant difference on the basis of gender or age. All P-values were above 0.05.

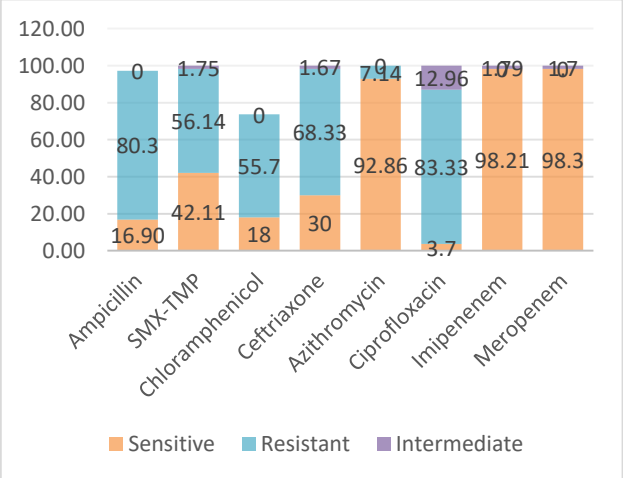


**Figure 1. Sensitivity Pattern of Antibiotics.**

# Discussion

The increase in typhoid cases among children is a public health issue of great concern, especially in low- and middle- income countries where access to clean water and sanitation is limited.[1] Increasing drug resistance in Salmonella Typhi poses serious health risks and complicates treatment options in this delicate group of patients. If left unchecked, antimicrobial resistance related deaths could rise 10-fold by 2025, due to excessive antimicrobial use and lack of new antimicrobials.[16] In a local study that included samples collected from big cities of all four provinces of Pakistan, including the capital, between 2018 and 2019, the resistance of ceftriaxone was found to be 31 (32.29%) and that of ciprofloxacin 95 (99%).[17] This is quite alarming.

This study reports a disturbing trend of increased antibiotic resistance in Salmonella Typhi isolates collected from paediatric patients in Islamabad, Pakistan. The present study reveals high resistance level to the first-line drugs, ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole, consistent with the global increasing trend of multi-drug resistant typhoid. Alarmingly, resistance is also considerable to second- and third-line drugs, such as ciprofloxacin and ceftriaxone, which further confines treatment. However, carbapenems such as imipenem and meropenem are still very effective. These represent a crucial treatment option in the management of infections.

These findings are consistent with other reports in literature of the rise and dissemination of extensively drug-resistant (XDR) typhoid, especially in South Asia. Similar resistance patterns have been documented from Pakistan and other neighbouring countries.[18,19] Emergence of XDR typhoid strains necessitates a shift in empirical treatment strategies where carbapenems play a central role. However, the possibility of carbapenem resistance development still exists, for which antibiotic use should be judicious and infection control measures should be in place.[20] Clinically, it highlights the necessity of accurate diagnosis and the prompt initiation of appropriate therapy.

The fact that resistance rates to conventional antibiotics are so high indicates that carbapenems should be considered first-line treatment in suspected XDR typhoid, especially in children who generally experience more severe disease. In addition, surveillance systems need to be strengthened for monitoring trends of resistance to

guide treatment guidelines. Moreover, improvements in sanitation, good hygiene practices, and vaccination campaigns can control the spread of typhoid.[21,22] A notable breakthrough in typhoid control came in March 2018 when the World Health Organization (WHO) prequalified the Typbar-TCV vaccine, a conjugate vaccine combining Vi polysaccharide and tetanus toxoid.[23] Several areas of research are of utmost importance for the future. The first need is new therapeutics to stem the tide of resistance. This involves new drug classes, alternative therapies such as phage therapy, and how to enhance the host immune response. Rapid diagnostic tests that would identify resistant strains at the point of care are also required. These would assist in decisions regarding treatment and optimal use of antibiotics.[24] The One Health approach, considering the human, animal, and environmental health, will be significant in understanding the multifaceted factors that may play a role in the development and spread of antibiotic-resistant typhoid. These future investments can help usher in control over this deadly public health threat, assuring the protection of health in the vulnerable population.[25] This study had some methodological limitations. The sample size was small and confined to a single tertiary care hospital in Islamabad, thereby limiting the generalizability of our findings. We did not investigate the genetic mechanisms responsible for antibiotic resistance, which may help explain mechanisms of resistance transmission and evolution. Future studies should focus on larger, multi-centre studies incorporating molecular analysis to better understand the dynamics of resistance development.

# Conclusion

This study highlights the alarming rise of antibiotic-resistant Salmonella Typhi infections among children. Our study demonstrates high level of resistance to first-line antibiotics, including ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, as well as significant resistance to second-and third-line drugs such as ciprofloxacin and ceftriaxone. However, the possibility of carbapenem resistance development necessitates judicious antibiotic use and stringent infectious control measures to combat the spread of antibiotic-resistant typhoid fever. Our findings underscore the need for a multi-faceted approach, including enhanced surveillance, improved diagnostics, and new therapeutics to protect vulnerable population.

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