Volume 3, Issue 7, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

FREQUENCY AND OUTCOME OF EXTENSIVELY DRUG RESISTANCE (XDR) ENTERIC FEVER ADMITTED IN CITY HOSPITAL KHAIRPUR MIRS

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DOI: https://doi.org/10.5281/zenodo.17052777

Keywords:
XDR Typhoid, Salmonella Typhi, antibiotic resistance, children, Pakistan

Article History
Received: 13 June 2025
Accepted: 23 August 2025
Published: 04 September 2025

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Abstract

Background: *Extensively Drug-Resistant (XDR) Typhoid fever, caused by* Salmonella Typhi, *has emerged as a major public health threat in Pakistan since 2016. With limited treatment options and increasing resistance to frontline antibiotics, XDR Typhoid poses significant challenges, particularly in children.*

Objective: *To determine the frequency and outcome of XDR enteric fever in children admitted to the Department of Pediatrics, KMC Hospital Khairpur Mirs.*

Methods: *A cross-sectional study was conducted over six months in 116 children (aged 2–10 years) admitted with enteric fever not responding to antibiotics. Diagnosis was confirmed by blood culture. Demographic, clinical, and laboratory data were collected. Antimicrobial susceptibility was tested against standard antibiotics. Data were analyzed in SPSS v25 using descriptive and chi-square tests;* $p<0.05$ *was considered significant.*

Results: *Among 116 children, 68 (58.6%) were male and 48 (41.4%) female, with mean age 6.4±2.1 years. Out of 116 blood cultures, 92 (79.3%) yielded growth of* S. Typhi, *while 24 (20.7%) showed no growth. Of these 92 isolates, 65 (70.7%) were classified as XDR and 27 (29.3%) as MDR. Resistance pattern showed universal resistance to ampicillin, co-trimoxazole, chloramphenicol, fluoroquinolones, and third-generation cephalosporins. All XDR isolates remained sensitive to carbapenems (100%) and azithromycin (92.3%), while 7.7% demonstrated azithromycin resistance. Clinical recovery with azithromycin monotherapy was seen in 54/65 (83.1%) of XDR cases, while 11 (16.9%) required escalation to meropenem/tigecycline. No mortality was recorded; complications occurred in 9 (13.8%) children, including hepatitis, intestinal perforation, and sepsis.*

Conclusion: *XDR enteric fever was found in more than two-thirds of culture-*

Volume 3, Issue 7, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

positive cases. While azithromycin remains largely effective, emerging resistance is alarming. Strengthening antimicrobial stewardship, improving water sanitation, and expanding TCV immunization are critical to controlling XDR Typhoid.

INTRODUCTION

Typhoid is a bacterial infection caused by *Salmonella Typhi* (S. Typhi), which exists as a gram-negative, rod-shaped, flagellum containing a polysaccharide capsule that provides virulence to the bacteria by protecting it from phagocytosis. Humans are the only source of this bacterium; if left untreated can cause life-threatening complications. It is usually transmitted via the oral-fecal route and predominantly presents as high fever, nausea, abdominal pain, and abnormal bowel movements.[1]

The world witnessed its first case of Extensively Drug-Resistant—Typhoid Fever (XDR-TF) in late 2016 when Pakistan's second most populated province—Sindh—reported a huge influx of blood-culture confirmed Typhoid Fever (TF) cases that were refractory to standard therapy.[2] Since then, according to the Weekly Field Epidemiological Report by the National Institute of Health (NIH) Islamabad, a total of 14,360 XDR-TF has been reported in Karachi from January 2017 till June 2021, and from November 2016 to June 2021 a total of 5,741 confirmed cases of XDR-TF were reported in all districts of Sindh province (excluding Karachi), while 69.5% cases were reported from District Hyderabad.[3] In 2019, Pakistan became the first country in the world to introduce the World Health Organization (WHO)-recommended typhoid conjugate vaccine (TCV) into its routine immunization program.[2]

Globally, around 21 million people are affected by this bacterium, with almost 161,000 deaths reported each year. While the introduction of antibiotics has limited the prevalence of typhoid fever, to our dismay, the causative agent has developed resistance to multiple drugs over the years via different mechanisms.[3] This has given birth to newer and more powerful strains, such as Multi-Drug Resistant (MDR)-Typhoid: resistant to three antibiotics; ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol, and XDR-Typhoid: resistant to five antibiotics; chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones, and third-generation cephalosporins.[4] Only three antimicrobial drugs, namely: azithromycin (oral), carbapenems, and tigecycline (parenteral) are effective against the XDR strains. This, in addition to restricting treatment options for physicians, also poses an increased threat to patients who might develop a severe life-threatening illness.[5]

According to the Pakistan National Institute of Health, Karachi witnessed 52 new cases of XDR-Typhoid fever in the week preceding August 14, bringing the total cases reported between January 01, 2017, and Aug 14, 2021, to 15,224.[6] ,[7] One common reason implicated to be involved in the spread of typhoid in these regions is the use of contaminated water for drinking and irrigation.[8] A study conducted by M.K. Daud et al. showed that water samples acquired from Karachi—the economic hub of Pakistan—had evidence of microbial contaminants.[9]

Recent studies, however, have shown that the XDR typhoid is now growing more insusceptible to the use of azithromycin.[10] According to a recent research, 57 cases of blood culture-proven patients of *Salmonella typhi* at CMH Lahore, Punjab were reported during January 2019 to August 2020, out of which only 10 cases were nonresistant, seven were confirmed as Multi-Drug-Resistant (MDR) and worryingly, 39 among these cases were Extensively Drug-Resistant (XDR). An even bigger matter of concern was that the *S. typhi* isolated from one of these cases was also resistant to azithromycin along with other first-line drugs.[11,12]

In a study, Out of 394 samples received for blood culture, 99 (25.12%) were gram-positive, 158 (40.10%) were gram-negative and 137 (34.7%) showed no growth. In 158 gram-negative samples, 92 (58.22%) were of *Salmonella typhi*, consisting of 40 (43.47%) cases of children aged 0-10 years. MDR and XDR *Salmonella typhi* isolates were 25 (27.2%) and 8 (8.7%) respectively, showing a male preponderance of 20 (60.60%). Both the MDR and XDR strains were sensitive to Meropenem and

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Azithromycin. Extended Spectrum β-Lactamase production was confirmed by combined disc test in all the XDR cases.[13]

RATIONALE OF STUDY:

The rationale of study is to find out the frequency and evaluate the outcome of XDR enteric fever so that the rational use of antibiotics be done. This study will help find out the frequency of enteric fever so that it may be dealt with early.

OBJECTIVE OF STUDY:-

To find out the frequency and outcome of extensively drug resistant (XDR) enteric fever admitted in City Hospital Khairpur Mirs.

OPERATIONAL DEFINITIONS

Enteric Fever: It is a prospectively, multisystemic illness caused by *Salmonella typhi* and *Salmonella paratyphi*. Enteric fever is a cumulative term that illustrates both typhoid and paratyphoid fever.

XDR: It is defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two antimicrobial categories).

MDR:

It is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.

MATERIAL AND Methods

Study Design:

Cross-sectional study

Duration:

6 months after synopsis approval

Results

Setting:

Department of Pediatrics, KMC Hospital Khairpur Mirs

Sample Size: 116 children (calculated at 8% prevalence, 95% CI, 5% margin of error)

Inclusion:

Children 2–10 years with enteric fever not responding to antibiotics

Exclusion:

>10 years, DR-TB patients, extra-pulmonary TB

Procedure:

Blood cultures, sensitivity testing, demographic and clinical data recorded

Analysis:

SPSS v25; Chi-square test used for associations

Data will be analyzed using SPSS version 25.0.0.0. Qualitative Data (frequencies and percentages) will be presented as n (%). Numerical data will be presented as Mean ± standard deviation. Confounder will be controlled by stratification of age, gender and educational status so the effect of these could be assessed on outcome by using chi square test. All the data will be calculated on 95% confidence interval. A p-value < 0.05 will be considered as statistically significant level.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study will be done after approval of Ethical Committee of KMC Khairpur Mirs. Then, the written consent will be obtained from each of the respondents and documented by the data collectors in the space provided within the participant information sheet.

Table 1. Demographic Characteristics (n=116)

Variable	Frequency (%)
Male	68 (58.6%)
Female	48 (41.4%)
Mean age	6.4 ± 2.1 years

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ISSN: (e) 3007-1607 (p) 3007-1593

Table 2. Blood Culture Results

Result	Frequency (%)
Growth of *S. Typhi*	92 (79.3%)
No growth	24 (20.7%)

Table 3. Distribution of MDR and XDR Typhoid Cases (n=92)

Type	Frequency (%)
MDR (*resistant to 3 antibiotics*)	27 (29.3%)
XDR (*resistant to 5 antibiotics*)	65 (70.7%)

Table 4. Antibiotic Sensitivity Pattern in XDR Typhoid (n=65)

Antibiotic	Sensitive	Resistant
Ampicillin	0%	100%
Co-trimoxazole	0%	100%
Chloramphenicol	0%	100%
Fluoroquinolones	0%	100%
3rd gen Cephalosporins	0%	100%
Azithromycin	92.3%	7.7%
Carbapenems (Meropenem)	100%	0%
Tigecycline	100%	0%

Table 5. Clinical Outcomes of XDR Typhoid (n=65)

Outcome	Frequency (%)
Recovery with Azithromycin	54 (83.1%)
Required Meropenem/Tigecycline	11 (16.9%)
Complications (hepatitis, perforation, sepsis)	9 (13.8%)
Mortality	0 (0%)

Discussion

Our study demonstrated that **70.7% of culture-positive enteric fever cases were XDR**, consistent with previous reports from Sindh and Punjab where resistance rates between 65–80% have been documented. The higher proportion in males (58.6%) aligns with regional studies, possibly reflecting greater exposure to contaminated outdoor environments.

The resistance pattern confirmed the **classic XDR phenotype** — universal resistance to ampicillin, chloramphenicol, co-trimoxazole, fluoroquinolones, and third-generation cephalosporins. Importantly, **7.7% of isolates showed azithromycin resistance**, echoing emerging concerns reported from Lahore and Karachi. If unchecked, this trend could leave carbapenems and tigecycline as the only therapeutic options, which are costly and impractical for community use.

Outcomes in our study were favorable, with **83% recovery on azithromycin alone** and no mortality,

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ISSN: (e) 3007-1607 (p) 3007-1593

reflecting early detection and inpatient management. However, **13.8% developed complications**, underscoring the burden of prolonged illness.

Our findings reinforce the urgent need for:

Strict antibiotic stewardship to preserve azithromycin efficacy

Expanded TCV coverage to prevent new infections

Safe water and sanitation measures to reduce transmission

Conclusion

XDR Typhoid constituted a major proportion (70.7%) of enteric fever cases in hospitalized children. While azithromycin remains the cornerstone of therapy, the detection of resistant strains is alarming. Immediate public health measures, vaccination, and rational antibiotic use are vital to prevent a post-antibiotic era of untreatable typhoid.

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