ORIGINAL ARTICLE

Extensively drug-resistant *Salmonella typhi* in febrile patients at a tertiary care hospital of South Punjab, Bahawalpur Pakistan

Muhammad Waseem Abbas, Sadiq Hussain, Afshan Zareen

Quaid-e-Azam Medical College Bahawalpur Pakistan

ABSTRACT

Background: Typhoid fever, caused by *Salmonella enterica serovar typhi* (*S. typhi*), persists as a significant public health challenge in low- and middle-income countries. This study aimed to assess the prevalence and antimicrobial resistance patterns of multidrug resistant (MDR), and extensively drug resistant (XDR) *Salmonella typhi (S. typhi)* among febrile patients.

Material and Methods: This cross-sectional study was carried out in the Department of Pathology, Bahawal Victoria Hospital, Bahawalpur, from January to October 2024. Febrile patients with suspected typhoid fever undergoing blood culture were included, while those with recent antibiotic use, alternative diagnoses, or incomplete records were excluded. Using consecutive sampling, 1,364 patients were enrolled. Demographic, clinical, exposure, water source, and vaccination data were recorded, and blood cultures with susceptibility testing were performed according to standard protocols.

Results: Of 1364 patients, 808 (59.2%) were male, and 556 (40.8%) females, while the median age was 15.0 (6.0-38.0) years. Recent travel to endemic areas was reported in 93 (6.8%), and household contact in 29 (2.1%) patients. Blood culture-confirmed *S. typhi* was found in 34 (2.5%) cases, peaking in August (29.4%). Among these 34-culture positive *Salmonella typhi* cases, 10 (29.4%) were non-MDR/non-XDR, 3 (8.8%) MDR, and remaining 21 (61.7%) were XDR, while none of the cases were sensitive to all the tested antibiotics. All isolates, including those classified as XDR, were sensitive to meropenem.

Conclusion: This study highlights an ongoing and evolving challenge posed by XDR *S. typhi* in febrile patients in South Punjab, Pakistan.

Keywords: Blood culture, Fever, Pakistan, Pathology, *Salmonella typhi*

BACKGROUND

Typhoid fever, caused by *Salmonella enterica serovar Typhi* (*S. typhi*), persists as a significant public health challenge in low- and middle-income countries, particularly in regions where safe water supply and adequate sanitation are lacking.[1,2] According to the World Health Organization (WHO), the global burden of typhoid fever is substantial, with an estimated 11 to 21 million cases and 128,000 to 161,000 deaths reported each year.[3] Typhoid fever is disproportionately concentrated in South Asia, sub-Saharan Africa, and Southeast Asia, where environmental and infrastructural barriers facilitate the continued transmission of *S. Typhi*.[4,5]

In recent years, extensively drug-resistant (XDR) strains of *S. typhi* have emerged as a particularly alarming threat, exhibiting resistance to first-line antibiotics.[6] The underlying mechanisms to XDR are driven largely by the horizontal transfer of resistance genes, often via plasmids, enabling rapid dissemination of resistance across bacterial populations.[7] Pakistan is among the countries with the highest incidence of typhoid fever globally, recording a reported rate of 493.5 cases per 100,000 population in 2018.[8,9] Locally, since the first documented outbreak of XDR *S. typhi* in Hyderabad in 2016, the number of reported cases has surged dramatically, with more than 15,000 XDR infections recorded nationwide by 2022.[10] Multiple factors contribute to the emergence and spread of resistant *S. typhi* in Pakistan, including poor hygiene, insufficient sanitation infrastructure, unsafe water source, and widespread misuse or over-the-counter availability of

Correspondence: Dr. Muhammad Waseem Abbas, Department of Pathology, Quaid-e-Azam Medical College Bahawalpur, Pakistan

Email: waseem17879@gmail.com

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antibiotics.[11] Given the scale of the challenge, there is an urgent need to generate region-specific evidence on the epidemiology, resistance profiles, and risk factors associated with MDR and XDR *S. typhi* in febrile populations. The present study is designed to address this knowledge gap by assessing the prevalence, antimicrobial resistance patterns, and associated risk factors of MDR and XDR *S. typhi* among febrile patients.

MATERIAL AND METHODS:

This cross-sectional study was conducted at the department of pathology, Bahawal Victoria Hospital, Bahawalpur, Pakistan, during January 2024 to October 2024. The study population comprised all febrile patients, irrespective of age or gender, who presented to the outpatient clinics with clinical suspicion of typhoid fever and subsequently underwent blood culture testing. Patients were eligible for inclusion if they presented with fever, defined as an axillary temperature of ≥38°C (100.4°F), and provided a blood sample for culture during their initial clinical evaluation. Patients were excluded if they had received systemic antibiotic therapy within 72 hours prior to blood sample collection, if they had a documented alternative diagnosis for fever, or if their clinical records were incomplete or missing critical information. Sample size calculation was conducted using online OpenEpi sample size calculator with anticipated proportion of blood culture proven salmonella typhi was considered as 2.0%,[12] with 95% confidence level, and 1% margin of error. The sample size turned out to be 753. The study involved 1364 febrile patients who fulfilled eligibility criteria, ensuring adequate statistical power with high precision. Non-probability, consecutive sampling technique was involved. The study protocol was reviewed and approved by the Institutional Review Board (2349/DME/QAMC Bahawalpur, dated: 09-12-2023). Written informed consent was obtained from all participants or from parents/guardians in the case of minors prior to enrollment and sample collection.

Demographic and clinical data were collected by trained research personnel. Variables recorded included age, gender, area of residence (rural or urban), primary source of drinking water (ground water, municipal supply, or filtered water), typhoid vaccination status (not vaccinated, single routine dose, or unknown), recent travel history to typhoid-endemic areas within the preceding 28 days, and household contact with a laboratory-confirmed case of typhoid or paratyphoid fever in the past 28 days. Blood specimens (5–10 mL for adults, 2–5 mL for children) were collected under aseptic conditions and immediately inoculated into BACTEC or similar automated blood culture systems according to standard hospital protocols. Positive cultures were sub-cultured, and *Salmonella typhi* was identified by standard biochemical tests and serological confirmation using specific antisera. Antimicrobial susceptibility testing of confirmed *S. typhi* isolates was performed using the Kirby-Bauer disk diffusion method in line with Clinical and Laboratory Standards Institute (CLSI) guidelines. Antibiotics tested included common antimicrobials, while MDR *S. typhi* was defined as resistance to all three first-line antibiotics (ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole). XDR *S. typhi* was defined as additional resistance to fluoroquinolones and third-generation cephalosporins. Non-MDR/non-XDR isolates were those that remained sensitive to at least one of the three 1st-line antibiotics and/or did not exhibit combined resistance to both fluoroquinolones and third-generation cephalosporins. A special format was designed to record all relevant study data.

Data entered, and analyzed using IBM Statistical Package for Social Sciences, version 26.0. Age (years) was summarized (non-normal distribution) as median with interquartile range (IQR) (normality checked using the Shapiro–Wilk test). Categorical variables including gender, area of residence, primary drinking water source, typhoid vaccination status, recent travel to endemic area, household contact with confirmed typhoid, and antimicrobial resistance pattern of isolates, were presented as frequencies and percentages, and compared between blood culture–positive and culture–negative patients using the Chi-square test or Fisher's exact test.

A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

In a total of 1,364 patients, 808 (59.2%) were male, and 556 (40.8%) female. The median age was 15.0 (6.0-38.0) years, while 742 (54.5%) patients were aged between 1–18 years, 517 (37.9%) as 19–60 years, and 105 (7.7%) aged over 60 years. There were 932 (68.3%) patients who resided in rural areas. Ground water was

the primary source of drinking water for 974 (71.4%) patients. Regarding typhoid vaccination status, 721 (52.9%) reported not being vaccinated. A history of recent travel to typhoid-endemic areas within the preceding 28 days was reported by 93 (6.8%) patients, while household contact with a confirmed case of typhoid or paratyphoid fever in the prior 28 days was present in 29 (2.1%) patients.

In a total of 1364 patients during the study period, 34 (2.5%) were found to have blood culture-confirmed *Salmonella typhi* infection. Analysis of the monthly distribution of positive cases revealed a marked seasonal trend (Table-I), with the highest number of *S. typhi* isolations occurring in August (10/34, 29.4%) and October (6/34, 17.6%). Smaller peaks were observed in March and June (5/34, 14.7% each), while February and July recorded the lowest (0% and 2.9%, respectively).

There was no statistically significant differences in age distribution of culture positive *Salmonella typhi* cases compared with culture-negative patients (p=0.081). Gender distribution showed that male gender comprised of 21 (61.8%) culture-confirmed cases, in comparison to 787 (59.2%), without any significant differences (p=0.761). Area of residence did not vary significantly among patients with and without *S. typhi* infection (rural, 61.8% vs 68.5%, p=0.405). The pattern of drinking water source among culture positive and negative cases did not reflect any significant variations (p=0.381). A significant association was observed between recent travel to typhoid-endemic areas and the development of culture-confirmed typhoid fever as among culture positive cases, 6 (17.6%) had traveled to endemic regions within 28 days prior to illness onset compared to 87 (6.5%) of culture-negative patients (p=0.011). Table-II is showing details about demographic and clinical characteristics of febrile patients according to blood culture results for *Salmonella typhi.*

Among these 34-culture positive *Salmonella typhi* cases, 10 (29.4%) were non-MDR/non-XDR, 3 (8.8%) MDR, and remaining 21 (61.7%) were XDR, while none of the cases were sensitive to all the tested antibiotics. Gender (p=0.978), and age (p=0.163) distribution were statistically similar among resistance groups. Area of residence was not found to have any significant association with *S. typhi* resistance patterns (p=0.978). The primary water source was ground water for 80.0% of non-MDR/non-XDR, 33.3% of MDR, and 61.9% of XDR cases (p=0.303). Among XDR cases, none reported receiving typhoid vaccination but the difference in vaccination status across resistance groups was not statistically significant (p=0.357). Recent travel to typhoid-endemic areas within the preceding 28 days was most common among MDR cases (66.7%), compared to 19.0% in XDR, and 0% in non-MDR/non-XDR groups, and the difference turned out to be statistically significant (p=0.028) (Table-III).

Antibiotic resistance patterns revealed high rates of resistance to traditional 1st-line agents among both MDR and XDR isolates. Overall resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole was found in 81.8%, 97.0%, and 81.8% of isolates, respectively. Resistance to ciprofloxacin and fluoroquinolones was observed in 72.9% and 63.6%, respectively. High resistance was also observed for third-generation cephalosporins, with 81.8% of isolates resistant to both cefixime and ceftriaxone. All isolates, including those classified as XDR, were sensitive to meropenem.

Table-I: Monthly distribution of blood culture-confirmed *Salmonella typhi* cases during the study period (n=34).

Months*	Number (%)
January	1 (2.9%)
February	-
March	5 (14.7%)
April	-
May	4 (11.8%)
June	5 (14.7%)
July	1 (2.9%)
August	10 (29.4%)
September	2 (5.9%)
October	6 (17.6%)

*Year 2024

Table-II: Demographic and clinical characteristics of febrile patients according to blood culture results for Salmonella typhi (N=1364).

Characteristics		Total (%)	Blood culture for salmonella typhi		P-value
			Yes (n=34)	No (n=1330)	
Gender	Male	808 (59.2%)	21 (61.8%)	787 (59.2%)	0.761
	Female	556 (40.8%)	13 (38.2%)	543 (40.8%)	
Age groups (years)	1-18	742 (54.4%)	24 (70.6%)	718 (54.0%)	0.081
	19 to 60	517 (37.9%)	10 (29.4%)	507 (38.1%)	
	>60	105 (7.7%)	-	105 (7.9%)	
Residence	Rural	932 (68.3%)	21 (61.8%)	911 (68.5%)	0.405
	Urban	432 (31.7%)	13 (38.2%)	419 (31.5%)	
Water source	Ground water	974 (71.4%)	22 (64.7%)	952 (71.6%)	0.381
	Municipality / water filters	390 (28.6%)	12 (35.3%)	378 (28.4%)	
Typhoid vaccination status	Not vaccinated	721 (52.9%)	13 (38.2%)	708 (53.2%)	0.179
	Routine 1 dose	10 (0.7%)	-	10 (0.8%)	
	Unknown	633 (46.4%)	21 (61.8%)	612 (46.0%)	
Travels history to endemic areas within last 28 days before illness onset		93 (6.8%)	6 (17.6%)	87 (6.5%)	0.011
Household contact with a confirmed case of typhoid or paratyphoid fever in the past 28 days before illness onset		29 (2.1%)	1 (2.9%)	28 (2.1%)	0.739

Table-III: Demographic and clinical characteristics of patients with multidrug-resistant, and extensively drug-resistant *Salmonella typhi* infections (N=33).

Characteristics		Total (%)	Non-MDR / Non-XDR (n=10)	MDR (n=3)	XDR (n=21)	P-value
Gender	Male	13 (38.2%)	4 (40.0%)	1 (33.3%)	8 (38.1%)	0.978
	Female	21 (61.8%)	6 (60.0%)	2 (66.7%)	13 (61.9%)	
Age groups (years)	1-18	24 (70.6%)	6 (60.0%)	1 (33.3%)	17 (81.0%)	0.163
	19- 60	10 (29.4%)	4 (40.0%)	2 (66.7%)	4 (19.0%)	
Residence	Rural	21 (61.8%)	6 (60.0%)	2 (66.7%)	13 (61.9%)	0.978
	Urban	13 (38.2%)	4 (40.0%)	1 (33.3%)	8 (38.1%)	
Water source	Ground water	22 (64.7%)	8 (80.0%)	1 (33.3%)	13 (61.9%)	0.303
	Municipality / water filters	12 (35.3%)	2 (20.0%)	2 (66.7%)	8 (38.1%)	
Typhoid vaccination status	Not vaccinated	13 (28.2%)	4 (40.0%)	-	9 (42.9%)	0.357
	Unknown	21 (61.8%)	6 (60.0%)	3 (100%)	12 (57.1%)	
Travels history to endemic areas within last 28 days before illness onset		6 (17.6%)	-	2 (66.7%)	4 (19.0%)	0.028
Household contact with a confirmed case of typhoid or paratyphoid fever in the past 28 days before illness onset		1 (2.9%)		-	1 (4.8%)	0.727

DISCUSSION

This study revealed the prevalence of blood culture-confirmed *Salmonella typhi* among febrile patients as 2.5%, with an overwhelming predominance of XDR (61.7%) strains. The low culture-confirmed prevalence among febrile patients aligns with the retrospective review at Aga Khan University Hospital, Karachi, which reported a positivity rate of 2% among blood cultures in suspected enteric fever cases.[12] Study by Qamar et al.,[13] and Rasheed et al,[14] observed relatively higher culture positivity rates of 5%, and 11.3%, within broader catchment areas and over longer study periods. The presence of XDR *S. typhi* in 61.7% of cases raises critical concerns for clinical management. Local data reported XDR rates as high as 57%, with certain outbreaks in Sindh and Punjab surpassing 70%.[13-15]

The majority of typhoid cases occurred in males (61.8%), and in children as well as adolescents age groups (cumulatively 70.6%). These demographic trends are consistent with reports from Khalil et al.,[16] in Peshawar, and Qamar et al.,[13] documented a male predominance, and a high proportion of pediatric cases. Zakir et al.,[17] and Memon et al.,[18] have described the heightened vulnerability of younger age groups to XDR and MDR *S. typhi*. The lack of statistically significant gender, and age differences in resistance patterns, as

observed in the present study, aligns with the findings of Zakir et al, and Irfan et al.[17,19] This finding is echoed in reports from Karachi by Memon et al.,[18] and from Hyderabad by Baloch et al.,[20] where water safety remains a critical driver of transmission.

Vaccination rates in this study were low, with only 0.7% reporting receipt of a routine typhoid vaccine and the majority either unvaccinated or with unknown status. This deficit is consistent with observations by Memon et al.,[18] where none of the XDR cases were vaccinated. The clinical implications of poor vaccine coverage are profound, as multiple studies have shown that unvaccinated children face significantly higher risks of infection with drug-resistant strains.[21] The data support recent endorsements to intensify immunization campaigns and to make conjugate typhoid vaccines widely available, particularly in high-burden provinces.[22]

A key risk factor identified in this study was recent travel to typhoid-endemic areas, which was significantly associated with culture-positive disease. This association is also reflected in Zaman et al.,[23] and Memon et al.,[18] where travel to slum areas and higher risk areas of infection were significantly associated with *S. typhi* infection. The contribution of intra- and inter-city travel to the spread of resistant strains is becoming increasingly evident in Pakistan's urbanizing landscape, supporting recommendations for targeted health education and surveillance in populations with recent migration or travel history.[18,23]

Seasonal trends in *S. typhi* isolation were observed, with peaks in August and October, and additional minor peaks in March and June. This pattern resembles data from Khalil et al.,[16] in Peshawar and Imran et al.,[15] in Islamabad, which also reported surges in the summer and monsoon months. Increased transmission during these periods is attributed to higher temperatures, rainfall, and resulting water contamination. Recent findings raise serious concerns about the continued reliability of azithromycin as one of the few remaining oral treatment options and echo calls from Irfan et al.,[19] and Khan et al.,[24] for judicious use and monitoring of macrolides. The persistence of 100% susceptibility to meropenem is reassuring but underlines the need to restrict carbapenem use to severe, culture-proven cases to avoid the rapid emergence of further resistance.[25]

Regarding limitations of this study, the reliance on blood culture, which has suboptimal sensitivity in typhoid fever, may have underestimated the true burden of disease. The study's focus on a tertiary care center may limit generalizability, as referral bias could inflate the proportion of resistant isolates. Genomic analysis of resistance mechanisms was not performed, which limits the ability to track specific transmission clusters or emerging resistance genes.

CONCLUSION

This study highlights an ongoing and evolving challenge posed by XDR *Salmonella typhi* in febrile patients in South Punjab, Pakistan. This study further affirms the urgent need for strengthened antimicrobial stewardship, targeted vaccination, and major investments in water and sanitation.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Muhammad Waseem Abbas: Substantial contributions to study design, acquisition of data, Manuscript drafting or reviewing it critical for important intellectual content, final approval, accountable for all aspects of publication.

Sadiq Hussain: Data Collection and interpretation, critical review, final approval, accountable for all aspects of publication.

Afshan Zareen: Data collection and interpretation, critical review, final approval, accountable for all aspects of publication.

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