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INCIDENCE OF SALMONELLA INFECTION IN PAEDIATRIC POPULATION IN SHAUKAT KHANUM MEMORIAL CANCER HOSPITAL AND RESEARCH CENTER, PAKISTAN

Original Research

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ABSTRACT

Background: Despite the introduction of antibiotics significantly reducing the mortality associated with Salmonella Typhi infections, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has created a critical public health challenge, particularly in endemic regions like Pakistan. The increasing resistance limits treatment options, complicates disease management, and underscores the need for continuous surveillance, especially among vulnerable pediatric populations including those with underlying malignancies.

Objective: This study aimed to assess the prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Salmonella Typhi infections among pediatric cancer and non-cancer patients treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan.

Methods: A retrospective multicenter study was conducted over a one-year period from June 30, 2023, to May 31, 2024. Blood cultures were processed using the Bact/Alert system, and isolates were confirmed as Salmonella Typhi or Salmonella Paratyphi. Antimicrobial susceptibility testing was performed via the Kirby-Bauer disk diffusion method against ampicillin, chloramphenicol, co-trimoxazole, cefixime, ceftriaxone, azithromycin, imipenem, meropenem, and ciprofloxacin, following Clinical Laboratory Standards Institute (CLSI) 2020 guidelines. MDR was defined as resistance to ampicillin, chloramphenicol, and co-trimoxazole, whereas XDR included MDR with additional resistance to fluoroquinolones and third-generation cephalosporins.

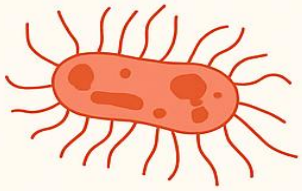
Results: Out of 3,146 positive blood cultures, 864 isolates (27.5%) were confirmed as Salmonella species. Among these, 60 cases (7%) involved pediatric cancer patients, and 804 (93%) were post-chemotherapy or non-cancer patients. Resistance profiling revealed 61 isolates (7.1%) as MDR, 409 isolates (47.3%) as XDR, and 394 isolates (45.6%) as non-MDR/XDR. Fluoroquinolone resistance was observed in 88% of isolates, while minimal resistance was noted against azithromycin, imipenem, and meropenem.

Conclusion: This study highlights a concerning prevalence of MDR and XDR Salmonella Typhi among pediatric patients, particularly emphasizing the pressing need for strengthened antibiotic stewardship, vigilant surveillance, and proactive vaccination strategies to mitigate the spread of drug-resistant strains.

Keywords: Antibiotics, Cancer, Enteric Fever, MDR, Pediatric, Salmonella Typhi, XDR.

Prevalence of MDR and XDR *Salmonella* in Pediatric Patients

INTRODUCTION



Multidrug-resistant (**MDR**) and extensively drug-resistant (**XDR**) ***Salmonelia Typhi*** Infections are rising in Pakistan

METHODS

One-year retrospective study

- Pediatric patients (≤ 18 years)
- Blood cultures with antimicrobial susceptibility testing

RESULTS

3,146
positive blood cultures

7,1% MDR

47,3% XDR

Male
Nise

37,4%
Female

Susceptibilityto

Azithromycin, imipenem, meropenem

CONCLUSION

High prevalence of **MDR** and **XDR** ***Salmonella*** underscores the need for enhanced surveillance and judicious antibiotic use

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INTRODUCTION

Enteric fever, a systemic infection caused by the gram-negative pathogens *Salmonella enterica* serovars Typhi and Paratyphi, remains a significant public health concern, particularly in low- and middle-income countries. Globally, typhoid fever and its associated complications are estimated to cause approximately 200,000 deaths annually (1). The disease is endemic across Asia, with the majority of cases reported in India, Bangladesh, China, and Pakistan (2). Poor sanitary conditions, overcrowding, and limited access to clean water in many developing nations perpetuate the spread of this infection, whereas developed countries generally report only sporadic cases, typically among travelers returning from endemic regions (3). Clinically, *Salmonella* infection presents with a wide spectrum of symptoms, including headache, malaise, high-grade fever, diarrhea, rashes, cough, and, in severe cases, complications such as intestinal perforation, peritonitis, and meningoencephalitis (4). Of these, persistent high-grade fever is the most prominent and distressing symptom, often exacerbating anxiety among caregivers (5). Transmission predominantly occurs through the consumption of contaminated food and water, particularly from street vendors offering items like ice cream or flavored ice drinks, with fecal contamination recognized as the principal source of infection (6).

Historically, treatment for typhoid fever relied on antibiotics such as ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol, the latter of which was introduced in the 1940s as a first-line therapy (7,8). However, by the 1980s, the widespread emergence of resistance to these antibiotics necessitated a shift toward the use of fluoroquinolones, particularly ciprofloxacin (9,10). Unfortunately, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Salmonella* Typhi strains has severely compromised the efficacy of traditional antimicrobial agents, leaving few therapeutic alternatives such as imipenem, meropenem, and azithromycin (11). This alarming resistance pattern demands the urgent development of novel therapeutic strategies to protect vulnerable populations. The first outbreak of XDR typhoid was documented in Hyderabad, Sindh province, Pakistan, in 2016, but since then, cases have been increasingly reported across the country. Understanding the classification of drug resistance in *Salmonella* Typhi is crucial for tailoring effective clinical interventions and preserving the limited treatment options available. Globally, typhoid fever continues to pose a formidable threat, with an estimated 128,000–161,000 deaths occurring annually, particularly in the WHO African Region, South-East Asia, Western Pacific, and Eastern Mediterranean countries (12). This ongoing burden highlights the need for robust prevention, timely diagnosis, and effective management strategies.

While various studies have explored typhoid fever incidence among non-cancer patients in Pakistan, there remains a noticeable gap in research focusing on pediatric oncology patients. Children undergoing cancer treatment are particularly susceptible to severe infections due to their immunocompromised status. Annually, around 400,000 children under the age of 19 are diagnosed with cancer worldwide, with approximately 7,000 to 7,500 new cases reported in Pakistan alone (13). Bacterial infections, especially by coagulase-negative *Staphylococcus* species, are commonly encountered in this group (14). However, data regarding the prevalence and characteristics of *Salmonella* Typhi infections, specifically MDR and XDR strains, in pediatric cancer patients are exceedingly scarce in Pakistan. Recognizing this critical gap, the present study was designed to evaluate the prevalence of multidrug-resistant and extensively drug-resistant *Salmonella* Typhi infections among pediatric patients, both with and without underlying malignancy, treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan.

METHODS

This retrospective multicenter study was conducted at Shaukat Khanum Memorial Cancer Hospitals and Research Centers (SKMCH&RC) in Lahore and Peshawar, Pakistan. Data were collected over a one-year period from 30th June 2023 to 31st May 2024. The study utilized a retrospective convenience sampling, including all eligible cases meeting the inclusion criteria. Institutional Review Board approval was obtained prior to data collection (IRB Reference No: EX-11-09-23-01). The study was conducted in compliance with ethical standards for retrospective research, and the data were used exclusively for research purposes without requiring informed consent, given the retrospective nature of the study.

Inclusion criteria encompassed all pediatric patients under the age of 18 years who underwent blood culture testing for fever during the study period. Adult patients and cases with incomplete records or irrelevant diagnoses were excluded from the study. Data was extracted from the hospital information system (HIS) and included the following variables: patient age, gender, site of sample collection (hospital-based laboratory versus external collection points), and resistance profile (MDR, XDR, or non-MDR/XDR) based on the operational definitions. (15).

Identification of Salmonella isolates was performed using standard blood culture techniques. Blood samples were processed using the Bact/Alert automated blood culture system. Positive blood culture bottles were sub cultured onto chocolate agar, blood agar, and MacConkey agar plates to isolate the organisms. Confirmed Salmonella isolates underwent antimicrobial susceptibility testing using the Kirby-Bauer disk diffusion method on Mueller-Hinton agar. The antibiotics tested included ampicillin, chloramphenicol, ceftriaxone,

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cefixime, co-trimoxazole, ciprofloxacin, azithromycin, imipenem, and meropenem. Interpretations of susceptibility were performed following the Clinical and Laboratory Standards Institute (CLSI) guidelines, 2020 edition (18).

Salmonella Typhi isolates were classified as multidrug-resistant (MDR) when resistance was observed against chloramphenicol, ampicillin, and co-trimoxazole. Isolates were designated as extensively drug-resistant (XDR) if they exhibited MDR characteristics along with non-susceptibility to fluoroquinolones and resistance to third-generation cephalosporins. Isolates that did not meet the criteria for MDR or XDR were classified as non-MDR/XDR. (15)

Although no prior sample size calculations were performed, a post hoc assessment of sample adequacy was conducted using the OpenEpi sample size calculator (16). This assessment was based on two primary outcomes: the prevalence of Salmonella Typhi and Paratyphi in blood cultures and the antimicrobial resistance patterns (MDR, XDR, and non-MDR/XDR). For estimating the prevalence of Salmonella Typhi, an expected prevalence of 50%, a confidence level of 95%, and a 5% margin of error were assumed, resulting in a required sample size of 289. Similarly, for MDR prevalence, an assumed rate of 23% with the same statistical parameters required a minimum of 273 isolates. The total sample of 864 isolates exceeded both thresholds, validating that the study's sample size was sufficient to detect significant findings related to pathogen prevalence and antimicrobial resistance (17).

Data were extracted from the Hospital Information System (HIS) and subsequently exported into Microsoft Excel sheets specifically designed for this analysis. All data were entered and analyzed using SPSS version 22. Descriptive statistics were utilized to summarize the data. Categorical variables such as gender, type of resistance (MDR, XDR, non-MDR/XDR), and sample collection site were presented as frequencies and percentages. The continuous variable age was categorized into three groups (1–5 years, 6–11 years, and 12–18 years) and was similarly described using frequencies and percentages. Results were illustrated using tables, bar charts, and pie charts to provide a clear overview of demographic distributions and resistance patterns.

RESULTS

In this retrospective study conducted over a one-year period, a total of 3,146 positive blood cultures were identified, out of which 864 cultures (27.5%) were confirmed positive for *Salmonella* species. Among the patients with Salmonella bacteremia, 60 patients (7%) were undergoing active chemotherapy, while 824 patients (93%) were categorized as post-chemotherapy and non-cancer patients. Analysis of resistance profiles revealed that out of the 864 positive blood cultures, 61 isolates (7.1%) were classified as multidrug-resistant (MDR), 409 isolates (47.3%) were extensively drug-resistant (XDR), and 394 isolates (45.6%) were neither MDR nor XDR. Gender-based distribution demonstrated a higher prevalence of XDR infections in male patients, with 261 cases (64%) compared to 148 cases (36%) in females. For MDR infections, a near-equal distribution was observed between genders, with males accounting for 32 cases (52%) and females 29 cases (48%). Non-MDR and non-XDR infections were more prevalent in males with 248 cases (63%) compared to 146 cases (37%) in females. Overall, the incidence of Salmonella infections was higher among males, with 541 cases (62.6%), whereas females represented 323 cases (37.4%). Age-wise analysis indicated that the highest burden of Salmonella infections was observed in the 6–11-year age group, accounting for 376 cases (43.5%), followed by the 1–5-year age group with 290 cases (33.5%), and the 12–18-year age group comprising 198 cases (23%). Both MDR and XDR infections were predominantly seen in the 6–11-year category, with 191 cases (47%) of XDR and 155 cases (39%) of MDR, respectively. Antimicrobial resistance patterns revealed that the highest resistance was observed against fluoroquinolones (88%), followed by penicillins (76.5%), chloramphenicol (75%), cephalosporins (69.5%), and sulfonamides (67.5%). Minimal resistance was noted against azithromycin, imipenem, and meropenem, suggesting these agents remain largely effective.

Table 1: Demographic Characteristics of Pediatric Patients

Variable	Category	Frequency (n)	Percentage (%)
Gender	Male	541	62.6
	Female	323	37.4
Age Group	1–5 years	290	33.5
	6–11 years	376	43.5
	12–18 years	198	23
Treatment Status	Active Chemotherapy	60	7
	Non-Cancer/Post Chemotherapy	824	93

Table 2: Distribution of Antimicrobial Resistance

Resistance Pattern	Frequency (n)	Percentage (%)
MDR	61	7.1
XDR	409	47.3
Non-MDR/Non-XDR	394	45.6

Table 3: Gender-Wise Distribution of Resistance Patterns

Resistance Category	Male (n, %)	Female (n, %)
MDR	32 (52%)	29 (48%)
XDR	261 (64%)	148 (36%)
Non-MDR/Non-XDR	248 (63%)	146 (37%)

Table 4: Antimicrobial Resistance Profile of Salmonella Isolates

Antibiotic Group	Resistance (%)
Fluoroquinolones	88
Penicillins	76.5
Chloramphenicol	75
Cephalosporins	69.5
Sulfonamides	67.5
Azithromycin	Low
Imipenem	Very Low
Meropenem	Very Low

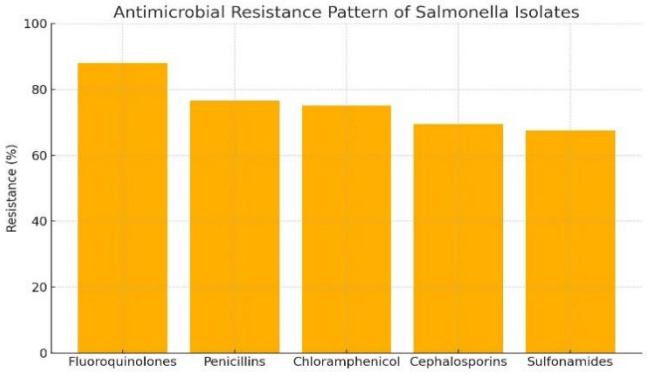

Figure 1 Antimicrobial Resistance Pattern of Salmonella Isolates

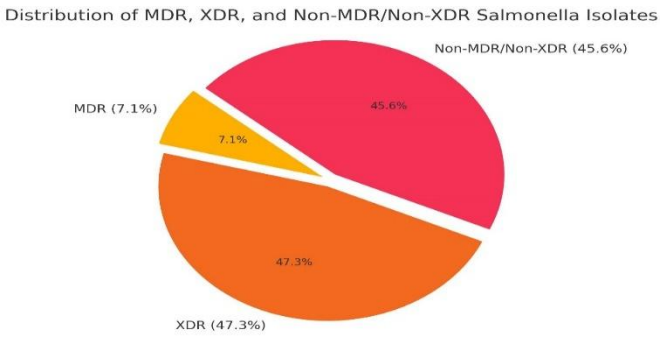

Figure 2 Distribution of MDR, XDR and Non-MDR/Non-XDR Salmonella Isolates

DISCUSSION

This multicenter retrospective study was conducted to determine the prevalence of extensively drug-resistant (XDR) and multidrug-resistant (MDR) *Salmonella* infections in pediatric cancer and non-cancer patients and to assess the incidence of these severe infections in a vulnerable population. Notably, a comparative evaluation of *Salmonella* infections between pediatric cancer and non-cancer groups has been largely absent in the available literature, emphasizing the novelty and relevance of this research. During the study period, 3146 positive blood cultures were evaluated, and 864 were confirmed as *Salmonella Typhi* or *Salmonella Paratyphi* infections. Among these, only 60 cases involved pediatric patients receiving active chemotherapy, suggesting a comparatively lower incidence of *Salmonella* bacteremia within this subgroup, likely due to strict hospital infection control measures. The predominance of XDR cases (47.3%) over MDR cases (7.1%) observed in the present study underscores the serious public health threat posed by resistant strains. A significant gender disparity was noted, with male patients showing higher rates of XDR infections compared to females, a pattern consistent across

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different resistance categories. This male preponderance aligns with global infection trends in pediatric populations. Age-wise analysis demonstrated the highest burden of infections in the 6–11-year group, deviating from some earlier reports that indicated peak incidence in younger children aged 1–5 years (13,14). However, findings from regional studies, including those conducted in Pakistan, Nepal, and India, support the observed age distribution, corroborating that infections are increasingly shifting toward older pediatric age groups (15,16).

In terms of antimicrobial susceptibility, the results revealed alarming resistance rates against fluoroquinolones, penicillins, chloramphenicol, cephalosporins, and sulfonamides. Minimal resistance was noted against azithromycin, imipenem, and meropenem, highlighting these agents as valuable therapeutic options in the current setting. When compared to previous literature, there is a clear evolution of resistance patterns. For instance, earlier studies documented higher susceptibility rates to cotrimoxazole and ceftriaxone (17), whereas the current study reflects a progressive decline in sensitivity, necessitating urgent reevaluation of empirical treatment protocols. The emergence of MDR and XDR *Salmonella* has compounded the management challenges associated with enteric fever, particularly in endemic areas. In addition to biological adaptability, environmental and sociocultural factors such as reliance on empirical therapies, over-the-counter antibiotic availability, and unregulated healthcare practices have contributed to the acceleration of resistance in countries like Pakistan (18,19). These factors underline the necessity for more robust surveillance systems, rational antibiotic stewardship programs, and the promotion of typhoid vaccination as preventive measures. The study carries several strengths. It is among the few to explore the differential burden of drug-resistant *Salmonella* infections between pediatric cancer and non-cancer patients in Pakistan, contributing valuable insights to an under-researched area. The large sample size and multicenter design further enhance the generalizability of the findings within similar healthcare settings.

Nevertheless, some limitations must be acknowledged. Data collection was restricted to two tertiary care centers, potentially limiting the external validity of the results to the broader national population. The retrospective design, while practical for this context, may also be associated with inherent biases such as incomplete clinical information. Additionally, the study did not stratify clinical outcomes, such as hospital stay duration, severity of illness, or mortality rates between cancer and non-cancer groups, which could have provided deeper clinical insights. Future studies should consider including a larger multicenter sample, prospective designs, and detailed clinical outcomes to comprehensively evaluate the burden and consequences of MDR and XDR *Salmonella* infections in pediatric oncology and general pediatric populations (20). In conclusion, this study highlights the growing challenge of drug-resistant *Salmonella* infections among pediatric patients, with XDR strains now representing a dominant threat. It underscores the critical need for strengthened infection control policies, targeted antibiotic stewardship, expansion of typhoid vaccination coverage, and ongoing surveillance to mitigate the impact of these formidable pathogens on vulnerable pediatric cohorts.

CONCLUSION

This study underscores the substantial burden of extensively drug-resistant *Salmonella* infections among pediatric patients, emphasizing the critical need for vigilant antibiotic stewardship and proactive infection control strategies. The persistence of susceptibility to a limited range of antibiotics highlights the urgency of preserving these treatment options through strict regulation of antibiotic use, enhanced hygiene practices, and the discouragement of over-the-counter antibiotic availability. Strengthening typhoid vaccination programs is essential to curb the rising threat of resistance, particularly within vulnerable pediatric cancer and non-cancer populations. These findings contribute valuable insights to guide clinical management and public health interventions aimed at mitigating the impact of drug-resistant enteric fever in high-risk settings.

AUTHOR CONTRIBUTION

Author	Contribution
Bakht Jamal	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Zeeshan Nawaz*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Saira Uzma	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Najma Shaheen	Contributed to Data Collection and Analysis

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	Has given Final Approval of the version to be published
Luqman khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published

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