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Evaluating the Rising Incidence of Multidrug-Resistant and Extensively Drug-Resistant *Salmonella typhi* and *Salmonella paratyphi* in Sialkot City

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ABSTRACT

In the Developing countries, Typhoid is one of the major health concerns. Most importantly the disease management is getting complicated due to multi and extensive drug resistance incidence. **Objective:** To investigate the incidence of causative agent's salmonella typhi and para-typhi in the affected patients of Sialkot who were either multi drug resistant or extensive drug resistant. **Methods:** This descriptive cross-sectional study was conducted at the department of microbiology, Khawaja Muhammad Safdar medical college, Sialkot from January, 2024 to July, 2024. A total of 2000 patients with febrile illness were examined for the study, 500 samples of neonates were excluded and blood samples of remaining 1500 patients were collected. The blood samples were cultured on MacConkey agar and blood agar. Among the 1500 patients, only 73 were found to be infected with either *Salmonella typhi* or *Salmonella paratyphi* according to CLSI criteria. Antibiotic sensitivity was investigated and resistant to trimethoprim-sulfamethoxazole (septran), chloramphenicol, and ampicillin were labeled as multi drug resistant while resistant to ciprofloxacin and third generation cephalosporins in addition to aforementioned antibiotics were labeled as extensively drug resistant. **Results:** From a total of 1500 samples, n=73 *salmonella* positive samples were included in this research. Incidence of extensively drug resistant *Salmonella* was 23 (32%) and multidrug drug resistant *Salmonella* was 7 (10%). **Conclusion:** This study highlighted significant resistance rates, emphasizing the need for sensible antibiotic prescriptions and judicious antimicrobial use to combat rising multidrug and extensive resistance.

INTRODUCTION

The causative agent of typhoid fever is *Salmonella enterica* serovar Typhi, which is a Gram-negative microbe, and it considerably contributes to the overall burden of the disease worldwide. In 2017, over 14 million individuals were affected by typhoid and paratyphoid fever, with more than 130,000 deaths reported. About 70 percent of these deaths occurred in South Asia [1]. In the 1940s, chloramphenicol was introduced as the first-line antibiotic for treating typhoid fever [2-4]. However, the emergence of resistance to chloramphenicol led to the introduction of other antibacterial drugs. This contains the inclusion of co-trimoxazole, in the 1970s. By the 1980s, research indicated that *Salmonella typhi* strains had developed resistance to all available antibiotics of that time [5]. Consequently, ampicillin and trimethoprim-sulfamethoxazole became the preferred choices for typhoid treatment. On the other hand resistance to these antibiotics also emerged globally within a few years. Clinicians then shifted to fluoroquinolones (e.g., ciprofloxacin) for the treatment of typhoid fever and enteric [6]. The growing prevalence of

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Multidrug-Resistance (MDR) as well as Extensively Drug-Resistance (XDR) in *Salmonella typhi* has severely compromised the efficacy of many treatment options. MDR strains are defined as resistant to at least one antibiotic in three or more different classes.These includes chloramphenicol, sulfonamides (trimethoprim-sulfamethoxazole) and ampicillin. Strains of XDR exhibit resistance to a broader spectrum of antibiotics which also includes third-generation cephalosporins, sulfonamides, ampicillins and ciprofloxacin [7, 8]. Alarmingly, resistance to fluoroquinolones has also increased globally, with South Asia as the epicenter. While cephalosporins and azithromycin remain options for treatment based on clinical efficacy, cases of cephalosporin-resistant Salmonella typhi have been reported worldwide. This showed the tendency of exacerbating the typhoid burden in regions like South Asia where XDR and MDR strains are predominant [9]. In Pakistan, the escalating rates of typhoid fever, driven by XDR and MDR *Salmonella typhi* has raised concerns about antibiotic treatment failure [10]. Between 2016 and 2017, in Hyderabad alone, over 800 cases of XDR typhoid were reported, leading to the declaration of the district as typhoid endemic [11, 12]. The first case of XDR *Salmonella typhi* in Karachi was documented in 2016, and over 17,000 cases have been reported in Sindh since then [13]. Although previous studies have primarily focused on Sindh, recent cases have emerged across Pakistan [14, 15] and internationally, often linked to travel [16]. Additionally, during the COVID-19 pandemic, an increase in typhoid cases resembling COVID-19 in clinical presentation was observed; in June 2020 alone, over 20,000 cases were diagnosed in Pakistan [17]. Despite the rising prevalence of MDR and XDR *Salmonella typhi*, there is limited data from cities like Sialkot, highlighting a critical gap in the regional understanding of antimicrobial resistance patterns.

This study aimed to determine the incidence of MDR and XDR *Salmonella typhi* and *Paratyphi* in Sialkot and investigate the antimicrobial sensitivity patterns of commonly prescribed antibiotics (chloramphenicol, ciprofloxacin, cefixime, azithromycin, and ceftriaxone) against typhoidal *Salmonella.*

METHODS

After receiving an approval from the Ethical Review Committee (approval number 133/REC/KMSMC), this descriptive cross-sectional study was conducted in the Microbiology Department of Government Khawaja Safdar Medical College and Allied Hospitals, Sialkot, from January, 2024, to July, 2024. The sample size of 73 cases was determined using the RAOSOFT sample size calculator with 5% margin of error and a 95% confidence level. An assumed prevalence rate of 10% based on local data to ensure statistical power. Written informed consent was obtained from all participants or their guardians in the case of children. A non-probability purposive sampling method was adopted to select the participants, ensuring the inclusion of cases clinically suspected of typhoid fever based on patient history and symptoms. Patients of all age groups, both male and female, with a history of fever and clinical suspicion of typhoid fever, were included. Out of the 2,000 suspected typhoid cases, neonates (500 cases) were excluded due to the inability to obtain large blood samples (8-10 mL) safely. The remaining 1,500 patients were selected for blood sample collection under aseptic conditions. Blood samples were injected into Bactec™ Plus Anaerobic and Aerobic culture bottles containing 20 mL of broth and incubated overnight at 37 ± 1°C, following standard microbiological measures. Blood cultures were administered using the BACT/ALERT 3D system (Biomerieux, France). Isolates were identified as *Salmonella typhi* and *Salmonella paratyphi* using the API 20E identification system (Biomerieux, France) and serological confirmation was done with polyvalent antisera (Bio-Rad). To evaluate the Antimicrobial susceptibility, the Kirby-Bauer disc diffusion protocol was employed. The inoculum density was adjusted to match the turbidity level of 0.5 McF standard (nearly 1.5×10.0^8 organisms/mL) and uniformly spread on the surface of Mueller-Hinton agar plates. Antibiotic susceptibility was tested using the following antibiotics, grouped and presented in table 1. Plates were incubated overnight at 36°C, and Zone of Inhibition (ZOI) for each plate was measured in millimeters. Outcomes were shown as "Resistant," "Intermediate," or "Susceptible" depending upon the Clinical and Laboratory Standards Institute (CLSI) guidelines [18]. The varying number of samples for each antibiotic test was due to availability constraints, clinical indications, and the focus of analysis on specific antibiotics most relevant to MDR/XDR cases. The descriptive cross-sectional design accounted for confounders by stratifying data based on age, gender, and comorbidities. This was essential for ensuring representative findings across the population. Data were examined using SPSS version 22.0. Descriptive statistics were adopted to compute the frequencies and percentages for qualitative variables.

RESULTS

Among 2000 recruited patients 500 (25%) of neonates were not included in the research. From remaining 1500 (75%) samples, 1200 showed no growth, from remaining 300, 73 (24%) yielded growth of *Salmonella typhi* and paratyphi. A total of 73 Salmonella positive samples were statistically analyzed. From positive, 62% female and 38 % were male. Mean age was 29 years ranging from 1 to 80 years. From total *Salmonella* species, 64 (88%) Salmonella typhi and 9 (12%) *Salmonella paratyphi.*Extensively drug

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resistance *Salmonella* species were 32% and multidrug drug resistance *Salmonella* species were 10%.

Table 1: Grouping of Antibiotics with Their Disc Concentrations Used in the Study

Antibiotic Groups	Antibiotics	Disc Concentration
Penicillins	Ampicillin	10.0 µg
Phenicols	Chloramphenicol	30.0 µg
Sulfonamides	Co-trimoxazole	1.250/23.750 µg
Quinolones	Ciprofloxacin	5.0 µg
Cephalosporins	Ceftriaxone, Cefixime	30.0 µg each
Macrolides	Azithromycin	15.0 µg
Carbapenems	Imipenem, Meropenem	10.0 µg each

The table 2 showed incidence of *Salmonella* from *salmonella typhi* there are 4 MDR and 9 XDR between age 1-20 years, 2 MDR and 9 XDR cases of age 21-40 years, only 4 XDR cases of age 41-60 years and no MDR or XDR cases between age 61-80 years. Similarly, there is only 1. MDR case of age 1-40 years and 1 case of XDR between ages 61-80 years of *Salmonella paratyphi.*

Table 2: Incidence of *Salmonella* spp. from Enrolled Samples (n=73)

Age Range	*Salmonella typhi*			*Salmonella paratyphi*			Total 73 (100%)
	MDR n =6	XDR n =22	Other n =36	MDR n =1	XDR n =1	Other n =7	
1-20	4	9	16	-	-	-	29
21-40	2	9	14	1	-	5	31
41-60	-	4	6	-	-	1	11
61-80	-	-	-	-	1	1	2

Inhibition zones were measured in millimeters (mm) and tabulated (Table 3). Each result represents the mean value (±SD) obtained from three independent replicates of susceptibility tests. Resistance categories were classified according to CLSI 2024 guidelines. MDR refers to resistance to at least three classes of antibiotics, including amoxicillin, co-trimoxazole, and chloramphenicol. XDR strains were resistant to all first-line agents (amoxicillin, co-trimoxazole, and chloramphenicol) and second-line fluoroquinolones but remained sensitive to azithromycin and carbapenems.

Table 3: Zone of Inhibition Measurements for MDR and XDR Strains

Antibiotics	Breakpoint (mm)	Mean Zone of Inhibition (Mean ± SD)	Category (R = Resistant, S = Sensitive)
Amoxicillin	≤13	10.5 ± 0.6	R
Ceftriaxone	≥23	30.2 ± 1.4	S
Ciprofloxacin	≤15	12.4 ± 0.7	R
Azithromycin	≥14	27.1 ± 1.2	S
Imipenem	≥16	28.8 ± 0.8	S

The results of the study presented in table 4 show that, most *Salmonella typhi* isolated have significant resistance to first-line antibiotics, with 56.3% resistant to amoxicillin and 64.1% resistant to ciprofloxacin.Comparatively, resistance rates in S. *paratyphi* were generally lower, except for azithromycin and ciprofloxacin, where resistance reached 77.8% and 66.7%, respectively. Multidrug Resistance (MDR) was higher in *Salmonella typhi* (44.4%) compared to *S. paratyphi* (12.5%). Extensively Drug-Resistant (XDR) strains were rare, with only 2.5% of *Salmonella typhi* isolates classified as XDR, and none in S. *paratyphi.*

Table 4: Antibiogram formation: A Pattern of Drug Resistant against *Salmonella typhi* and *Salmonella paratyphi* Isolates

Drugs	*Salmonella typhi*		*Salmonella paratyphi*	
	Cases Tested	Resistant Frequency (%)	Cases Tested	Resistant Frequency (%)
Amoxicillin	64	36 (56.3%)	9	3 (33.3%)
Azithromycin	50	30 (60.0%)	9	7 (77.8%)
Cefixime	35	3 (8.6%)	5	1 (20.0%)
Ceftriaxone	64	4 (6.3%)	9	1 (11.1%)
Chloramphenicol	63	28 (44.4%)	9	2 (22.2%)
Ciprofloxacin	64	41 (64.1%)	9	6 (66.7%)
Co-trimoxazole	61	38 (62.3%)	9	3 (33.3%)
Imipenem	50	2 (4.0%)	8	0 (0%)
Nalidixic acid	62	56 (90.3%)	9	8 (88.9%)
MDR tested (a)	45	20 (44.4%)	8	1 (12.5%)
XDR tested (b)	40	1 (2.5%)	6	0 (0%)

a Amoxicillin, chloramphenicol, and *co-trimoxazole* were tested together.
b Amoxicillin, ceftriaxone, ciprofloxacin, co-trimoxazole, and *chloramphenicol* were all *tested together.*

For the MDR strains, sensitivity to third-generation cephalosporins such as cefixime and ceftriaxone persisted to be high, with 92.0% and 92.5% of *Salmonella typhi* isolates, respectively, showed sensitivity. *Salmonella paratyphi* also showed 100% sensitivity to cefixime and ceftriaxone. Resistance to ciprofloxacin was substantial, with only 10.0% of *Salmonella typhi* MDR strains and none of the *Salmonella paratyphi* MDR strains being sensitive. Importantly, imipenem showed excellent efficacy, with 96.7% of *Salmonella typhi* MDR strains and all *Salmonella paratyphi* MDR strains being sensitive. All XDR *Salmonella typhi* strains were sensitive to azithromycin and imipenem table 5.

Table 5: Pattern of Drug Susceptibility MDR and XDR strains of *Salmonella* Isolates

Drugs	*Salmonella typhi*		*Salmonella paratyphi*	
	Cases Tested	Sensitive Frequency (%)	Cases Tested	Sensitive Frequency (%)
Multidrug-Resistant				
Azithromycin	30	10 (33.3)	2	1 (50.0%)
Cefixime	25	23 (92.0)	2	2 (100%)
Ceftriaxone	40	37 (92.5)	3	3 (100%)
Ciprofloxacin	40	4 (10.0)	3	0 (0%)
Imipenem	30	29 (96.7)	2	2 (100%)
Extensively Drug-resistant	-	-	-	-

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Azithromycin	2	2 (100)	-	-
Imipenem	2	2 (100)	-	-

DISCUSSION

The results of this study highlighted the alarming rise of Extensively Drug-Resistant (XDR) Salmonella typhi, which accounted for the majority of infections, alongside a smaller proportion of Multidrug-Resistant (MDR) Salmonella cases. Historically, the treatment of typhoid fever relied on first-line antibiotics such as chloramphenicol, ampicillin, and co-trimoxazole. However, the emergence of MDR strains resistant to these antimicrobials in the late 1980s led to the adoption of fluoroquinolones and third-generation cephalosporins as the primary treatments. This transition provided effective alternatives but also contributed to increasing resistance rates due to overuse and misuse of these drugs [19, 20]. These findings revealed that alarmingly high resistance to ciprofloxacin, with only 4% of organisms showing sensitivity. Resistance to third-generation cephalosporins was also significant, with 45% of isolates showing resistance to ceftriaxone. These results underscore the dwindling efficacy of critical antibiotics. This trend is consistent with previous studies in South Asia that reported increasing resistance due to widespread over-prescription of fluoroquinolones [21]. The implications of these findings are profound, as both ciprofloxacin and ceftriaxone are considered essential components of current typhoid treatment protocols. The emergence of resistance jeopardizes the effective management of enteric fever. Particularly in resource-limited settings where alternative therapies like azithromycin may not always be accessible. Azithromycin which is often reserved for cases of MDR and XDR typhoid, also showed high resistance rates in this study. These rates are higher particularly among Salmonella paratyphi isolates (77.8%). This resistance trend is concerning, given the limited availability of other oral therapeutic options and the potential for cross-resistance with related macrolides. These findings emphasize the urgent need to rationalize antibiotic use in typhoid management, and enhance diagnostic capabilities for tailored treatments. These also emphasize on the importance to invest in public health measures to mitigate further resistance escalation. The gender distribution in this study, with a higher prevalence of infection among females (62%), aligns with prior research. This suggests that women may be more susceptible to typhoid fever, particularly those with underlying biliary morbidities such as cholelithiasis [22]. Furthermore, these results reinforced the established epidemiological trend that Salmonella typhi is more prevalent than Salmonella paratyphi infections [23]. Typhoid fever remains a significant public health concern in Pakistan. The increasing antibiotic resistance is adding to the burden. The lack of basic hygiene, inadequate sanitation, and unregulated antimicrobial usage have been identified as major drivers of resistance in low- and middle-income countries [24, 25]. The COVID-19 pandemic may have exacerbated this situation by increasing the use of azithromycin and other antibiotics as off-label treatments, inadvertently fostering resistance among typhoidal and non-typhoidal Salmonella strains [26]. Similar factors, combined with urban overcrowding, unvaccinated populations, and inadequate water supplies, contribute to the ongoing emergence and spread of XDR strains, as observed in previous outbreaks in Lyari town of Karachi, Pakistan [27]. Limitations of this study should be acknowledged. The exclusion of neonates (25% of initially recruited participants) may have introduced selection bias, potentially limiting the generalizability of these findings to all age groups. Additionally, the reliance on non-random sampling may have led to overrepresentation of certain demographic groups or resistance profiles. Future research should aim to incorporate broader and more illustrative sampling frameworks to improve the robustness and applicability of results.

CONCLUSIONS

This research discovered a significant rate of resistance and antibiotic susceptibility changes among Salmonella isolated to fluoroquinolones and ceftriaxone necessitating the importance of adhering to the sensible antibiotic prescription and judicious usage of antimicrobials. A pattern of drug susceptibility unique to the samples was found for the first time from Sialkot city suggesting a need to continuously monitor drug susceptibility profiles for better treatment outcomes especially in underrepresented areas.

Authors Contribution

Conceptualization: UZ
Methodology: JA
Formal analysis: SN, SA
Writing, review and editing: JA, RMAK, AKS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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