

# Trends in antibiotic susceptibility of enteric fever isolates among children attending a tertiary care hospital of Peshawar, KP

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**ABSTRACT**

**Introduction:** The rising trend of multi-drug resistance in bacteria has also been documented in the organism *Salmonella enterica* causing Typhoid or Enteric Fevers, and cases of multidrug and extended drug resistance are on the rise. Determining the trends of antibiotic susceptibility provides an important therapeutic aid to the practicing clinician.

**Objective:** To evaluate the ten-year trends in antibiotic susceptibilities of *Salmonella typhi* and *Salmonella paratyphi* isolated from blood cultures in the paediatric patients of a tertiary care hospital of Peshawar, Khyber Pakhtunkhwa, Pakistan.

**Materials & Methods:** A descriptive study was conducted in the department of Paediatrics, Rehman Medical Institute, Peshawar from June 2019 to May 2020 based on ten years retrospective data of children with positive blood culture for *Salmonella spp.* Data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). The level of significance was set at  $p \leq 0.05$ .

**Results:** A total of 168 cases *Salmonella enterica spp.* were isolated over the 10-year study period, of which 97(64.88%) isolates were identified as *Salmonella typhi* and 71(42.26%) as *Salmonella paratyphi A*; 94(55.95%) patients were male and 74(44.04%) were female, with mean age of  $4.76 \pm 2.65$  years (range 2 to 12 years); majority, 69(41.07%) of patients were of ages 5-8 years. *S. typhi* strains showed the highest sensitivity to Imipenem and Meropenem; the lowest sensitivity seen was to Ampicillin. Bacterial sensitivity to Ceftriaxone was 79.76% and to Ciprofloxacin 58.97%. In the *S. typhi* group, there were six (2.6%) cases of MDR typhoid and four (2.38%) cases of XDR typhoid which was only sensitive to Imipenem.

**Conclusion:** Increased resistance to Ampicillin, Ciprofloxacin and Ceftriaxone was found, however complete sensitivity was found to Imipenem along with Meropenem.

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**INTRODUCTION**

Enteric Fever (commonly called Typhoid fever), a disease endemic to tropical and subtropical regions, is caused by the bacterium *Salmonella enterica serovar typhi*. It is spread by feco-oral route and is common globally, especially in underdeveloped countries due to contamination of food and liquids with salmonella species. Typhoid fever is related to poor hygiene and sanitation, and is among the common febrile illnesses, involving multiple body systems with serious complications. Symptoms might range from mild to moderate or severe, and so are its complications, which might prove fatal if left untreated. This disease is mostly thought of as a disease of developing countries because of poor sanitary conditions.<sup>1</sup> Typhoid fever has been mostly eradicated from developed countries due to improved sanitary and hygienic conditions.<sup>2</sup> With an estimated annual incidence of 540 per 100,000 or about 17 million cases worldwide,<sup>3</sup> it is a major public health problem, and accounts for a sizable number of cases of global morbidity and mortality.<sup>4</sup>

The causative organism, *Salmonella typhi*, has rapidly gained Multidrug Resistance (MDR) and now Extended Drug Resistance (XDR) to antibiotics like Ampicillin, Ceftriaxone, and Cotrimoxazole, and also to previously efficacious drugs like Ciprofloxacin,<sup>5</sup> thereby further complicating the treatment and management of enteric fever, and posing the greatest challenges to paediatric consultants in managing paediatric *Salmonella typhi* infections. In 2017, Global Health Data Exchange reported approximately 116,800 deaths due to typhoid fever. Of these, there were about 79,000 deaths in South Asia, with 6,700 reported from Pakistan.<sup>6</sup>

The incidence of MDR typhoid is reported to be 17% to 23% in South Asia which led to shift from first-line antityphoid drugs to first- and third-generation Cephalosporins and Fluoroquinolones (FQ) (second-line agents for typhoid), and azithromycin.<sup>7</sup> Concurrently, newer studies have started to report increasing antimicrobial resistance to one or more second-line antityphoid agents.<sup>8</sup>

Contributory factors to emergence of antibiotic resistance include monotherapy, incomplete directions for antibiotic use, cessation of antibiotic therapy by patients, and prescriptions given without biochemical testing. Finally, in 2016, the first case of XDR typhoid was reported from Hyderabad, a small city in the South of Pakistan. XDR typhoid is defined as the isolate resistant to all first-line antityphoid agents, Ceftriaxone (CFX), and FQ.<sup>9</sup> Since then, the World Health Organization has reported more than 5,200 cases of XDR typhoid from Pakistan, all of which were from Southern Pakistan. The present study was done to evaluate the current trends in antibiotic susceptibilities of *S. typhi* and *S. paratyphi* isolated from blood cultures in the paediatric population of Peshawar, Pakistan.

## MATERIALS & METHODS

An observational study was conducted at Department of Paediatrics, Rehman Medical Institute, Peshawar, retrospective data of all patients with positive blood culture for salmonella in the last 10 year from RMI database through consecutive sampling. Inclusion criteria were children age less than 18 years, children with positive blood culture for salmonella, and both genders. Exclusion criteria were incomplete or ambiguous relevant records.

### Sample collection procedure

For each child, 5 mL of venous blood was taken and collected in special blood culture bottles containing 30 mL brain heart infusion (BHI) broth and was incubated for five to seven days at  $35 \pm 2^\circ\text{C}$ . Blood samples that were positive for *S. typhi* or *S.*

*paratyphi* were subcultured on McConkey agar for another two days at  $35 \pm 2^\circ\text{C}$  as per standard methods. API-20E (Biomerieux, France), the analytical profile index system specific for differentiating between members of Gram-negative Enterobacteriaceae, was utilized for biochemical testing. Serotyping was done by group and type-specific antisera (Bio-Rad). Kirby-Bauer disc diffusion technique on Mueller Hinton agar was utilized to determine the patterns of antimicrobial sensitivity. The agar plated will be incubated aerobically, at  $35 \pm 2^\circ\text{C}$ , for 24 hours.

### Data analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). Continuous variables were reported as mean and standard deviation and categorical variables as number (percent). The level of significance was set at  $P \leq 0.05$ .

## RESULTS

Of the total 168 *Salmonella enterica* spp. isolated over the 10-year study period, 97(64.88%) isolates were identified as *Salmonella typhi* and 71(42.26%) as *Salmonella paratyphi A*; Among patients, 94(55.95%) were male and 74(44.04%) were female, with mean age of  $4.76 \pm 2.65$  years, ranging from 2 to 12 years. Majority 69(41.07%) of the patients were in age group 5-8 years. The frequency and percentages of *S. typhi* and *S. paratyphi* strain according to the age and gender of the children are shown in Table 1.

**Table 1: Demographic characteristics of the study population**

Variables	Salmonella typhi (n=97)	Salmonella paratyphi (n=71)	Total (n=168)
<b>Gender</b>			
Male	56(57.73%)	38(53.52%)	94(55.95%)
Female	41(42.26%)	33(46.47%)	74(44.04%)
<b>Age group (years)</b>			
2-5	14(14.43%)	9(12.67%)	23(32.39%)
5-8	41(42.26%)	28(39.43%)	69(97.18%)
8-11	27(27.83%)	8(11.26%)	35(49.29%)
11-14	29(29.89%)	12(16.90%)	41(57.74%)

The most frequent presenting concern among the study sample was non focal pyrexia (87, 51.8%) and one child complicated into intestinal perforation which was surgically managed. A previous trial of antibiotics was taken by 97(58.9%) children.

The most common antibiotics taken were Cefixime by 86 (51.2%) children. The antimicrobial sensitivity patterns are shown in Table 2.

**Table 2: Showing antibiotic sensitivities of *Salmonella typhi* and *paratyphi*.**

Antibiotic	Salmonella typhi (n=97) f (%)	Salmonella paratyphi (n=71) f (%)
Ampicillin	48 (49.48)	23 (32.39)
Ciprofloxacin	57 (58.76)	36 (50.70)
Chloramphenicol	53 (54.63)	32 (45.07)
Ceftriaxone	83 (85.56)	51 (71.83)
Azithromycin	93 (95.87)	67 (94.36)
Imipenem	97 (100)	71 (100)
Meropenem	97 (100)	71 (100)

*S. typhi* strains showed the highest sensitivity to Imipenem and Meropenem; the lowest sensitivity seen was to Ampicillin. Bacterial sensitivity to Ceftriaxone was 79.76% which is alarming since these are commonly used empirical agents against salmonella. Only half of the *S. typhi* isolates showed sensitivity to ciprofloxacin (58.97%) which is also a rising concern. In the *S. typhi* group, there were six (2.6%) cases of MDR typhoid and four (2.38%) cases of XDR typhoid which was only sensitive to Imipenem.

## DISCUSSION

In Pakistan enteric fever is a growing concern, due to emergence of multidrug resistant salmonella in the last few years. The worldwide emergence of MDR strain of salmonella in last decade has led to withdrawal of certain antibiotics, like replacement of Chloramphenicol with Fluoroquinolones and Ceftriaxone. However, recently the efficacy of Ciprofloxacin as well as Ceftriaxone in Pakistan for enteric treatment has been seriously jeopardised.<sup>10</sup>

In our study, the prevalence of *S. typhi* was 64.8% and for paratyphi it was 42.26%. Majority 69(41.07%) of the patients were in age group 5-8 years. Globally in all microbes the antimicrobial resistance is increasing at an alarming rate. Research data shows that MDR typhoid prevalence rose from 12.14% in 1987 to 75.41% in 1995 in Pakistan.<sup>11</sup> Another study reported MDR prevalence in Asian countries at 23%.<sup>12</sup> Hassan et al. conducted a study in which they showed MDR rates of 34.2% to 48.5% for Typhi from 2001 to 2006.<sup>13</sup> The Quinolone resistance in *S. typhi* and paratyphi A rose dramatically (1.6 to 64.1%,  $p < 0.001$ ; and 0 to 47%,  $p < 0.001$ , respectively). Current data on MDR shows that it is prevalent up to 66%, 28.6% and 64.28% in Pakistan, India and Bangladesh, respectively.

Rahman BA et al,<sup>14</sup> showed that among Middle East and Central Asian countries the MDR prevalence is highest in Iraq (83%) and Pakistan (52%).

In our study resistance was found to Ampicillin and Ciprofloxacin and to third generation Cephalosporin. This was supported by other studies in literature from Pakistan and other neighbouring countries.<sup>15,16</sup> A recent study from developing countries showed resistance of against Chloramphenicol and Ciprofloxacin was observed.<sup>17</sup> In the late 2000, since the 1st line antibiotics for Salmonella Typhi showed resistance, the Fluoroquinolones and 3rd generation of Cephalosporin had been used in many endemic places and countries including Pakistan. However, shortly after the frequent use of Fluoroquinolones, *Salmonella typhi* resistance to this group of antibiotic has widely reported. Variation in the susceptibility patterns of *Salmonella typhi* against antibiotics is worth noting.

Our study showed that sensitivity to Imipenem and Meropenem to typhoid isolates was highest. Bacterial sensitivity to Ceftriaxone is 79.76%. One half of *Salmonella typhi* showed sensitivity to Ciprofloxacin. Imipenem and Meropenem showed 97% sensitive in our study. Due to the emerging resistance to a wide range of antimicrobials in Asian countries, the cost of typhoid infection has increased much over the years. This cost can be reduced by effective immunisation as recommended by the WHO and improvement in sanitation in developing countries.

## CONCLUSION

Increased resistance of *Salmonella spp.* was found to Ampicillin, Ciprofloxacin and Ceftriaxone, however there was complete sensitivity to Imipenem along with Meropenem.

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