

## Emergency Of Multi Drug Resistant And Extensive Drug Resistant Strains Of Salmonella Typhi Isolated From Children presenting to Hayatabad Medical Complex Peshawar

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### Abstract

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#### Background

Salmonella typhi is a non-spore-forming, motile, pathogenic bacterium responsible for causing typhoid fever, a potentially life-threatening systemic infection. Typhoid fever is characterized by a prolonged and debilitating febrile illness, accompanied by symptoms such as abdominal pain, headaches, and gastrointestinal disturbances. Inadequate sanitation and poor hygiene practices contribute to the prevalence of Salmonella typhi.

#### Methodology

This study aims at determining the prevalence of XDR and MDR strains of Salmonella typhi at Hayatabad Medical Complex Hospital, Hayatabad Peshawar, Pakistan. All the blood samples (n=287) were analyzed aseptically after fulfilling the inclusion and exclusion criteria. Initial incubation was performed by employing the BacT/ALERT-3D system. Sub-culturing of the samples was done using bacteriological culture media (Blood agar, MacConkey agar). Identification of the organisms was done on the basis of morphological characteristics of bacterial colonies, Gram staining, and biochemical tests. Antimicrobial susceptibility testing and result

interpretation were carried out according to the Kirby-Bauer disc diffusion method, following CLSI, 2021 guidelines.

#### Results

Out of 287 cases 119(41.4%) blood samples were found culture positive. Overall frequency of MDR and XDR strains of Salmonella typhi was 76.5% and 14.3%

respectively. Least number (9.2%) of cases was found susceptible to antimicrobial agents. Imipenem, aminoglycosides and azithromycin were drugs of choice against MDR cases of *Salmonella typhi*. Imipenem was considered only drug of choice against XDR cases of *Salmonella typhi*.

### **Conclusion**

It is concluded that overall prevalence of *Salmonella typhi* was 41.4%. Frequency of MDR *Salmonella typhi* strains was higher than XDR strains. Carbapenem was considered drug of choice against both MDR and XDR cases of *Salmonella typhi*.

### **Introduction**

*Salmonella* is a non-spore-forming, motile, pathogenic bacterium that is a member of the Enterobacteriaceae family that spreads through unsanitary environments. [1] *Salmonella* is a rod-shaped, flagellated, gram-negative bacteria. [2] Currently, *Salmonella Enterica* and *Salmonella bongori* are the two varieties that make up the genus *Salmonella*. [3] Using the usual Kauffman–White system, over 2600 serotypes of *Salmonella* have been identified within the genus. Of these serotypes, *Salmonella typhi* and *enteritidis* have been found to cause severe and occasionally fatal infections, as well as having major negative consequences. [4]

*Salmonella typhi* is a pathogenic bacterium which spreads by unhygienic circumstances. The Faecal-oral route serves as a primary form of transmission; however, because the bacteria may persist in the environment for lengthy periods of time, new data indicate that indirect transmission may also occur. [5] The "five Fs"—food, fingers, flies, fomites, and faeces—play a significant part in the disease's transmission. Infected individuals and healthy carriers are one of the major source of infection. [6] Human-to-human transmission is the mode of propagation for *Salmonella typhi*, which lacks a zoonotic reservoir and has a limited capacity for extended environmental survival. [7]. Typhoid fever, also known as enteric fever, is predominantly found in tropical and subtropical areas. While it's a global disease, it's mainly seen in developing nations with substandard sanitation. In developed countries, typhoid fever has become rare, with most cases either contracted during international travel or brought in by immigrants.[8] Around 3.5 billion individuals are believed to be impacted, with 450 million experiencing illness from these infections, predominantly children. Intestinal parasites and enteropathogenic bacteria are transmitted either directly or indirectly via items tainted with feces. [9] A 2018 research in Pakistan analyzed 798,137 blood cultures and found 17,387 positive for *Salmonella typhi* and 8,286 positive for *Salmonella paratyphi* A and B. The data indicates a decreasing trend in typhoid cases. Specifically, the rate of *Salmonella typhi* positivity dropped from 6.42% in 1992 to 1.32% in 2015, while *Salmonella paratyphi* (A and B) decreased from 1.29% to 0.39%. A more detailed analysis showed that *Salmonella typhi* was more prevalent in adults over 18, whereas *Salmonella paratyphi* was more common in children between 5-18 years. Interestingly, the proportion of *Salmonella paratyphi* cases out of the total confirmed cases grew from 16.8% in 1992 to 23% in 2015. [10] In 2017, worldwide figures revealed that enteric fever led to 14.3 million cases and 135,900 deaths, with *Salmonella* being responsible for 76.3% of these cases. Additionally, on an annual basis, enteric fever accounts for around 11–20 million cases and results in 128,000 to 161,000 deaths. Paratyphoid fever, on the other hand, causes 6 million cases and leads to 54,000 deaths globally each year. [11] In 2019, the Global Burden of Disease study approximated that there were 9.25 million typhoid fever cases, leading to 110,000 deaths. The vast majority of these fatalities took place in sub-Saharan Africa. [12] Each year in South Asia, over 7 million individuals contract infections, resulting in a mortality rate of 10%. The development of antimicrobial resistance is a natural process where infectious organisms evolve in response to exposure to antimicrobial substances. [13]. The study conducted on the calculated frequency of positive blood culture in the diagnosed cases of enteric fever

and antibiotic sensitivity patterns in culture positive cases of *Salmonella typhi*. According to the findings multidrug resistant (MDR) and extensive drug resistant (XDR) strains of *Salmonella* strains are a crucial clinical concern. Azithromycin remains the best oral antibiotic with a sensitivity of up to 96.7% in the aforementioned cases. In 100% of the cases Meropenem was sensitive and was the sole antibiotic with no documented resistance in the performed study. [14]

Similarly, the investigation of the patterns and frequency of multidrug resistant and antibiotics resistance lead to several results, involving an extensive study of resistant strains of *Salmonella typhi* and *Salmonella paratyphi* amongst children showing signs of enteric fever. The conclusion showcased an alarming pattern of antibiotic drug resistance mainly in children with enteric fever located in Lahore. The lowermost resistance was recorded for meropenem, imipenem and azithromycin. Their results claimed an immediate application of custom-made infection control strategies and antibiotic stewardship. [15]

The study described the typhoid vaccination in children reporting limited efficacy. While, Vi-polysaccharide and live attenuated vaccines provide 60 to 80% protection but its disadvantage lies in its needful re-administration within 24–36 and 60 months. Furthermore, both vaccines fail to work in children aging less than 24 months, making it difficult to incorporate typhoid vaccination into their vaccination programs, mainly in under developing countries. In addition, new drugs can be produced to restrain the resistance to antibiotics with proper monitoring of drug usage. This altogether with prescription and awareness of how to use will possibly lessen the burden of *Salmonella typhi* infection across the globe. [16].

## **AIM AND OBJECTIVES**

The aim of the study was to determine antimicrobial resistant pattern of *Salmonella typhi* isolated from children under age twelve years. Following the objectives of the propose study:

- To find out frequency of Multi drug resistant and Extensive drug-resistant strains of *Salmonella typhi* in children.
- Determination of antimicrobial susceptibility profile of the isolated strains.

## **Methodology:**

### **Study Design**

The current study was cross sectional and conducted between periods of February to July 2025.

### **Study Setting**

This study was conducted in Microbiology Laboratory of Hayatabad Medical Complex Hospital Peshawar.

### **Sampling Technique**

Convenient sampling technique was employed in the current study. Only blood sample referred to laboratory for culture sensitivity profile were analyzed.

### **Sample Size**

In the present study total sample size was 287. The sample size was calculated through online sample size calculator on the basis of prevalence of *Salmonella typhi* (50%) with 95% confidence interval and 5% margin of error as shown in Figure 3.1.

**Sample Size: 287**

This means 287 or more measurements/surveys are needed to have a confidence level of 95% that the real value is within  $\pm 5\%$  of the measured/surveyed value.

### Sample Selection

#### Inclusion Criteria

Confidence Level: ?	95%	▼	
Margin of Error: ?	5	%	
Population Proportion: ?	50	%	Use 50% if not sure
Population Size: ?	70000		Leave blank if unlimited population size.
<b>Calculate</b> ▶		Clear	

Children refer to laboratory for blood culture sensitivity test were included.  
All blood culture positive samples for *Salmonella typhi* were included in the study.  
Children of both gender with age limit between 2 and 12years were included.

#### Exclusion Criteria

Children age limit less than 2years and above 12years were excluded.  
Blood culture positive for other bacterial strains were excluded.

### Sample Processing

#### Sample Collection

All the blood samples were collected aseptically according to standard microbiological protocols. About 5-10ml of blood was collected and dispensed into blood culture bottles and transported into microbiology section for further process.

#### Initial Incubation

After the collection of the blood sample, the initial incubation was done at 35-37°C in BacT/ALERT-3D system (Abbott). The BacT/ALERT is an automated blood culturing system continuously monitored the bottles for signs of microbial growth, often by detecting CO<sub>2</sub> production or other metabolic indicators. The machine often signaled a positive result based on the detection of bacterial metabolism. If no growth was detected after 5-7 days of incubation, the culture was typically reported as negative.

#### Preparation of blood agar

Blood agar was prepared according to the instructions provided by company (Oxoid) by dissolving 40gram powder in one liter of distilled water. Boiled to dissolved powder completely and autoclaved at 121<sup>0</sup>C for 15-20 minutes. After cooling to 50<sup>0</sup>C, sheep blood (5%) was added and mixed well. About 15-20ml of media was dispensed into each petri-dish.

#### Preparation of MacConkey agar

MacConkey agar was prepared according to the instructions provided by company (Oxoid) by dissolving 40gram powder in one liter of distilled water. Boiled to dissolved powder completely and autoclaved at 121<sup>0</sup>C for 15-20 minutes. After cooling, about 15-20ml of media was dispensed into each petri-dish.

#### Sub-Culturing

A blood culture bottle signaled positive or showed sign of growth was sub cultured on solid bacteriological media. About 1-2ml of blood samples collected from culture

bottle and streaked on blood agar and MacConkey agar plates. All the inoculated plates were incubated at 37<sup>0</sup>C for 24 hours

### **Identification of Organism**

Identification of the organism was done on the basis of colonial characteristics, gram stain and biochemical tests like triple sugar iron (TSI), Indole, Urease and Citrate Utilization.

### **Growth characteristics on Blood agar and MacConkey agar**

Salmonella produced grey white, non-hemolytic colonies measuring about 2-3mm in diameter (Annexure A). While on MacConkey agar it produced non lactose fermenting, colourless colonies measuring about 2-3mm in diameter (Annexure B).

### **Gram Staining**

Gram stain is used to differentiate between Gram positive and Gram negative bacteria. Gram smear was prepared by using a single isolate colony and mixed with normal saline drop on clean glass slide. After fixation covered the smear with crystal violet stain and waited for 1 minute. Washed with tap water and applied gram iodine for 30 seconds. Again washed with tap water and applied Gram decolorizer for 30 seconds. After washing with tap water covered the slide with counter stain (safranin) and waited for 60 seconds. After washing and drying examined the smear under microscope by using 100 power lens. *Salmonella* was looking pink color red and considered Gram negative.

### **Biochemical Tests**

We performed a series of biochemical tests to confirm the identity of the isolated colonies as *Salmonella typhi*. Some common tests included:

#### **Triple Sugar Iron (TSI) Agar Test**

We observed the reaction on TSI agar. *Salmonella typhi* typically produced an alkaline/alkaline reaction with no gas production and no H<sub>2</sub>S production. The slant and butt of the TSI agar were red.

#### **Indole Test**

We determined if the bacterium produced indole. *Salmonella typhi* was typically indole- negative.

#### **Antimicrobial susceptibility**

The Kirby-Bauer disk diffusion method for *Salmonella typhi* involved inoculating a Mueller- Hinton agar plate with a standardized bacterial suspension of the pathogen. Antibiotic disks containing specific antibiotics were placed on the agar surface, and the plates were incubated at 35-37°C for 16-18 hours. After incubation, the diameters of the clear zones of inhibition around each antibiotic disk were measured and compared to established interpretive criteria, typically provided by organizations like CLSI (2021). These criteria helped determine the susceptibility or resistance of the *Salmonella typhi* strain to the tested antibiotics, guiding the selection of appropriate treatment options. Results were recorded, reported, and used for clinical decision-making. Quality control measures ensured the accuracy and reliability of the test.

#### **Ethical Consideration**

Approval for data collection was obtained from the director of Hayatabad Medical Complex Hospital Peshawar Pakistan. The entire dataset was maintained confidential, and only the primary data collectors and supervisors were granted access.

**Results:**

Overall distribution of culture positive and culture negative cases shown in Table 4.1. A total of 287 cases were examined. Prevalence of *Salmonella typhi* was 119 (41.4%), while 168(58.6%) were culture negative, Gender wise distribution of culture positive cases are shown in Table 4.2, where number and percentage of male patients was higher 79(66.4%) than female 40(34.6%).

Table 4.1 Overall distribution of culture positive and culture negative cases

<b>cases</b>	<b>number</b>	<b>Percentage</b>
Culture Positive	119	41.4
Culture Negative	168	58.6
Total	287	100

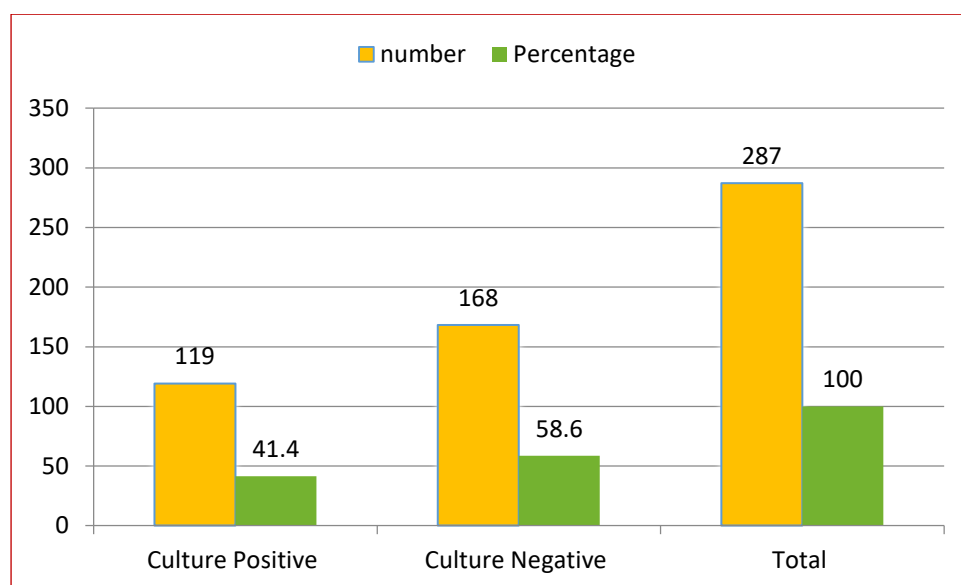


Figure 4. Distribution of culture positive and culture negative cases

Table 4.2 Gender Wise distribution of Positive cases

<b>Gender</b>	<b>Number</b>	<b>Percentage</b>
Male	79	66.4
Female	40	33.6

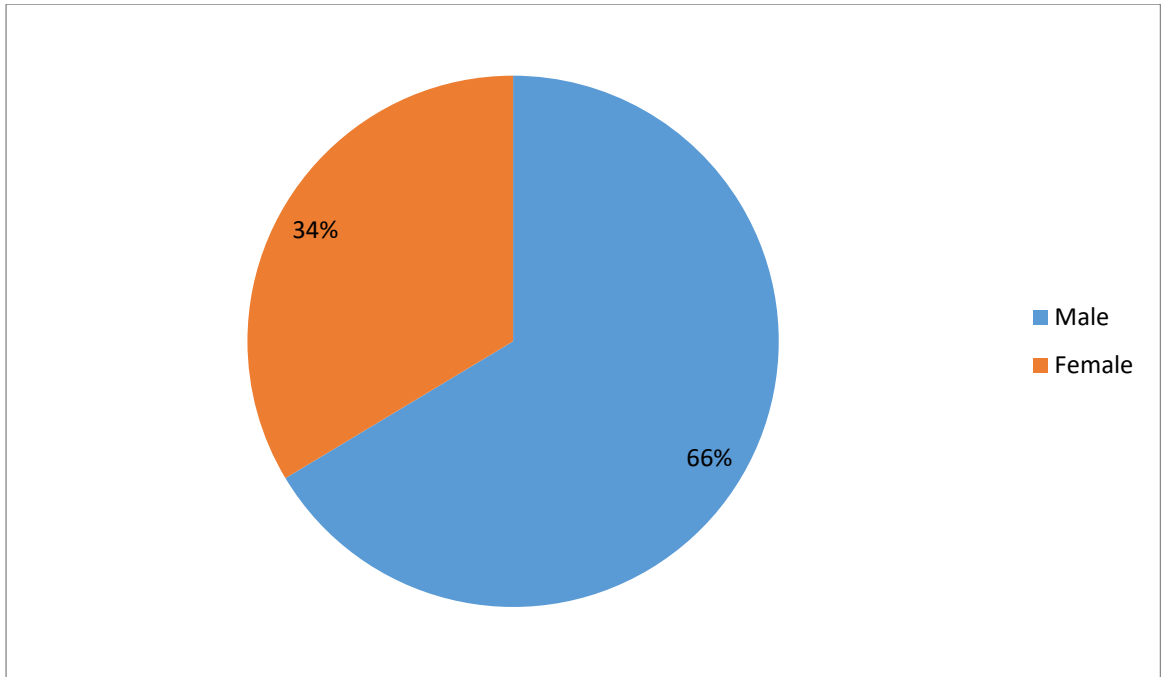


Figure 4.2 Gender wise distributions of culture positive cases

Age wise distribution of culture positive cases were shown in Table 4.3. Highest number of culture positive 40 (33.7%), 22 (18.5%) and 21 (17.6%) was observed in age groups (10-12 Years), (6.7 Years) and (8-9 years) respectively. Least number of patients 16 (13.4%) were noted in age group 2-3 years.

Table 4.3 Overall distributions of culture positives cases in different age Groups

Age Group	Culture Positive cases (Numbers)	Percentage
2-3 Years	16	13.4
4-5 Years	20	16.8
6-7 Years	22	18.5
8-9 Years	21	17.6
10-12 Years	40	33.7

Table 4.3 summarizes the distribution of cases based on their drug resistance patterns. Frequency of MDR strains was higher 91 (76. %) than XDR stains 17 (14.3%), while last number of cases 11 (9.2%) were found susceptible to antimicrobial agents.

Table 4.4 Distribution of MDR and XDR strains of Salmonella typhi cases

Cases	Number	Percentage
MDR	91	76.5
XDR	17	14.3
Susceptible	11	9.2

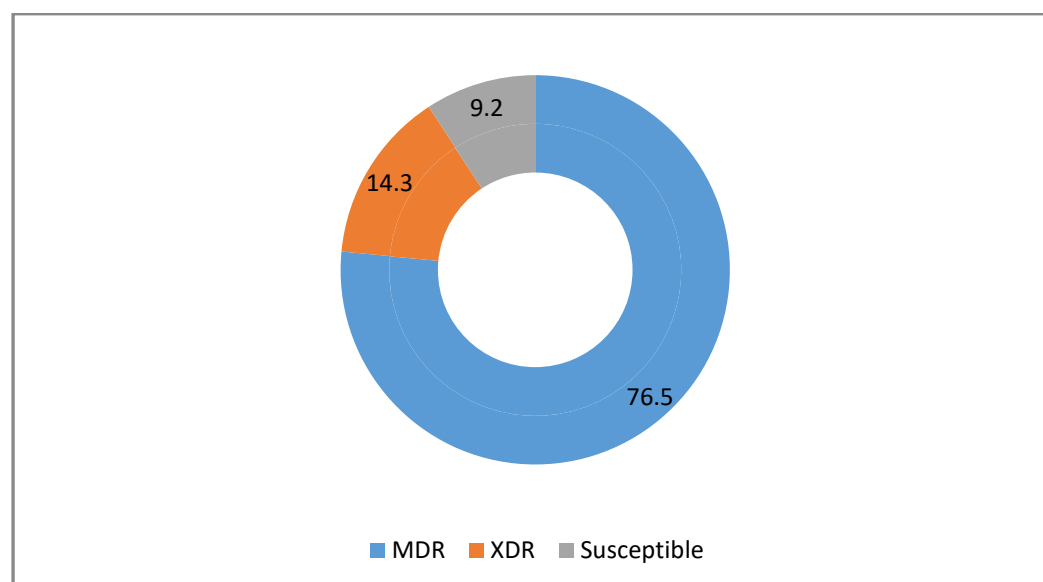


Figure 4.3 Distribution of MDR and XDR cases

Gender wise distribution of MDR and XDR Salmonella typhi strains summarized in Table 4.4 Multidrug resistant pattern was found higher 74.7% (Male) and 80% (Female) respectively. While frequency of XDR in male and female patients were 16.5% and 10% respectively. Least number of susceptible Salmonella typhi strains (male (8.8%) and female (10%) noted in both.

Table 4.5 Gender wise distribution of MDR and XDR cases

Gender	MDR		XDR		Susceptible	
	n	%	n	%	n	%
Male	59	74.7	13	16.5	7	8.8
Female	32	80	4	10	4	10

Distribution of Multidrug Resistant (MDR) and Extensively Drug-Resistant (XDR) cases across various age groups are shown in Table 4.5. Prevalence of MDR strains was higher 31 (34%) in age group (10-12 years) followed by 18 (19.8%) in age group (8-9 Years) and 15 (16.5%) and 15 (16.5%) in age groups (4-5 Years) and (6-7 Years) respectively. Least number 12 (13.2%). While on other hand frequency of XDR Salmonella typhi was 5 (29.4%), 4 (23.5%) and 3 (17.6%) in age groups (4-5 Years),

6-7 Years), (10-12 years) and 2-3years) respectively. Only one case of XDR Salmonella typhi strains noted in age group (8-9years).

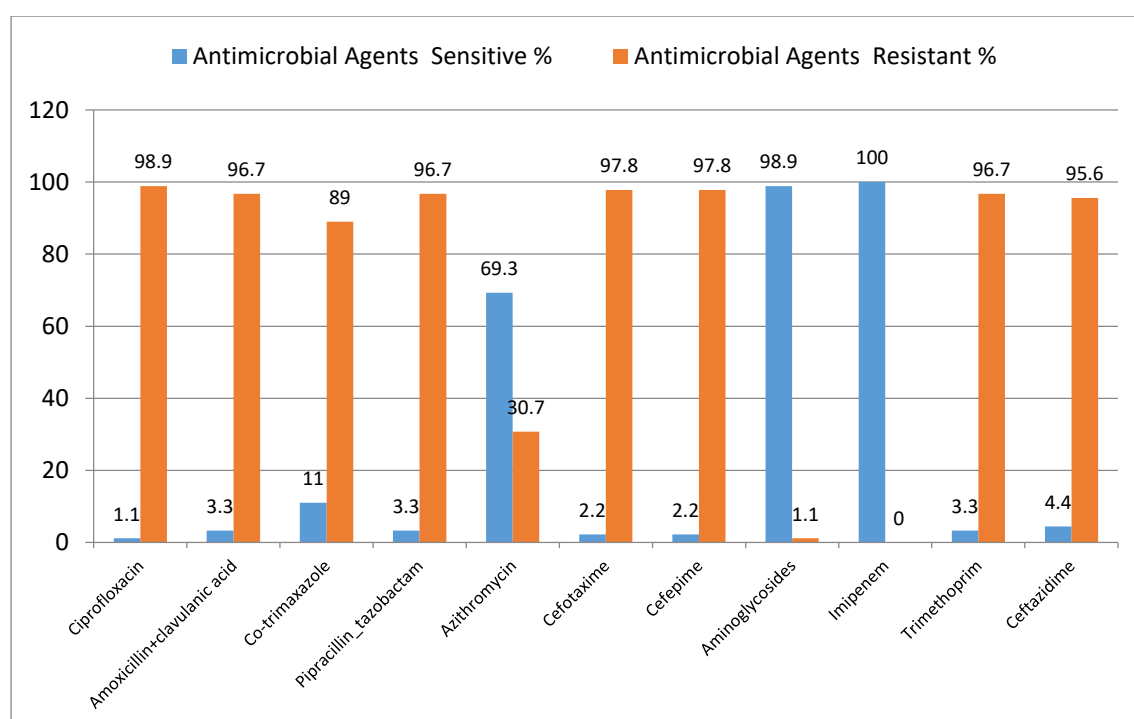
Table 4.6: Overall distribution of MDR and XDR cases in different age groups

Age Groups	MDR n (%)	XDR n (%)	Susceptible n (%)
2-3 Years	12 (13.22)	03 (17.6)	01 (9.1)
4-5 Years	15 (16.5)	05 (29.4)	00
6-7 Years	15 (16.5)	04 (23.5)	03 (27.3)
8-9 Years	18 (19.8)	01 (5.9)	02 (18.2)
10-12 Years	31 (34)	04 (23.5)	05 (45.4)
Total	91 (100)	17 (100)	11 (100)

Antimicrobial susceptibility profile of MDR Salmonella typhi shown in Table 4.6. Salmonella typhi showed high resistance against ciprofloxacin (98.9%) followed by cefepime (97.8%), cefotaxime (97.8%), trimethoprim (96.7%), amoxicillin+clavulanic acid (96.7%), piperacillin+tazobactam (96.70%), Ceftazidime (95.6%) and co-trimoxazole (89%). Imipenem, aminoglycoside and azithromycin were 100%, 98.9% and 69.3% effect typhi against Salmonella typhi respectively.

Table 4.7 Resistant and Sensitivity of MDR case to drugs.

Antimicrobial Agents	Sensitive		Resistant	
	n	%	n	%
Ciprofloxacin	1	1.1	90	98.9
Amoxicillin+clavulanic acid	3	3.3	88	96.7
Co-trimaxazole	10	11	81	89
Pipracillin_tazobactam	3	3.3	88	96.7
Azithromycin	63	69.3	28	30.7
Cefotaxime	2	2.2	89	97.8
Cefepime	2	2.2	89	97.8
Aminoglycosides	90	98.9	1	1.1
Imipenem	91	100	00	00
Trimethoprim	3	3.3	88	96.7
Ceftazidime	4	4.4	87	95.6



## DISCUSSION

In a study conducted by Shah et al., [17] involving a total of 81 patients with confirmed culture positivity, a gender distribution of 59% male and 41% female was observed. The research findings highlighted that *Salmonella typhi* exhibited the highest sensitivity to imipenem (100%) and azithromycin (95%), while showing the lowest sensitivity to ciprofloxacin. These findings are an agreement with the current study, encompassing 119 positive cases, revealed a gender breakdown of 66.4% male and 33.6% female. Notably, in cases of multi-drug resistance and extensive drug resistance strains of *Salmonella*, imipenem showed highest sensitivity 100% and 64.7%, respectively. This emphasizes the significant role of imipenem in the context of drug-resistant strains of *Salmonella typhi*.

A previous study conducted by Zakir et al., [18] where 600 culture positive cases of *Salmonella typhi* were obtained. Majority of cases were XDR (46.1%) followed by MDR (24.5%). Only 21.3% cases were susceptible to various antimicrobial agents. In the current study 119 culture positive of *Salmonella typhi* were examined. Prevalence of MDR and XDR *Salmonella typhi* strains were 76.5% and 14.3% respectively. Small number of cases (9.2%) were found susceptible to various antimicrobial agents. Some dissimilarities observed between the findings in the current study and former study. This difference in antimicrobial resistance pattern in *Salmonella typhi* in the present study may be contributed by irrational use of antibiotics, sub-optimal doses, self-prescription and quack practices common in this region.

In the current study highest positive cases of *Salmonella typhi* were noted in the age group 10-12 years (33.7%). In the previous study of Zakir et al., (2021), frequency of this bacterial strains were higher 69.8% in the same age group. Furthermore, the later study also showed frequency of *Salmonella* strains in other age groups. This difference in both studies may be due to large sample size in the later study.

A study conducted by Hussain et al., [19] they noticed that *Salmonella typhi* showed high resistance to ciprofloxacin (91%). Frequency of MDR and XDR strains of *Salmonella typhi* were 64% and 22% respectively and 14% cases were found susceptible. In the current study *Salmonella typhi* was also highly resistant to ciprofloxacin (98.9%). While frequency of MDR (76.5%), XDR (14.3%) and susceptible *Salmonella typhi* was 76.5%, 14.3% and 9.2% respectively. These findings showed similarities with aforementioned study.

In the present study azithromycin was considered drug of choice in cases of multi drugs resistant strains of *Salmonella typhi*, while on other hand this antimicrobial agent was found less effective against extensive drug resistant strains of *Salmonella* species. In the previous study of Shahid et al., [41]. Azithromycin and meropenem in combination were found effective against this bacterial species in children of age group 2-8years. According to gender wise distribution in the present study, frequency of XDR *Salmonella typhi* cases in male and female were (76.5%) and (23.5%) respectively. These findings nearly similar to the previous study.

A previous study conducted by Ghumee et al., [20] in their study they noticed that ciprofloxacin showed no effect against tested isolates and aminoglycosides were most sensitive against XDR and MDR strains of *Salmonella typhi*. In the current study, ciprofloxacin showed no effect against *Salmonella typhi*, which support the previous study however, aminoglycoside was found less effective against this bacterial strains. Imipenem was only drug of choice against MDR and XDR strains. It has been noted that carbapenem is last option for treatment of typhoid fever caused by XDR strains of *Salmonella typhi*.

A study was conducted by Rasheed et al., [21] they include 235 cases in their study among which (70.6%) were MDR and (29.4%) were XDR. *Salmonella typhi* show maximum resistance to 1 line drugs i-e ampicillin (79.4%) and co-trimaxazole (67.2%). In current study 119 cases are included in study out of which (76.5%) were

MDR and (14.3%) were XDR cases. In current study *Salmonella typhi* showed maximum resistant to nucleic acid inhibitor and cell wall inhibitors.

A previous study done by Amber et al., [22] where the frequency of XDR strains of *Salmonella typhi* was 32.6%, while in the present study only 14.3% strains were found extensive drug resistance. This disagreement may be due to small sample size in the present study.

In the comprehensive investigation conducted by Izhar et al. in [23] they delved into the sensitivity patterns of various antibiotics in the context of *Salmonella typhi* infections. Their findings unequivocally indicated that Meropenem emerged as an antibiotic with heightened sensitivity, showcasing its potential efficacy in combating *Salmonella typhi*. Intriguingly, the study also spotlighted chloramphenicol and augmentin as antibiotics with the highest resistance rates, underscoring the challenges associated with their use in treating this particular bacterial infection. In the present study these MDR and XDR strains of *Salmonella typhi* showed high resistance to the aforementioned antimicrobial agents. Based on the evidence of the current study seeks to contribute to the evolving landscape of antibiotic efficacy against *Salmonella typhi*. In our investigations, we have identified imipenem as the antibiotic exhibiting the highest sensitivity, suggesting its potential as a frontline treatment option for *Salmonella typhi* infections. This new insight adds a nuanced layer to the existing knowledge base, potentially influencing clinical practices and antibiotic prescription strategies.

## CONCLUSION

Overall prevalence of *Salmonella typhi* was (41.4%) in children. Prevalence of MDR strains was higher (76.5%) than XDR strains (14.3%), while least number of cases (9.2%) was found susceptible to antimicrobial agents. Imipenem, Aminoglycosides and azithromycin were highly effective against Multi drug resistant cases of *Salmonella typhi*. Imipenem is the only drug which was found effective against extensive drug resistant cases of *Salmonella typhi*. High prevalence of MDR and XDR was observed in the age group 10-12years as 33.7%.

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