

Current Rise of Extensive Drug Resistant Salmonella Cases in a Tertiary Care Hospital of Karachi, Pakistan

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ABSTRACT

Objective: To assess antimicrobial surveillance of bacteremia isolates of Salmonella typhi and paratyphi.

Study Design: A descriptive retrospective observational study

Place and Duration of Study: This study was conducted at the Department of Microbiology, Dow University Research and Referral Laboratory from April 2021 to, March 2022.

Materials and Methods: Blood culture Reports from April 2021 to, March 2022 was obtained from laboratory data. About 8329 laboratory reports were collected. The data transferred to Microsoft excel and final analysis was performed by using Statistical Package for Social Science (SPSS) version-20. The categorical variables were interpreted as frequencies and percentages of isolated organism and their antibiotic susceptibility pattern was presented graphically.

Results: Majority of the typhoid cases were seen in children less than 15 years of age (mean value and standard deviation for age statistically was 9.6 and 9.2 respectively). Males were more affected (59%). There is no association of age and gender with the occurrence of typhoid fever as the p-value was more than 0.05. Total of 8329 cases were suspected for typhoid during April 2021 to March 2022, out of which 699 (8%) cases were positive for typhoid. Among 699 positive typhoid cases, 71% were extremely drug resistant while 15% cases were multi drug resistant. Maximum confirmed cases of typhoid were reported during the month of September to November. Out of 699 confirmed typhoid cases, only 173 (24%) cases were having known vaccination status.

Conclusion: The susceptibility of Salmonella typhi and paratyphi against recommended antibiotics is 8% while majority of cases were having extremely drug resistant (71%) followed by multi drug resistant strain (15%). The most commonly affected age group was children under 15 years of age.

Key Words: Surveillance, Typhoid, Salmonella typhi, Extremely drug resistant, Multi drug resistant.

Citation of article: Fatima A, Gohar H, Siddiqui HZ, Mehdi RF, Naseem S, Khan FZ. Current Rise of Extensive Drug Resistant Salmonella Cases in a Tertiary Care Hospital of Karachi, Pakistan. Med Forum 2023;34(9):32-36. doi:10.60110/medforum.340908.

INTRODUCTION

Enteric fever (typhoid fever) is still a major health problem in Pakistan. It is caused by Gram negative bacteria called Salmonella enterica serovars typhi and paratyphi, which is acquired through ingestion of fecal contaminated food and water.¹

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Received: January, 2023

Accepted: June, 2023

Printed: September, 2023

The clinical presentation of the acute infection is nonspecific and indistinguishable from other infection diseases. However, if not treated timely it can progress to serious complications that can result in death of a patient.² Case fatality rate of typhoid fever is 10-30 % and it goes down to 1-4% with proper therapy. According to updated statistic, it account for between 11 and 21 million cases and responsible for mortality of around 1280000 to 161000 per year globally.³⁻⁵ It has been reported that about 0.25 million deaths in Pakistan are due to water-borne diseases specially typhoid fever.⁶

Antibiotics are being used to cure Enteric fever and decreases the mortality related to complicated cases. However, bacteria acquired resistance against first line antibiotic that includes ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol which were labelled as Multi drug resistant (MDR) typhoid . Next option that was used to treat these infections was use of fluoroquinolones. Yet again in early 2000 it loses its efficacy and bacteria acquired resistant against it especially in Southern part of Asia.^{7,8} This has led to

the usage of third-generation cephalosporin (e.g. Ceftriaxone) as a recommended first-line treatment.⁹ Similarly high level of fluoroquinolones and third generation cephalosporin resistance in *S.typhi* has been reported from Pakistan.^{8,10}

Recently, outbreak of extensive drug resistance (XDR) has been reported in November 2016 in Hyderabad district of Sindh and 339 cases were reported till September 2017. XDR typhi strains are resistant to ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol, ciprofloxacin and third generation cephalosporins(cefixime, ceftriaxone).

Most of the cases were from Karachi and Hyderabad.³ Moreover, a country like Pakistan where antimicrobial surveillance is not strengthened it has been a serious concern. Keeping surveillance of resistance trends among isolates, monitoring rational use of antibiotics, and standardized clinical treatment guidelines can be useful strategies in restricting the development of resistance against the carbapenems and azithromycin which are the current treatment options for XDR typhi. So the aim of study was to find out antimicrobial surveillance of bacteremia isolates of *Salmonella typhi*.

MATERIALS AND METHODS

A descriptive retrospective observational study was carried out in the Department of Microbiology, Dow University Research and Referral Laboratory. Study got ethical approval from the concerned institute (Ref: IRB-2586/DUHS/EXEMPTION/2022/931). After approval blood culture reports from April 2021 to March 2022 was obtained from laboratory data. Convenient sampling technique was used for data collection. Patients who were admitted or visited outpatient department with history of fever of more than three days were included, while patients whose blood culture did not show growth of *Salmonella typhi* and patients whose blood culture did show growth of *Salmonella typhi* but had history of fever of less than three days were excluded from the study.

BacT /ALERT, a totally automated system was used to monitor blood cultures. Gram stain was performed on positive blood cultures for organism identification and inoculated for isolation on Chocolate, Sheep Blood and Mac Conkey agar. Chocolate and Sheep Blood agar were incubated at 35°C and Mac Conkey agar in ambient air for 24 hours. Biochemical tests like sulphide, indole, motility, urea, citrate and triple sugar iron along with serologic testing and API20E was performed for organism identification. Antimicrobial susceptibility testing (AST) was done against following antibiotics with their disc content are ampicillin (AMP) 10µg, ceftriaxone (CRO) 30µg, ciprofloxacin (CIP) 5µg, trimethoprim-sulfamethoxazole (SXT) 1.25/23.75µg, cefixime (CFM) 5µg, chloramphenicol (C) 30µg, azithromycin (AZM) 15µg and meropenem (MEM) 10µg. These antibiotics were interpreted as per CLSI guidelines.

The data transferred to Microsoft excel and final analysis was performed by using Statistical Package for Social Science (SPSS) version-20 to find out antimicrobial susceptibility pattern of bacteremia isolates of *Salmonella enterica* serovars typhi. The categorical variables were interpreted as frequencies and percentages of isolated organism and their antibiotic susceptibility pattern was presented graphically.

RESULTS

Majority of the typhoid cases were seen in children less than 15 years of age with frequency of 33%, 28% and 14% in the age group of 1-5 years, 5-10 years and 10 to 15 years respectively as presented in Figure 1.

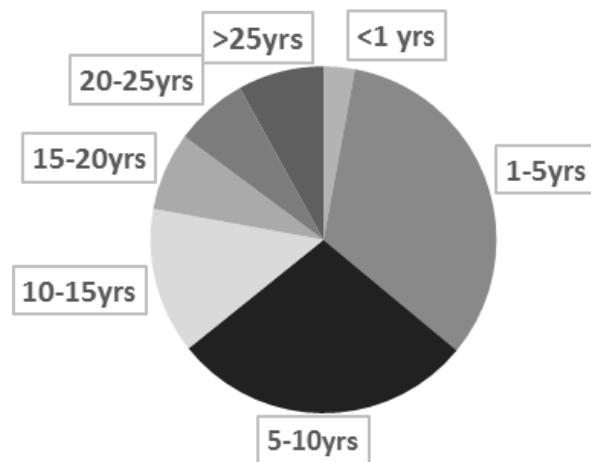


Figure No. 1: Age distribution of confirmed typhoid cases

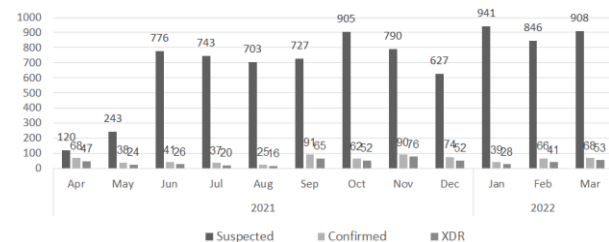


Figure No. 2: Suspected Typhoid, Confirmed & XDR cases by month

Males were more affected (59%) as compare to females (41%). There is no association of age and gender with the occurrence of typhoid fever as the p-value was more than 0.05. Total of 8329 cases were suspected for typhoid during April 2021 to March 2022, out of which 699 (8%) cases were positive for typhoid in blood culture. Out of total confirmed cases, majority of cases (71%) were extremely drug resistant while 15% cases were multi drug resistant and 14% cases were non-resistant to antibiotic. In all non-resistant cases maximum confirmed cases of typhoid were reported during the month of September to November as mentioned in Table-1.

Table No. 1: Lab Confirmed Typhoid Report with culture and sensitivity

Month	Confirmed Cases	Non-resistant		Multi-drug resistant		Extensive-drug resistant	
		n	%	n	%	n	%
Apr-21	68	12	39.7	9	13.2	47	69.1
May-21	38	6	15.8	8	21.1	24	63.2
June-21	41	8	19.5	7	17.1	26	63.4
July-21	37	4	10.8	13	35.1	20	54.1
Aug-21	25	6	24.0	3	12.0	16	64.0
Sept-21	91	16	17.6	10	11.0	65	71.4
Oct-21	62	5	8.1	5	8.1	52	83.9
Nov-21	90	12	13.3	2	2.2	76	84.4
Dec-21	74	10	13.5	12	16.2	52	70.3
Jan-22	39	3	7.6	8	20.5	28	71.8
Feb-22	66	5	7.7	20	30.3	41	62.1
Mar-22	68	8	11.8	7	10.3	53	77.9
Total	699	95	14	104	15	500	71

The monthly suspected, confirmed, non-resistant, MDR and XDR cases of typhoid are presented Figure 2. The susceptibility pattern of all positive cases are presented in Table 2.

Table No. 2: Antibiotic susceptibility pattern of Salmonella typhi

Susceptibility of antibiotics		
Antibiotics	Salmonella.typhi n=699	
	Resistance in numbers	Resistance in %
Ampicillin (AMP)	604	86.4
Chloramphenicol (C)	604	86.4
Trimethoprin-Sulfamethoxazole (SXT)	604	86.4
Ciprofloxacin (CIP)	699	100
Cefixime (CFM)	500	71.5
Ceftriaxone (CRO)	500	71.5
Azithromycin (AZM)	0	0
Meropenem (MEM)	0	0

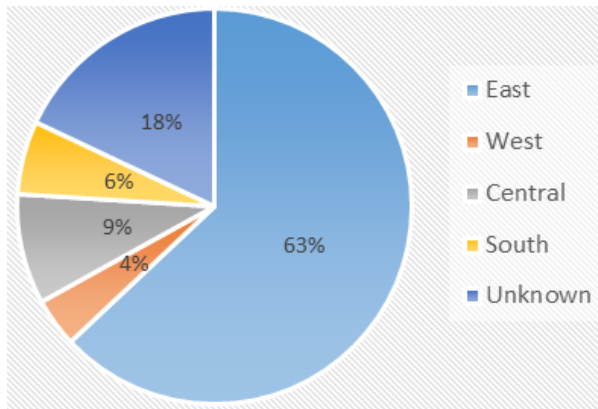


Figure No. 3: District wise Confirmed typhoid and XDR cases April 2021 to March 2022

Majority of confirmed typhoid XDR cases were reported from east district of Karachi (63%) while very few of the cases (6%) from south district as presented in Figure 3.

Out of 8329 suspected typhoid cases, about 2695 cases were having known vaccination status, on the other hand, out of 699 confirmed typhoid cases, only 173 cases were having known vaccination status.

DISCUSSION

Current study found a high incidence rate among children younger than 15 years of age. The finding is supported by many other studies as well.¹¹⁻¹⁴ Literature review revealed that majority of cases are seen under two years of age.^{13,15} Suherti et.al in 2022, did a systematic review of population in Karachi and reported 506 cases of typhoid per 100000 were under 12 months of age which is a very high incidence rate. In his study he also noted the risk factors and reported that lack of exclusive breast feeding might be the possible cause of this high incidence rate among infants.¹⁶ Another study conducted in Lahore found only two cases of typhoid with age less than six months, among them one was 12 days old.¹⁵ But the current study reported about 21 confirmed cases of typhoid were having age less than 12 months. Current study found that males were more affected (59%) as compare to their counterpart. The same results are reported in other studies like Yousafzai et.al found 56.4% affected cases were male¹³ while Qamar et.al reported 65.7% of male cases.⁸

Literature revealed that the XDR strain of S.typhi is increased while MDR strain is decreased in 2019 in comparison to 2018.¹⁵ In Pakistan there is the outbreak of typhoid in Hyderabad, Sindh during the year of 2016-2017, in which majority of typhoid strains were extensive drug resistant.³ After the outbreak in Sindh, a study conducted in Punjab in

2018-2019, the study reported 14 confirmed XDR S.typhi strains cases in 2018 which was increased to 58 XDR S. typhi strains in 2019, so the study concluded a rising trend of XDR typhoid cases.¹⁵ Current study found a further increase, out of 699 confirmed typhoid cases, 500 cases were of XDR S.typhi strains. The first line agents for typhi including ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole showed resistance of 86.4%. Bacterial resistance to cefixime and ceftriaxone was 71.5% which is alarming since these are commonly used empirical agents against Salmonella. According to latest report of National institute of health (NIH Islamabad), total of 7646 cases of typhoid were reported out of which 4763 cases were XDR S.typhi.¹⁷

Current study also found that majority of confirmed typhoid XDR cases were from east district of Karachi (63%) while only 6% cases from south district of Karachi. This variation is might be due to the illiteracy, poor hygienic condition and poor sanitation status in the east region of Karachi. Few other studies conducted in Karachi also favored this finding by reporting higher incidence of typhoid fever in those areas of Karachi where people poorly maintained their hygienic conditions.^{18,19} A study conducted in Dhaka metropolitan area reported higher incidence rate during the season of monsoon because of increased transmission of water borne pathogens in densely populated area and less awareness but the association was non-significant.²⁰ A study conducted in Fiji concluded that poor sanitation facilities appear to be a major source of Salmonella typhi, with transmission by drinking contaminated surface water and consuming unwashed produce.²¹ Preventive strategies such as immunization and improvements in water and sanitation conditions should be the focus of typhoid control.²²

High incidence rate of typhoid among children raises the question about vaccination status as shown by the local studies.^{23,24} In Pakistan, the current protocol of typhoid vaccination is for children above two years of age but the current study and few other studies reported the infected cases before reaching the age of two years. Besides that, typhoid vaccination is not included in the extended program of immunization (EPI) in Pakistan but countries like China, India and Vietnam have a routine program of typhoid vaccination.²⁵ This is the reason behind poor typhoid vaccination status and high incidence rate of typhoid cases in Pakistan. Current study also observed a poor vaccination status, only 24% of cases were having known vaccination status. There is a need to strengthen the EPI program and vaccination of high risk areas, beside that there should be public awareness campaign regarding the spread of typhoid fever.

Limitations: Due to budget constraint findings cannot be confirmed by molecular level.

CONCLUSION

The study concluded that out of 699 positive isolates of Salmonella typhi, 71% were extremely drug resistant followed by 15% multi drug resistant strain and 14% nonresistant typhoid. The most commonly affected age group was children under 15 years of age.

Author's Contribution:

Concept & Design of Study: Ambreen Fatima
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 Revisiting Critically: Ambreen Fatima, Hareem Gohar
 Final Approval of version: Ambreen Fatima

Conflict of Interest: The study has no conflict of interest to declare by any author.

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