ORIGINAL ARTICLE

The frightening disease burden of blood culture proven XDR typhoidal isolates in pediatric population in federal territory: Time to implement a holistic approach countrywide

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ABSTRACT

Background: Typhoid fever is a deadly enteric bacterial infection and millions of people all over the globe are endangered of acquiring it. Since the first outbreak of XDR typhoid in Pakistan in 2016, the ever-rising resistance of typhoid has become a major threat faced by the pediatric population of Pakistan. There is a dearth of available data in children harboring this extensively drug resistant pathogen countrywide. The objective of this study is to highlight the alarmingly increasing prevalence of XDR S. typhi in pediatric population in Federal territory in Pakistan.

Material and Methods: This Cross-sectional study was conducted at Microbiology Lab, Children Hospital, PIMS from June 2022 to May 2023. Blood culture samples of children (with strong clinical suspicion of typhoid) ranging one till 12 years (both genders).

Result: Out of a total of 245 typhoid suspected blood culture samples, 153 (62%) samples yielded growth of typhoidal Salmonella isolates with 109 (71 %) isolates proved as XDR *Salmonella Typhi* ,35 (23%) as MDR *Salmonella Typhi* and the rest 09 cases (6 %) were *Salmonella paratyphi A.* There was a male predominance of 96(63%) and the rest 57(37%) were females. Age range most commonly affected was 5-8 years followed by 9-12 yrs. There was 100% susceptibility to Meropenem in XDR typhoid cases and 99% XDR cases were susceptible to Azithromycin.

Conclusion: We concluded that there is widespread existence of MDR/ XDR *S.typhi* in pediatric population in federal territory as well as all over Pakistan but there is scarcity of documented data nationwide. Hence, our study signifies that a holistic approach should be implemented along with continuous ongoing surveillance to combat this frightening MDR/ XDR disease burden in this particular population.

Key Words: *Salmonella Typhi*, Extensively Drug Resistant (XDR), Typhoidal isolates

BACKGROUND

Typhoid fever is a deadly enteric bacterial infection caused by Salmonella enterica serotype typhi.[1] This disease is marked by clinical manifestations such as step-ladder patterned high-grade fever, chills, headache, muscle aches, loss of appetite and gastrointestinal issue (nausea, vomiting, constipation or diarrhea).[2,4] In addition, Paratyphoid fever caused by Salmonella enterica serovar paratyphi A, B, and C (*S. paratyphi*) also depicts a similar clinical picture but is often less severe.[1,2] Salmonella bacterium has a fecal-oral transmission and is usually contracted by consuming this microbe in contaminated food or water. It predominantly proliferates in poverty-stricken areas with poor socioeconomic conditions. Therefore, countries with underdeveloped and weak infrastructure, poor sanitation practices and neglected food safety guidelines are more prone to have a higher burden of disease.[3,4] Millions of people all over the globe are endangered of acquiring typhoid and paratyphoid fever due to exposure to this pathogen which further contribute to the disease complications and even mortality.[5] More fresh reports propose that around 21 million contract typhoid every year, yielding to 161,000 cases ending in fatalness worldwide.[6]

It is alarming that despite of all major advances that have been made in health care and medicine, there is a lack of universal control over typhoid; posing a serious menace to human health due to the emergence of multi-drug resistance in this pathogen over the years through multiple mechanisms.[5] Hence, more powerful strains have emerged with the passage of time, namely Multi-Drug Resistant (MDR) typhoid i.e

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This article can be cited as: Wazir S, Farwa U, Khursheed S, Mushtaq M, Shafiq M, Ali MM. The frightening disease burden of blood culture proven XDR typhoidal isolates in pediatric population in federal territory; time to implement a holistic approach countrywide. Infect Dis J Pak. 2024; 33(1): 17-22.
DOI: https://doi.org/10.61529/idjp.v33i1.270

Receiving date: **06 Dec 2023** Acceptance Date: **27 Feb 2024**
Revision date: **14 Feb 2024** Publication Date: **30 Mar 2024**

resistant to all first line antibiotics; ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol, and extensively drug resistant (XDR) typhoid i.e resistant to all five antibiotics (including both first & second line anti- typhoidal antibiotics); chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones, and third- generation cephalosporins. The outbreak of XDR typhoid was perceived by the world for the first time in November 2016 when health care experts in Pakistan started to report cases of extensively drug- resistant (XDR) typhoid fever, originating in Hyderabad, Sindh. Afterwards, a huge inflow of blood-culture proven extensively resistant typhoid Fever (XDR -TF) cases that were noncompliant to customary therapy were reported.[7] During November 2016 till December 2018, 5274 cases of XDR typhoid fever were recorded out of a total of 8188 cases as per WHO reports. A big chunk among these cases belonged to two major cities of Sindh province with Karachi accounting for 69% of all cases of XDR followed by Hyderabad (27%). The residual 4% cases were dispersed amid other provincial districts of Sindh.[8,9]

It is noteworthy that beyond 80% XDR cases that emerged in the Sindh area consists of children less than 15 years and 18% are below 2 years.[10] Hence, the ever-rising resistance of typhoid has become a major threat faced by the pediatric population of Pakistan over the last few years. It is one of the key issue and main danger faced by the pediatric population sparing neither any region nor any of the pediatric age. Moreover, unluckily there is a dearth of available data in children harboring this extensively drug resistant pathogen countrywide.

The purpose of this study is to report the alarming rising trend of blood culture-proven XDR typhoidal isolates along with their antimicrobial susceptibility patterns in pediatric population in the Federal territory of Pakistan, hence signifying the urgent need to implement a holistic approach at national level to combat the disease burden of this resistant isolate in our population.

MATERIAL AND METHODS

This descriptive, cross-sectional study was conducted at Microbiology lab, Children Hospital, PIMS from June 2022 till May 2023 after taking ethical approval. Children Hospital comprises of a 250 bedded tertiary care set-up which accepts patients from Federal territory as well as AJK and northern areas of Pakistan. Blood cultures from patients of age one year till 12 year (both genders) who presented with the history of fever for last 3 days or beyond, lacking any other recognizable site of infection and strong clinical suspicion of typhoid fever were incorporated in the study. Samples were collected from outpatient as well as indoors. Children with a known focus of infection like upper respiratory tract infection, Otitis Media, and Pneumonia etc. or with a negative culture for Salmonella and identical samples of similar patient were omitted from the study. A simple, well-structured proforma was used to collect the relevant information including socio-demographic data of every patient as well as their water & sanitation practices. Blood sample was drawn from the patient for blood culture, inoculated in Versa TREK bottles, labeled and dispatched to pathology department as soon as possible. These bottles were then incubated in Automated microbial detection system i.e Versa TREK blood culture machine (Thermo Fisher Scientific, USA) and observed continuously for growth for five days. On the basis of machine identification, a positive signaled blood culture bottle was sub-cultured on Blood, Chocolate and MacConkey agar media plates. These media plates were incubated overnight and growth characteristics were observed the next day. Colonies suggestive of Salmonellae were identified and further dealt with based on the colony morphology and rapid biochemical tests.

The definitive identification of Salmonella upto species level was done with API 20E (Biomerieux, France). Serological confirmation was done with Salmonella serology kit (Bio-Rad, France). Antimicrobial susceptibility testing was carried out on Muller Hinton (MH) agar by using Kirby Bauer disc diffusion technique. The standard antibiotic disks i.e Ampicillin (10 µg), Co- trimoxazole (1.25/23.75 µg), Chloramphenicol (30 µg), Ciprofloxacin (5 µg), Ceftriaxone (30 µg) Azithromycin (15 µg) and Meropenem (10 µg) were tested and zone sizes were interpreted according to CLSI guidelines 2022. For quality control of antibiotic disks, *Escherichia coli* ATCC 25922 was used. For quality control of anti-sera, *Salmonella Typhi* ATCC 700931 and *Salmonella paratyphi* ATCC 9150 were used. SPSS version 28 was used for data analysis.

RESULTS

Over the study period from June 2022 to May 2023, a total of 245 blood culture samples with provisional diagnosis / strong clinical suspicion of typhoid fever

patients were dealt with in microbiology department. Out of these, 153 (62%) samples yielded growth of typhoidal *Salmonella* isolates and the rest 48% either yielded no growth or some other bacteria was identified. Of the isolated *Salmonella* typhoidal isolates, 109 (71%) isolates proved to be XDR *Salmonella Typhi* on further work up. 35 cases (23%) came out to be MDR *Salmonella Typhi* and the rest 09 cases (6%) were recorded as *Salmonella paratyphi A.* None of these isolates came out as paratyphi *B or C* Table-I. Mostly, age range of patients was 5-8 years followed by 9-12 yrs. According to gender distribution, male children were 96 (63%) and the rest 57 (37%) were females. Table-II. Among XDR typhoidal isolates, the most susceptible antibiotic was meropenem i.e 100% followed by azithromycin with susceptivity of 98%. Among all MDR cases, the susceptibility of ceftriaxone was around 24%, ciprofloxacin susceptibility was only 1%, ampicillin was sensitive in 16%, chloramphenicol in 20% and cotrimoxazle in 15% cases (Table-III).

Table-I: Species breakup along with antimicrobial susceptibility pattern of Blood culture proven typhoidal Salmonella (n= 153).

Species	Total no. of cases (%)	Antimicrobial pattern (no. %)
Salmonella Typhi	144 cases (94 %)	XDR= 109 (76 %) MDR= 35 (24 %)
Salmonella parayphi A	09 cases (06 %)	MDR= 02 (22%) XDR= Nil
Salmonella parayphi B & C	Nil	Nil

Table-II: Age & Gender distribution of Blood culture proven typhoidal Salmonella (n= 153).

Characteristic		no (%)
Age (Years) Group	1 -< 5	23 (15 %)
	5 -< 8	81 (53%)
	8 -< 12	49 (32%)
Gender	Male	96 cases (63 %)
	Female	57 cases (37 %)

Table-III: Pattern of Antimicrobial Susceptibility among typhoidal isolates; *S. typhi & S. paratyphi* (n=153).

	***Salmonella Typhi* (n= 144, 62%)**			***Salmonella paratyphi* (n= 09, 06%)**		
	R	**I**	**S**	**R**	**I**	**S**
AMP	121 (84%)	0 (0%)	23 (16%)	2(22 %)	0 (0%)	7 (77%)
CAP	116 (80%)	0 (0%)	28 (20%)	2(22 %)	0 (0%)	7 (77%)
SXT	123 (85%)	0 (0%)	21 (15%)	4 (44%)	0 (0%)	5 (55%)
CIP	134 (93%)	9 (6%)	01 (1 %)	5 (55%)	2 (22%)	2 (22%)
CRO	109 (76%)	0 (0%)	35 (24%)	0 (0%)	0 (0%)	9 (100%)
AZT	3 (02%)	0 (0%)	141 (98%)	0 (0%)	0 (0%)	9(100%)
MEM	0 (0%)	0 (0%)	144(100%)	0 (0%)	0 (0%)	9 (100%)

NT= Not Tested, S= Susceptible, I= Intermediate, R= Resistant
AMP-Ampicillin, CAP- Chloramphenicol, SXT-Trimethoprim-sulfamethoxazole, CIP-Ciprofloxacin, CRO-Ceftriaxone, AZT-Azithromycin, MEM-Meropenem

DISCUSSION

Currently, Pakistan is among one of the highly prevalent typhoid fever countries of the world.[11] Inhabitants of Sindh and Punjab province have been stated to be endangered most among the 16 countries of Asia where typhoid disease is prevalent[6]. Since then, there has been an upsurge of both MDR and XDR typhoidal isolates in Pakistan. This is mostly attributable to an antimicrobial resistant strain carrying a mutant, endemic H58 gene that harbours a very strong tendency to disperse this XDR clone worldwide, hence elevating the fear of antibiotic treatment failure.[6,11] There have been reports of emerging cases countrywide and elsewhere due to provincial and international travel, however, the degree of spread in rest of Pakistan still remains poorly understood.[12] Reports of XDR typhoid cases occurring in other parts of Pakistan are now being informally reported as well as in individuals travelling to UK and USA.[13] To our dismay, azithromycin is the

only oral antibiotic available for treating uncomplicated XDR S.typhi cases.[14] On the other hand, the only drug available to treat hospitalized and complicated cases is Meropenem, which is an injectable antibiotic.[15] This heightens the dilemma of limited antibiotic options that we are left with to treat typhoid fever. It is noteworthy and alarming that this resistant typhoid isolate is highly prevalent in pediatric population of Pakistan amplifying the fear of treatment failure and grave outcome in this population.

In our study, the predominant age group involved is 5-9 years (53%) mainly because of informal and frequent visits to street sellers, lack of cognizance about food quality and non-adherence to hygienic practices. Comparable observation was reported by Iftikhar *et al* in a tertiary care set up in Lahore in 2018 with 52% of the affected patients aged 5- 10 years.[16] Another study done by Memon *et al* in Karachi in 2019-2020 reported that the age bracket mainly affected was 5-7.5 years which is also similar to our findings.[17]During another study conducted by Fivizia and colleagues in Karachi in 2017-2018, it was observed that the predominant age range in children was 5-6 years.[18] In a study by Gul *et al* in Lahore, most children were between 4-8 years of age i.e 44.8%.[22] On contrary, a study done at Indus hospital Karachi by Saba Shahid and colleagues showed that children below 5 years of age suffered the most with XDR S.Typhi fever which coincides with our findings.[19] Our finding is also in contrast to the study conducted by Saeed N *et al*. in 2019 where only 33% of the registered patients had the age range of five to 10 years.[12]

There was a distinct high proportion of male children in our study i.e. 63%, most probably due to more outdoor exposure, and extra vulnerable and care-free behavior in boys. This finding is comparable with the study done by Khan and Mohammad in 2012.[20] Similar predominance was observed by Fatima *et al* who found out that almost two- thirds (63%) of their patients were males.[21] Study done by Memon *et al* in Karachi also showed a male preponderance of 61.5%.[17] Moreover, there was male predominance with 56.4% boys and 43.6% girls in study done by Gul *et al* in Lahore that also corresponds to our findings.[22] On contrary, Mubashir *et al* reported that 54.9% cases out of all blood culture positive patients were females and 28 (55.1%) were males which is in contrast to our findings.[26]

In our study, out of 245 blood culture samples, 153 (62%) samples yielded growth of typhoidal Salmonella isolates (both MDR & XDR) and the rest 48% either yielded no growth or some other bacteria was isolated. Similar findings were reported in another study done at Department of Pediatrics, Combined Military Hospital, Lahore by Gul *et al* where 55.2% cases were found to have XDR Salmonella on blood cultures, 34.7% had MDR Salmonella and only 43 (10.1%) children were non-resistant to usual antibiotics.[22] In congruence with our study, Aslam *et al*. also found XDR Salmonella in 54% of cases however their data included both children and adults.[23] Other studies by Yousafzai *et al*. and Hussain *et al*. in Karachi documented 60% and 48% XDR cases respectively[9,24] being consistent with our findings. Qamar *et al* also showed that a almost 67% of the isolates displayed multidrug resistance (MDR), besides out of them, 53% were XDR in their study.[25] On contrary, in a study done by Mubashir *et al* in Lahore in 2020-2021, among 246 patients enrolled, blood culture was positive for Salmonella in only 62 (25.2%) patients, and majority cases came out to be negative i.e 184 (74.8%) patients.[26] Another large hospital-based study conducted in Karachi by Yousafzai *et al*, Pakistan showed a culture positive rate for Salmonella of 22% which also coincides with our results.[9]

By March 2018, WHO endorsed the use of typhoid conjugate vaccine in children aged six months and beyond to combat the highly resistant typhoidal isolates in prevalent areas or countries.[14]In 2019, Pakistan turned out to be the leading country in the world to include the World Health Organization (WHO)-recommended typhoid conjugate vaccine (TCV) into its expanded programme immunization schedule. However, under vaccination in Pakistan is a problem in general due to limited supply of vaccine, lack of trust in vaccinations, in awareness, education barrier and casual attitude of healthcare worker for advocacy of vaccines. Therefore, despite of all preventive measures introduced, we are still facing challenges in combating this disease mainly due to lack of commitment and negligence at mass level both administratively and politically. There is a lack of quality control and standardization of laboratories in

Pakistan and rural areas lack facilities where blood cultures are available. A lot of work needs to be done to improve the health care facilities and diagnostic modalities for timely diagnosis and adequate treatment. Moreover, the common trend of prior medications from quacks, frequent use of over-the-counter drugs to treat fever and prevalence of poor health seeking behavior in our population is also an important contributing factor for spread of XDR strain. Considering the limited alternative therapeutic options, timely diagnosis, and judicious use of antibiotics and preventive management of XDR typhoid fever especially in the pediatric population is becoming very important. It is the need of time that to establish antibiograms in all major tertiary care hospitals countrywide to make the clinicians aware about the current trend of disease, choice for empirical therapy as well as for MDR/ XDR typhoid cases. In addition, widespread use of typhoid vaccines, improvements in water supply and sanitation and community awareness campaigns can extensively help overcome this disease burden constituting a vital part of long- term intervention measures. Moreover, issuing guidelines for judicious use of antibiotics, launching informative campaigns and educational sessions for effective implementation of antimicrobial stewardship program in healthcare settings at national level could make the difference, since XDR typhoid is a battle that needs to be fought against collectively by all stakeholders of society i.e healthcare workers, authorities and civil society.

CONCLUSION

This study lays emphasis on the alarmingly increasing prevalence of XDR ***S.typhi*** in pediatric population in Federal territory and keeping in view the other local studies, we can conclude that there is widespread existence of MDR/ XDR *S.typhi* all over Pakistan. Hence, our study signifies that a holistic approach should be implemented along with continuous ongoing surveillance to combat this frightening MDR/ XDR disease burden country wide.

LIMITATIONS OF STUDY

It was a single-center study. More data from other hospitals in federal territory as well as peripheral health care facilities of Islamabad should have been included to deduce more precise conclusions.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Samia Wazir: literature search, study concept, questionnaire design, data analysis, data interpretation, drafting, final approval to be published

Umme Farwa: Conception/design of the work, interpretation of data, revised it critically, final approval to be published

Soffia Khursheed: literature search, study concept, questionnaire design, data analysis, data interpretation, drafting

Mehreen Mushtaq: Conception/ design of the work, interpretation of data, data analysis

Muhammad Shafiq: Data collection, data analysis

Muhammad Moaaz Ali: Conception/ design of the work, interpretation of data, data analysis

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