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ORIGINAL ARTICLE

Prevalence and trends in the antimicrobial susceptibility pattern of *Salmonella enterica* serovars Typhi and Paratyphi A among children in a pediatric tertiary care hospital in South India over a period of ten years: a retrospective study

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Abstract The aim of this study was to determine the prevalence and trends in the antimicrobial resistance of typhoidal salmonellae in children and adolescents at a pediatric tertiary care hospital in South India. Typhoidal salmonellae were isolated from 483 of the 77,713 blood cultures received during the ten-year study period (2007–2016). Isolates were speciated by conventional biochemical reactions and serotyping. Antimicrobial susceptibility testing was performed and interpreted according to the British Society for Antimicrobial Chemotherapy (BSAC)/European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. The overall blood culture isolation rates of *Salmonella enterica* serovars Typhi and Paratyphi A in children were 0.5% (408 cases) and 0.1% (73 cases), respectively, with the highest isolation rates in school [299 (61.9%)] and preschool children [113 (23.4%)]. A decreasing prevalence of enteric fever was seen from 2012 to 2015, with a sudden surge in 2016. From 2011 onwards, a high fluoroquinolone resistance (90–100%) was observed. Multidrug resistance was observed in only four (0.9%) *S.* Typhi isolates. 100% susceptibility to third-generation cephalosporins and azithromycin was noted. Enteric fever as seen in a pediatric tertiary care hospital in India affects children and adolescents of all age groups, with greater isolation rates in school children, followed by those in preschool years, calling for targeted interventions against these age groups. The study findings support the use of third-generation cephalosporins and azithromycin as first-line therapy and ampicillin and co-trimoxazole as step-down therapy in pediatric enteric fever. However, continued local surveillance should be done to detect antimicrobial resistance trends to optimize treatment.

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Introduction

Enteric fever is a global health problem. There is a huge disease burden in developing countries due to poor sanitation coupled with lack of food and water safety. In developed countries, it is seen in returning travelers from endemic nations [1]. A study of typhoid fever in five Asian countries highlighted the high incidence in India and Pakistan, especially among children and adolescents, an intermediate incidence in Indonesia, and low incidence in China and Vietnam [2]. Whilst many studies have dealt with the prevalence and antimicrobial susceptibility trends of typhoidal salmonellae from India [3–6], few have dealt with the vulnerable age group: children and adolescents.

Hence, a ten-year retrospective study on blood culture-confirmed cases of typhoidal salmonellae infections was

carried out to determine the prevalence and trends in antimicrobial resistance of typhoidal salmonellae in children and adolescents at a pediatric tertiary care hospital in South India.

Materials and methods

This was a retrospective study conducted by the Department of Clinical Microbiology at Rainbow Hospital for Women and Children, which is a 500-bed pediatric tertiary care hospital in Hyderabad, South India, over a period of ten years from January 2007 to December 2016. A total of 77,713 blood cultures were received at the microbiology department during the study period. Every patient was included only once in the study. Cognizance was taken of the first positive blood culture from every patient included in the study. Subsequent blood cultures from the same patient were not included in the analysis. Demographic details and laboratory findings were noted for all patients with bloodstream typhoidal salmonellae infection, whereas clinical findings were recorded for only admitted patients from the inpatient case records. Blood cultures were performed using BD BACTEC 9120/9050/FX200 systems (Becton, Dickinson and Company, Sparks, MD, 21152, USA). Blood for culture was collected under strict aseptic conditions and an appropriate volume of blood was inoculated into a BD BACTEC Peds Plus/F bottle or a BD BACTEC Plus Aerobic/F bottle, depending upon the weight and age of the child. All blood culture bottles were loaded onto the BACTEC machine and incubated aerobically at 37 °C following a 7-day protocol. The bottles that were flagged positive on the automated system were removed and 2–5 mL of the blood broth mixture was withdrawn from the blood culture bottle after gentle shaking to mix the contents. The fluid was inoculated directly on 5% sheep blood agar, MacConkey agar, chocolate agar, and brain heart infusion agar, and a smear prepared according to the protocol followed in the department. The slide was stained by the Preston and Morrell's modification of the Gram stain (1962) and the smear was observed for Gram-negative bacilli. Lactose non-fermenting pale colonies on MacConkey agar were subject to further testing. Speciation of the isolates was done using conventional biochemical reactions and serotyping performed using the slide agglutination technique with standard *Salmonella* antisera (Bio-Rad, 3, boulevard Raymond Poincaré, 92430, Marnes-la-Coquette, France). Antimicrobial susceptibility testing was done by the disk diffusion method for the following antimicrobial agents: ampicillin (10 μg), trimethoprim/sulfamethoxazole (1.25/23.75 μg), chloramphenicol (30 μg), nalidixic acid (30 μg), ciprofloxacin (1 μg), and ceftriaxone (30 μg). Nalidixic acid was initially considered a surrogate marker of quinolone non-susceptibility till 2011. Minimum inhibitory concentrations (MICs) were determined using Epsilometer test strips (E-test, bioMérieux SA, RCS Lyon 673 620 399, 69280, Marcy-l'Etoile, France) for ciprofloxacin, azithromycin, and ceftriaxone. From 2007 to 2010, ciprofloxacin MICs of 0.125–1 μg/mL were considered as reduced susceptibility and >1 μg/mL was considered resistant (BSAC January 2007). From 2011 to 2016, ciprofloxacin MIC >0.06 μg/mL and ≤0.06 μg/mL were considered resistant and susceptible, respectively (BSAC January 2011). MIC testing for azithromycin and ceftriaxone was done from 2012 onwards, with MICs ≤16 μg/mL and ≤1 μg/mL considered as susceptible for azithromycin and ceftriaxone, respectively (BSAC March 2012). *Salmonella* isolates were screened for extended-spectrum beta-lactamase (ESBL) production using a cefpodoxime (10 μg) disk as the indicator cephalosporin. The double disk synergy test using ceftazidime (30 μg) and cefotaxime (30 μg) with an amoxicillin/clavulanic acid (20/10 μg) disk was used as a confirmatory test [7]. The interpretation of antimicrobial susceptibility testing (disk diffusion and E-test) was done according to the British Society for Antimicrobial Chemotherapy (BSAC)/European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines (as applicable each year) [8]. Isolates were considered to be multidrug-resistant (MDR) if they were resistant to ampicillin, co-trimoxazole (trimethoprim/sulfamethoxazole), and chloramphenicol [9].

Results

Of the 77,713 blood cultures received at our microbiology department during the study period, 2517 (3.2%) were true pathogens, comprising 2234 (2.9%) bacterial pathogens and 283 (0.3%) yeast pathogens. 1707 (2.2%) of the blood cultures showed contaminants. Typhoidal salmonellae were isolated from 483 (0.6%) specimens, with the most common serovar being *Salmonella enterica* serovar Typhi (*S.* Typhi) [408 (0.5%)], followed by *Salmonella enterica* serovar Paratyphi A (*S.* Paratyphi A) [73 (0.1%)]. A single case each of *Salmonella enterica* serovar Paratyphi B (0.001%) and *Salmonella enterica* serovar Paratyphi C (0.001%) was found in the present study.

Nontyphoidal salmonellae (*Salmonella enterica* serovar Typhimurium) were isolated from 3 (0.004%) specimens.

Out of the 483 typhoidal salmonellae cases, 257 (53.2%) were males and 226 (46.8%) were females. The patient's ages ranged from 23 days to 17 years (median age: 6.4 years). The age-wise frequency of isolation of typhoidal salmonellae was: school children (5–15 years) [299 cases (61.9%)], preschool children (2–5 years) [113 cases (23.4%)], (1–2 years) [43 cases (8.9%)], (> 15 years) [14 cases (2.9%)], (6 months to 1 year) [13 cases (2.7%)], and (0–6 months) [1 case (0.2%)]. 233 (48.2%) cases were admitted for treatment and the clinical features at admission is shown in Table 1. 250 cases (51.8%) were managed as outpatients.

Table 1 Clinical features at admission (n = 233)

Symptoms	No. of cases (%)
Fever	233 (100)
Vomiting	69 (29.6)
Diarrhea	38 (16.3)
Abdominal pain	35 (15)
Anorexia	18(7.7)
Dry cough/throat congestion	15 (6.4)
Neurological manifestations (irritability, altered sensorium, convulsions)	4 (1.7)
Headache	3 (1.3)
Rash (erythematous)	3 (1.3)
Jaundice	2 (0.9)
Decreased urine output	1 (0.4)
Constipation	1 (0.4)
Signs	
Fever	119 (51.1)
99–100 °C	15 (6.4)
101–103 °C	99 (42.5)
>103 °C	5 (2.1)
Hepatomegaly	36 (15.5)
Throat congestion	12 (5.2)
Abdominal tenderness	11 (4.7)
Splenomegaly	10 (4.3)
Tachycardia	9 (3.9)
Hepatosplenomegaly	5 (2.1)
Coated tongue	5 (2.1)
Neurological signs (low Glasgow Coma Scale score, altered sensorium, tonic posturing, hyperreflexia)	3 (1.3)
Respiratory signs (decreased air entry, wheeze, crepitations)	3 (1.3)
Bradycardia	2 (0.9)
Icterus	2 (0.9)

Typhoidal salmonellae infections were reported throughout the year: 176 (36.4%) seen in the monsoon season (June–September), 165 (34.2%) cases in winter (October–February), and 142 (29.4%) cases in summer (March–May), with the month-wise distribution depicted in Fig. 1.

The prevalence of enteric fever due to *S.* Typhi and *S.* Paratyphi A each year from 2007 to 2016 is depicted in Table 2.

The antimicrobial resistance of typhoidal salmonellae against antimicrobial agents tested by disk diffusion and by the E-test method is depicted in Tables 3 and 4 and 5 and 6, respectively. The number of isolates of *S.* Typhi and *S.* Paratyphi A for which MICs were determined by the E-test method against ciprofloxacin/ceftriaxone/azithromycin were 371/208/217 and 62/25/25 isolates, respectively.

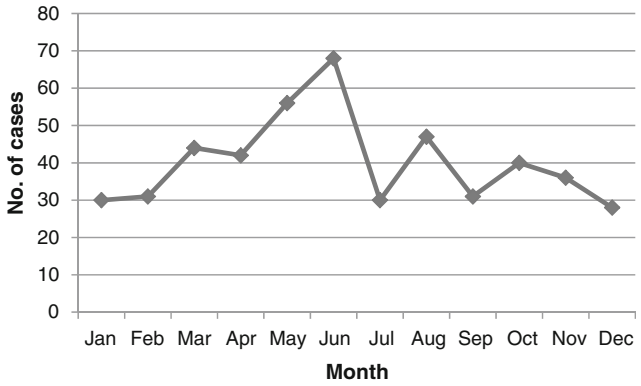

Fig. 1 Month-wise distribution of typhoidal salmonellae isolates during 2007–2016 (n = 483)

The ciprofloxacin MIC range (μg/mL) for *S.* Typhi and *S.* Paratyphi A was 0.006 to >32 (MIC_{50} = 0.25 μg/mL) and 0.047–2 (MIC_{50} = 0.38 μg/mL), respectively.

100% susceptibility to ceftriaxone and azithromycin was observed for *S.* Typhi and *S.* Paratyphi A. The ceftriaxone MIC range (μg/mL) for *S.* Typhi and *S.* Paratyphi A was 0.016–1 (MIC_{50} = 0.064 μg/mL) and 0.047–1 (MIC_{50} = 0.094 μg/mL), respectively. The azithromycin MIC range (μg/mL) for *S.* Typhi and *S.* Paratyphi A was 0.047–16 (MIC_{50} = 2 μg/mL) and 0.094–8 (MIC_{50} = 4 μg/mL), respectively.

187 of the 233 (80.3%) admitted patients received combination therapy. The most frequently used regimens were a combination of third-generation cephalosporin with a fluoroquinolone [110 (47.2%)], co-trimoxazole [63 (27%)], and azithromycin [6 (2.6%)]. 5 (2.2%) and 3 (1.3%) patients received a combination of co-trimoxazole with fluoroquinolone and azithromycin, respectively. 46 (19.7%) of the 233 admitted patients received monotherapy with the third-generation cephalosporins ceftriaxone/cefixime [35 (15%)] and co-trimoxazole [11 (4.7%)].

Table 2 Year-wise prevalence of enteric fever due to *S.* Typhi and *S.* Paratyphi A

Year	No. of blood cultures received	No. of *S.* Typhi isolates (%)	No. of *S.* Paratyphi A isolates (%)
2007	2787	7 (0.25)	2 (0.07)
2008	4091	16 (0.39)	6 (0.15)
2009	5889	45 (0.76)	23 (0.39)
2010	6450	36 (0.56)	7 (0.11)
2011	7998	51 (0.64)	5 (0.06)
2012	8452	49 (0.58)	9 (0.11)
2013	8736	36 (0.41)	6 (0.07)
2014	9949	41 (0.41)	3 (0.03)
2015	11,171	37 (0.33)	2 (0.02)
2016	12,190	90 (0.74)	10 (0.08)

Table 3 Antimicrobial resistance pattern (%) of *S.* Typhi ($n = 408$)

AMA	2007, $n = 7$	2008, $n = 16$	2009, $n = 45$	2010, $n = 36$	2011, $n = 51$	2012, $n = 49$	2013, $n = 36$	2014, $n = 41$	2015, $n = 37$	2016, $n = 90$
Amp	3	4	12 (26.6)	3 (8.3)	1 (1.9)	4 (8.2)	2 (5.5)	1 (2.4)	0	1 (1.1)
SXT	0	2	0	1 (2.8)	1 (1.9)	3 (6.1)	2 (5.5)	1 (2.4)	2 (5.4)	3 (3.3)
CH	0	1	0	1 (2.8)	1 (1.9)	2 (4.1)	1 (2.8)	0	0	0
NA	3	4	16 (35.5)	20 (55.5)	49 (96.1)	48 (97.9)	34 (94.4)	38 (92.7)	34 (91.9)	90 (100)
MDR	0	1	0	0	1 (1.9)	2 (4.1)	0	0	0	0

Amp, Ampicillin; SXT, co-trimoxazole; CH, chloramphenicol; NA, nalidixic acid; MDR, multidrug-resistant

Three of the 233 (1.3%) admitted patients died despite antimicrobial therapy, of which two patients had an underlying comorbid condition, acute myeloid leukemia and thalassemia major, and one patient died due to septic shock and multiorgan dysfunction syndrome.

Discussion

Enteric fever is an important public health problem in India. The pediatric blood culture isolation rates of *S.* Typhi and *S.* Paratyphi A were 0.5% and 0.1%, respectively, during the ten-year study period. Our study also shows a decreasing prevalence of enteric fever from years 2012–2015. A systematic review and meta-analysis on the burden of enteric fever in India showed estimated prevalences of 9.7% and 0.9% for typhoid and paratyphoid fever, respectively, in adults and children detected through culture or serology. The aforementioned study also reported a decline in prevalence over time for typhoid, but no trend was seen for paratyphoid fever [10]. The low isolation rate reported in our study could be because of the use of effective antibiotics prior to blood collection for culture, before patients were referred to our tertiary care hospital. Also, our study population was restricted to children and adolescents, and cases were detected only by blood cultures and not serological tests. The decreasing prevalence of enteric fever seen in our study could have been due to typhoid vaccination. A sudden surge in cases was seen in our study in the year 2016. We speculate that this could be due to the unpredictable intermittent heavy showers in the city throughout 2016, which could have resulted in increased contamination of drinking water supply by surface water.

Knowledge of the age-specific prevalence of enteric fever helps in targeted intervention programs. In the present study, we found that enteric fever affected children and adolescents of all age groups, though the highest number of cases was reported in school children (5–15 years of age) (61.9%), followed by preschool children (2–5 years of age) (23.4%). Similar findings have been reported by a World Health Organization (WHO) study conducted in five Asian countries (China, India, Indonesia, Pakistan, and Vietnam) [2]. Only one case of enteric fever in a neonate on bottle feeding was reported before 6 months of age and was due to the use of contaminated water for formula feeds. The very low occurrence of enteric fever before 6 months of age in India is probably because of higher rates of exclusive breastfeeding in India and avoidance of contaminated water before 6 months of age. However, an increasing number of cases was reported from 6 months onwards, coinciding with the time of weaning and introduction of complementary foods. This highlights the importance of suspecting enteric fever in febrile children of all age groups.

The most common serovar isolated in the present study was *S.* Typhi, followed by *S.* Paratyphi A. Other Indian studies have reported similar findings [3, 5, 11]. Early initiation of appropriate antimicrobial therapy decreases complications and mortality in enteric fever. A high ciprofloxacin resistance (varying between 90 and 100%)

Table 4 Antimicrobial resistance pattern (%) of *S.* Paratyphi A ($n = 73$)

AMA	2007, $n = 2$	2008, $n = 6$	2009, $n = 23$	2010, $n = 7$	2011, $n = 5$	2012, $n = 9$	2013, $n = 6$	2014, $n = 3$	2015, $n = 2$	2016, $n = 10$
Amp	1	0	10	1	1	0	0	0	0	0
SXT	0	0	0	0	0	1	0	0	0	0
CH	0	0	0	0	0	0	0	0	0	0
NA	2	3	18	4	4	9	6	3	2	10
MDR	0	0	0	0	0	0	0	0	0	0

Amp, Ampicillin; SXT, co-trimoxazole; CH, chloramphenicol; NA, nalidixic acid; MDR, multidrug-resistant

Table 5 Antimicrobial resistance pattern (%) of *S.* Typhi for ciprofloxacin ($n = 371$)

MIC	2007, $n = 2$	2008, $n = 8$	2009, $n = 38$	2010, $n = 30$	2011, $n = 44$	2012, $n = 46$	2013, $n = 35$	2014, $n = 41$	2015, $n = 37$	2016, $n = 90$
>0.06 μg/mL	2	8	36 (94.7)	30 (100)	44 (100)	46 (100)	35 (100)	39 (95.1)	34 (91.9)	90 (100)
0.125–1 μg/mL	2	8	29 (76.3)	18 (60)	42 (95.4)	41 (89.1)	31 (88.6)	31 (75.6)	29 (78.4)	73 (81.1)
>1 μg/mL	0	0	0	0	1 (2.3)	4 (8.7)	3 (8.6)	7 (17.1)	5 (13.5)	17 (18.9)
Resistant isolates as per BSAC interpretation*	0	0	0	0	44 (100)	46 (100)	35 (100)	39 (95.1)	34 (91.9)	90 (100)

*BSAC interpretation as applicable each year

among *S.* Typhi and *S.* Paratyphi A isolates was seen from year 2011 onwards following the use of revised BSAC breakpoints. *Salmonella* Typhi isolates with ciprofloxacin MIC >1 μg/mL increased gradually every year (2.3% in 2011 to 18.9% in 2016). Increasing fluoroquinolone resistance in typhoidal salmonellae has been reported in other studies too [5, 12]. This is attributed to the widespread indiscriminate prescription of fluoroquinolones, as they can be given orally, are easily available over the counter, and are affordable [12]. Although no admitted patient in our study received fluoroquinolone monotherapy, 115 (49.4%) of the 233 admitted patients received fluoroquinolones as a part of combination therapy. The high ciprofloxacin resistance rates observed in our study makes them poor choices for empirical therapy, as well as an adjunct drug in combination therapy.

None of the *Salmonella* isolates in the present study were resistant to ceftriaxone nor produced ESBLs. Although resistance to extended-spectrum cephalosporins due to ESBL or Amp C type beta-lactamases has been recognized in nontyphoidal salmonellae since the mid-1980s [9], only sporadic cases of high-level resistance to ceftriaxone in typhoidal salmonellae due to CTX-M and SHV ESBLs have been reported in studies from Bangladesh, Nepal, Philippines, Kuwait, United Arab Emirates, Germany, and Guatemala [13–18]. Whilst no ESBLs have been reported so far in India, an isolated case of enteric fever caused by ceftriaxone-resistant *S.* Typhi due to ACC-1 beta-lactamase (Amp C type beta-lactamase) production was reported from a 14-year-old girl from Bangalore, India [19]. All the *S.* Typhi and *S.* Paratyphi A isolates in the present study were susceptible to azithromycin, as compared to other studies that have reported azithromycin resistance and treatment failure in India and in returning travelers from endemic nations [20–22]. Improved susceptibility to ampicillin, co-trimoxazole, and chloramphenicol was observed in the present study (MDR *S.* Typhi/*S.* Paratyphi A isolates being 4/0). From 2013 onwards, no MDR isolate of typhoidal salmonellae was seen in our study. Studies performed all over India have reported decreased multidrug resistance among typhoidal salmonellae [5, 11, 12]. This is probably due to the restricted use of the aforementioned drugs for the treatment of enteric fever in the last decade [12]. However, the rampant reuse of these antimicrobial agents as first-line agents could lead to rapid reemergence of multidrug resistance. Therefore, in endemic areas with high fluoroquinolone resistance, empiric treatment options for pediatric enteric fever are limited to third-generation cephalosporins and azithromycin, and treatment should be further optimized based on the antimicrobial susceptibility pattern of the isolate.

Our study has limitations that may possibly limit its generalizability to other settings. Regional variations in the antimicrobial susceptibility pattern of typhoidal salmonellae do occur and empiric therapy should, therefore, be based on the local antimicrobial susceptibility trends. The low isolation rate of typhoidal salmonellae in children reported in our study may be due to our center being a pediatric tertiary care hospital and, hence, may not reflect the true prevalence in the community.

Table 6 Antimicrobial resistance pattern (%) of *S.* Paratyphi A for ciprofloxacin ($n = 62$)

MIC	2007, $n = 1$	2008, $n = 3$	2009, $n = 20$	2010, $n = 5$	2011, $n = 4$	2012, $n = 8$	2013, $n = 6$	2014, $n = 3$	2015, $n = 2$	2016, $n = 10$
>0.06 μg/mL	1	3	19	5	4	8	6	3	2	10
0.125–1 μg/mL	1	3	19	4	3	8	6	3	2	10
>1 μg/mL	0	0	0	0	1	0	0	0	0	0
Resistant as per BSAC interpretation	0	0	0	0	4	8	6	3	2	10

*BSAC interpretation as applicable each year

Conclusion

Enteric fever as seen in a pediatric tertiary care hospital in India affects children and adolescents of all age groups, with a greater isolation rate in school children, followed by those in preschool years, calling for targeted interventions against these age groups. Cases were reported throughout the year, with a decreasing prevalence from 2012 to 2015 during the study period and a sudden surge in cases observed in 2016. *Salmonella* Typhi was the most common serovar isolated. The study indicates high fluoroquinolone resistance among typhoidal salmonellae, significant decrease in multidrug resistance, and 100% susceptibility to third-generation cephalosporins and azithromycin, making third-generation cephalosporins and azithromycin rational choices for empiric/first-line therapy and ampicillin and co-trimoxazole step-down therapy in pediatric enteric fever in our center. However, regional variations do occur and therapy should be based on the local antimicrobial susceptibility pattern of typhoidal salmonellae isolates.

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Author's contributions Iyer RN conceived and supervised the study. Iyer RN, Jangam RR, and Jacinth A analyzed and interpreted the data. Iyer RN and Jangam RR wrote the manuscript. Iyer RN, Venkatalakshmi A, and Nahdi FB reviewed and approved the final version of the study.

Compliance with ethical standards

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Conflict of interest The authors declare no conflicts of interest in relation to this study.

Ethical approval For this type of retrospective study, formal consent is not required.

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