

Non-Typhoidal *Salmonella* Infections Among Children in Fuzhou, Fujian, China: A 10-Year Retrospective Review from 2012 to 2021

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Purpose: Non-typhoidal *salmonella* (NTS) infection is a leading cause of acute gastroenteritis in children. Recently, NTS infections have increased, especially those associated with *Salmonella* Typhimurium, which has become a global problem because of its high level of drug resistance. Diseases caused by NTS serotypes vary considerably. We summarised NTS infections among children in Fuzhou, Fujian, China, from 2012 to 2021, and synthesised studies indicating the clinical symptoms, laboratory test results, and drug resistance associated with *S. Typhimurium* and non-*S. Typhimurium* to enhance the knowledge of these infections and improve their diagnoses and treatment.

Patients and Methods: Between January 2012 and December 2021, 691 children with NTS infections confirmed by positive culture test results were recruited from Fujian Children's Hospital and Fujian Maternity and Child Health Hospital. Clinical demographic data of each case were collected from the electronic medical records and analysed.

Results: A total of 691 isolates were identified. The number of NTS infections increased significantly in 2017 and increased sharply during 2020 and 2021, especially *S. Typhimurium* greatly increased and was the dominant serotype (58.3%). *S. Typhimurium* infection was commonly occurred in children younger than 3 years and most of them were gastrointestinal infection, while non-*S. Typhimurium* more often observed in older children and associated with extra-intestinal infection. The rate of multidrug-resistant *S. Typhimurium* was significantly higher than that of non-*S. Typhimurium*, especially during the last 2 years of this study (2020 and 2021).

Conclusion: *S. Typhimurium* was the dominant serotype and greatly increased among children in Fuzhou city. There are significant differences in clinical symptoms, laboratory test results, and drug resistance between *S. Typhimurium* and non-*S. Typhimurium*. More attention should be paid on *S. Typhimurium*. Long-term high-quality surveillance and control measures should be conducted to prevent salmonella infections and drug resistance.

Keywords: *S. Typhimurium*, non-*S. Typhimurium*, clinical symptoms, laboratory test results, drug resistance

Introduction

Salmonella enterica constitutes a major public health concern and it is estimated to cause more than 300,000 annual deaths, mostly in developing countries.^{1,2} This highly ubiquitous species consists of more than 2600 different serotypes that can be divided into typhoidal and non-typhoidal *salmonella* (NTS) types.^{3,4} Despite their genetic similarity, these two groups elicit very different diseases and distinct immune responses in humans; therefore, they are often discussed separately.⁵ NTS infections are an important cause of illness in children. A study performed in the United States, including children younger than 5 years of age with laboratory-confirmed bacterial enteritis reported that NTS was the most commonly isolated (42%) bacterial enteric pathogen, followed by *Campylobacter* (28%), *Escherichia coli* O157, *Shigella*, and *Yersinia enterocolitica*.⁶ In Taiwan, NTS is the most common pathogen associated with childhood bacterial enterocolitis requiring hospitalization.⁷ In China, 70% to 80% of food poisoning incidents were caused by NTS.⁸

Therefore, NTS infections among children remains a significant burden on health care and are global public health concern.⁹ Despite extensive government and industry efforts to reduce the incidence of NTS, not much progress has been made in the reduction of the number of salmonellosis cases each year.^{10,11} Limited information on NTS infections in children is available in China. In recent years, NTS increased notably especially *S. Typhimurium* (one of serotypes in NTS) raised sharply, being one of the dominant serotypes in many countries.^{12–14} Meanwhile, increasing numbers of multidrug-resistant strains, including those resistant to first-line treatment such as cephalosporin and quinolones, have been observed for *S. Typhimurium* in many countries,^{15–17} and most infection outbreaks have been associated with *S. Typhimurium*.^{18–21} With the rapid growth and high drug resistance rate of *S. Typhimurium* in children,^{14,22} to enhance the knowledge of these infections and improve their diagnoses and treatment, pediatricians have paid great attention to the differences between *S. Typhimurium* and non-*S. Typhimurium*. Indeed, relevant studies have reported the genetic differences between serotypes suggest that several mechanisms are serotype-specific. Diseases caused by different serotypes vary significantly with the infection site and severity of illness. Some serotypes are more likely to cause gastrointestinal symptoms, and others are more likely to cause extra-intestinal infection especially invasive disease even death.²³ Therefore, the use of specific serotypes should be considered when studying the clinical pathogenicity of NTS. Most reviews have compared the host response to both NTS and typhoidal salmonella.^{5,24} However, a better understanding of the diversity of NTS serotypes and clinical symptoms is lacking, and few published studies have reported the differences between *S. Typhimurium* and non-*S. Typhimurium* based on the combination of clinical symptoms, laboratory test results, and drug resistance. Therefore, this study summarised NTS infections among children in Fuzhou, Fujian, China, from 2012 to 2021, and synthesised studies indicating the diversity of clinical symptoms, laboratory test results, and drug resistance associated with *S. Typhimurium* and non-*S. Typhimurium* to enhance the understanding of these infections and improve their diagnoses and treatment in clinical settings.

Materials and Methods

Sample Collection

This retrospective study was conducted at Fujian Children's Hospital and Fujian Maternity and Child Health Hospital between January 2012 and December 2021. Fujian Children's Hospital is a comprehensive, domestic, first-class children's medical center and the Fujian branch of Shanghai Children's Medical Center. Fujian Maternity and Child Health Hospital, which is affiliated with Fujian Medical University, is the first tertiary maternal and child health hospital and one of the first neonate-specific hospitals in China. The annual number of inpatient visits is approximately 70,000, and the annual number of outpatient visits is nearly 2 million. A total of 691 children younger than 14 years of age with positive NTS culture test results were enrolled in this study. Clinical demographic data of each case were consecutively collected from the electronic medical records, including the unique sample number, name, sex, age, specimen type, serotypes, clinical symptoms, laboratory tests and results, bacterial antibiotic resistance, date of disease onset, and date of sample collection. Isolates were confirmed to be infected with *Salmonella* using VITEK Gram-negative identification cards (bioMérieux, Inc., Marcy-l'Étoile, France) and serotyped with salmonella diagnostic serum (Ningbo Tianrun Bio-Pharmaceutical Co., Ltd., Zhejiang Sheng, China). The isolates were stored in Baso preservative tubes (Baso Diagnostics Inc., Zhuhai, China) at -80°C until analysis.

Definitions

We defined “*S. Typhimurium*” infection confirmed by positive culture test results with “*S. Typhimurium*” concluding typical strains and monophasic variants. “non-*S. Typhimurium*” as NTS infection except for “*S. Typhimurium*” infection concluding typical strains and monophasic variants.

We defined “non-invasive” cases as those in which *Salmonella* had been isolated from stool, urine and vaginal secretions specimens and “invasive” cases as those in which *Salmonella* had been isolated from specimens, such as blood, cerebrospinal fluid, other normally sterile fluids, pus and urine, which from sterile sites.

Multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (classes), such as aminopenicillins (ampicillin), β -lactam combination agents (ampicillin-

sulbactam, piperacillin-tazobactam), cephalosporins (ceftriaxone, ceftazidime, cefepime), monobactams (aztreonam), carbapenems (imipenem), dihydrofolate reductase inhibitors (trimethoprim-sulfamethoxazole), and fluoroquinolones (ciprofloxacin, levofloxacin).²⁵

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility was evaluated using VITEK Gram-negative drug susceptibility cards (GN09) for the following nine antimicrobial agents: amoxicillin, ampicillin-sulbactam, ceftriaxone, ceftazidime, cefepime, piperacillin-tazobactam, imipenem, meropenem, and trimethoprim/sulfamethoxazole. Antimicrobial susceptibility was evaluated using the disk diffusion test for the antimicrobial agents ciprofloxacin (5 µg) and levofloxacin (5 µg).²⁶ All disks were obtained from Oxide Ltd. (Cambridge, UK). The results were interpreted according to the Clinical and Laboratory Standards Institute guidelines.²⁶ *E. coli* ATCC25922 was used for routine quality control. Multidrug-resistance (MDR) was defined as the resistance to more than three types of antimicrobials.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism 7.04 data editor. Data were described using frequencies and their proportions, and the chi-squared (χ^2) test was used for comparisons. Measurement data were described as the median ($\pm$ standard deviation) and compared using the unpaired *t*-test. For all analyses, statistical significance was set at $P < 0.05$.

Results

Prevalence

The number of NTS infections in children was stable and low during 2012 to 2016; however, infections increased significantly in 2017, and increased sharply during 2020 and 2021 (Figure 1). Serogroup B (68.2%) was the predominant serogroup isolate, followed by serogroups C (15.2%), D (9.3%), E (5.4%), F (0.1%), and ungrouped (0.3%). Among serogroup B, *S. Typhimurium* was the most predominant serotype, accounting for 54.7% (378/691) of cases comprising

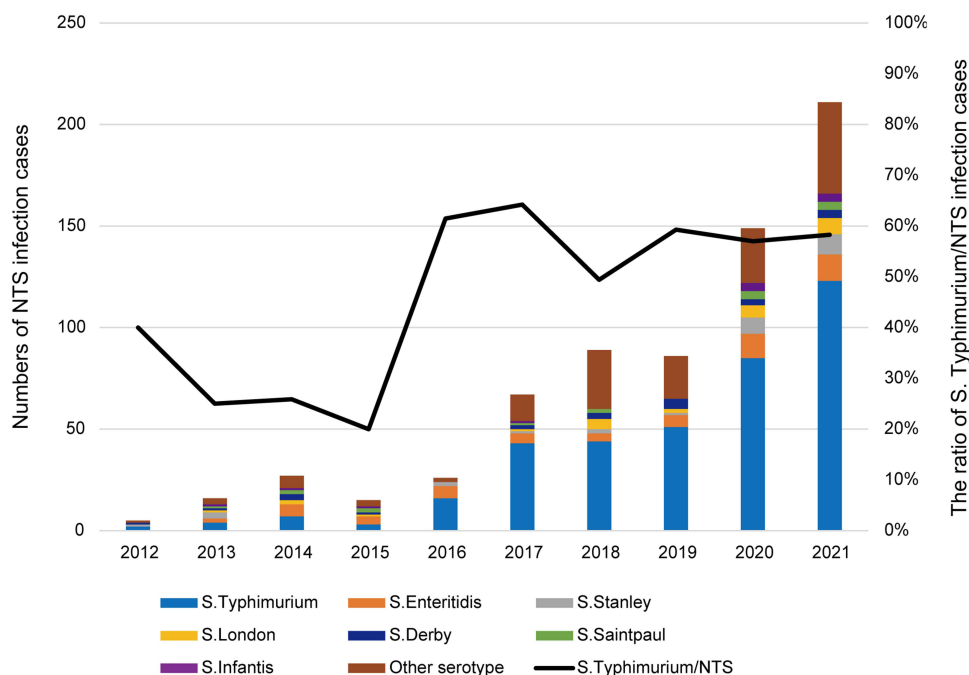


Figure 1 Distribution of 691 isolates of different serotypes and the ratio of *S. Typhimurium*/NTS in children <14 years old with NTS infection by year, Fuzhou, China, 2012–2021.

Table 1 Distribution of 691 NTS Isolates of Different Serotypes, Fuzhou, China, 2012–2021

Serogroup and Serotype	Isolates from NTS Infection (n=691)	
	No	%
Serogroup B	471	68.2
<i>Salmonella</i> Typhimurium	378	54.7
<i>Salmonella</i> Stanley	28	4.1
<i>Salmonella</i> Derby	23	3.3
<i>Salmonella</i> Saintpaul	16	2.3
<i>Salmonella</i> Agona	6	0.9
Untyped B	20	2.9
Serogroup C	105	15.2
Serogroup C1	57	8.3
<i>Salmonella</i> Infantis	12	1.7
<i>Salmonella</i> Potsdam	11	1.6
<i>Salmonella</i> Thompson	4	0.6
Untyped C1	30	4.3
Serogroup C2	48	7.0
<i>Salmonella</i> Bovismorbificans	11	1.6
<i>Salmonella</i> Manhattan	6	0.9
<i>Salmonella</i> Neupot	5	0.7
<i>Salmonella</i> Kottbus	2	0.3
<i>Salmonella</i> Glostrup	2	0.3
Untyped C2	22	3.2
Serogroup D	64	9.3
<i>Salmonella</i> Enteritidis	58	8.4
<i>Salmonella</i> Gallinarum-pulorum	2	0.3
<i>Salmonella</i> javiana	1	0.1
Untyped D	3	0.4
Serogroup E1	37	5.4
<i>Salmonella</i> London	26	3.8
<i>Salmonella</i> Newlands	6	0.8
<i>Salmonella</i> Meleagridis	1	0.1
Untyped E1	4	0.6
Serogroup F <i>Salmonella</i> Aberdeen	1	0.1
Serogroup J <i>Salmonella</i> Jangwani	1	0.1
Serogroup M <i>Salmonella</i> Pomona	2	0.3
Serogroup X <i>Salmonella</i> Moulaine	1	0.3
<i>Salmonella</i> enteritidis subsp. Arizona	7	1.0
Ungrouped	2	0.3
Total	691	100.0

more than half of all isolates. Notably, the average rate of *S. Typhimurium* infections was 27.7% (2012–2015) before 2015; however, this rate increased to 58.3% after 2015 (2016–2021) (Figure 1). The next most common serotypes were *Salmonella Enteritidis* (8.4%; 58/691), *Salmonella Stanley* (4.1%; 28/691), *Salmonella London* (3.8%; 26/691), and *Salmonella Derby* (3.3%; 23/691). The distribution of 691 NTS isolates, serogroups, and serotypes are presented in Table 1.

NTS infections occurred throughout the year, but they were more frequently observed during summer and autumn (May–October), accounting for 80.9% of cases; most cases occurred in July (13.5%), August (17.8%), and September (21.4%). During each month, the proportion of *S. Typhimurium* infections was approximately 50% (Figure 2).

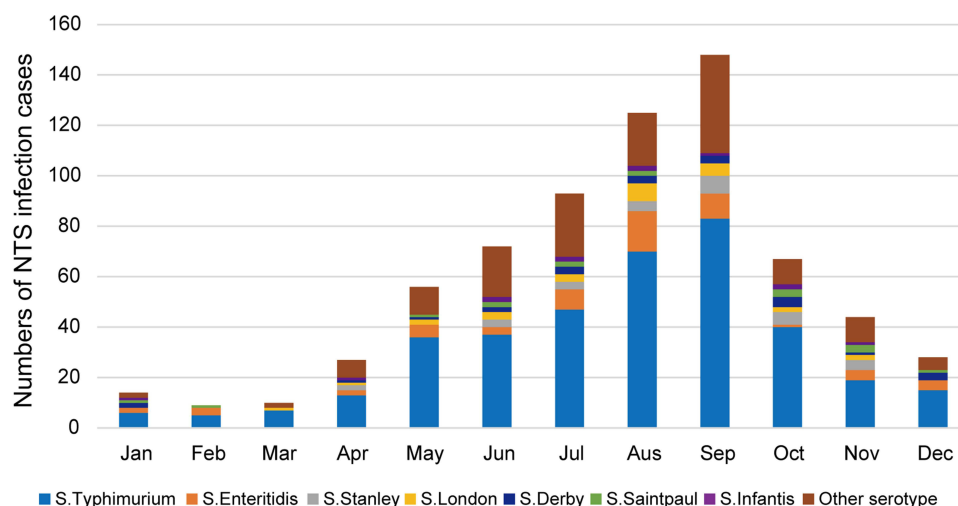


Figure 2 Distribution of 691 isolates of different serotypes in children <14 years old with NTS infection by month, Fuzhou, China, 2012–2021.

Demographic and Clinical Manifestations

During the 10-year study period, 105,326 blood, 6327 urine, 6781 cerebrospinal fluid and 18215 stool (1861 in 2012, 1255 in 2013, 1362 in 2014, 1127 in 2015, 1200 in 2016, 1847 in 2017, 1959 in 2018, 2032 in 2019, 2772 in 2020, 2800 in 2021), 53 vaginal secretions culture, 10 Joint fluid culture samples were screened in total; 691 cases of NTS infections were confirmed (among which 656 (94.9%) were only positive in faeces culture, 21 (3.0%) were only positive in blood culture, 4 (0.6%) were only positive in joint fluid culture and 1 (0.1%) was only positive in vaginal secretions culture, urine culture, abdominal culture and cerebrospinal fluid culture, respectively. Both faecal and blood culture were positive in 6 cases (0.9%) (Table 2).

Most of the NTS infections confirmed by blood samples were observed in children younger than 2 years of age (26 cases; 96.3%); however, 21 cases (77.8%) were observed in children younger than 1 year of age and 2 cases were observed in newborns. Among these infections, only one was observed in a child older than 2 years of age. Among the 691 NTS infections, the male-to-female ratio was 1.4:1. NTS infections commonly occurred in children 1 month to 3 years of age, accounting for 91.9% of the isolates (635/691). Laboratory test results indicated white blood cell, neutrophil, and C-reactive protein levels of 11.23 ± 0.1871 , 52.43 ± 0.7153 , and 30.36 ± 1.611 , respectively (Table 2). Among these patients, 91.5% (617/674) had diarrhea (mostly watery or sticky stools). Pus was detected in 68.1%, erythrocytes were detected in 40.1%, and occult blood was detected in 78.7% of the stool samples. A total of 65.6% of the patients had fever. Respiratory symptoms, such as cough, expectoration, and shortness of breath, were relatively common in children with NTS infections (25.8%).

We compared the demographics and clinical manifestations of *S. Typhimurium* infections and non-*S. Typhimurium* infections. *S. Typhimurium* infections commonly occurred in children 1 month to 3 years of age, accounting for 92.6% of isolates (350/378), which was significantly higher than the rate of non-*S. Typhimurium* infections (87.6%; 274/313). However, the opposite was observed in those older than 3 years. Significantly more stool samples were positive for *S. Typhimurium* infections than for non-*S. Typhimurium* infections; furthermore, invasive infections, such as blood infections, were significantly more frequently observed with non-*S. Typhimurium* than with *S. Typhimurium*. Among the 371 patients with *S. Typhimurium* infections, 352 (94.9%) had diarrhea. However, 265 patients (87.5%) in the non-*S. Typhimurium* group had diarrhea. The rate of diarrhea of patients with *S. Typhimurium* infections was significantly higher than that of patients with non-*S. Typhimurium* infections. Among children with diarrhea, 74.3% with *S. Typhimurium* infections had mucus in their stool samples; this rate was significantly higher than that of children with non-*S. Typhimurium* infections (60.5%) (Table 2).

Table 2 Demographic and Clinical Manifestations of Children with NTS Infection, Fuzhou, China, 2012–2021

Characteristic	NTS Infection (n=691)	S. Typhimurium Infection (n=378)	Non-S. Typhimurium Infection (n=313)	χ^2	P
Demographic Age and Sex					
<1 months	1.6%(11/691)	2.1%(8/378)	0.96%(3/313)	1.465	0.2261
1–12 months	43.3%(299/691)	40.2%(152/378)	47.0%(147/313)	3.181	0.0745
1–3 years	47.0%(325/691)	52.4%(198/378)	40.6%(127/313)	9.58	0.0020*
>3 years	8.1%(56/691)	5.3%(20/378)	11.5%(36/313)	8.868	0.0029*
Male	57.9%(400/691)	58.2%(220/378)	57.5%(180/313)	0.03374	0.8543
Female	42.1%(291/691)	41.8%(158/378)	42.5%(133/313)	0.03374	0.8543
Laboratory studies					
Blood routine examination				t	P
WBC	11.23±0.1871 (n=607)	10.95±0.2269 (n=343)	11.59±0.3122 (n=264)	t=1.693	0.091
NE	52.43±0.7153 (n=607)	52.21±0.9311 (n=343)	52.73 ± 1.116 (n=264)	t=0.3591	0.7196
CRP	30.36±1.611 (n=607)	31.67 ± 2.199 (n=343)	28.64 ± 2.356 (n=264)	t=0.9315	0.3519
Stool routine examination				χ^2	P
Pus	68.1%(457/671)	74.3%(275/370)	60.5%(182/301)	14.68	0.0001*
Erythrocyte	40.1%(269/671)	42.2%(156/370)	37.5%(113/301)	1.475	0.2245
OB	78.7%(528/671)	77.8%(288/370)	79.7%(240/301)	0.3559	0.5508
Stool culture: positive NTS	98.8%(662/691)	98.7%(373/378)	92.3%(289/313)	17.14	<0.0001*
Blood culture: positive NTS	3.9%(27/691)	1.3%(5/378)	7.0%(22/313)	14.85	0.0001*
Joint fluid culture: positive NTS	0.6%(4/691)	0.3%(1/378)	1.0%(3/313)	1.433	0.2313
Vaginal secretions culture: positive NTS	0.1%(1/691)	0	0.3%(1/313)	1.206	0.2721
Urine culture: positive NTS	0.1%(1/691)	0	0.3%(1/313)	1.206	0.2721
Abdominal culture: positive NTS	0.1%(1/691)	0	0.3%(1/313)	1.206	0.2721
Cerebrospinal fluid culture: positive NTS	0.1%(1/691)	0	0.3%(1/313)	1.206	0.2721
Invasive positive NTS	4.8%(33/691)	1.6%(6/378)	8.6%(27/313)	18.65	<0.0001*
Symptoms					
Fever(>37.3)	65.6%(442/674)	63.1%(234/371)	68.6%(208/303)	2.296	0.1297
Diarrhea	91.5%(617/674)	94.9%(352/371)	87.5%(265/303)	11.86	0.0006*
Bloody stools	13.1%(88/674)	14.3%(53/371)	11.6%(35/303)	1.099	0.2946
Vomiting	10.4%(70/674)	11.1%(42/371)	9.2%(28/303)	0.5948	0.4406
Convulsion	4.0%(27/674)	2.7%(10/371)	5.6%(17/303)	3.686	0.0549
Respiratory symptoms	25.8%(174/674)	27.5%(102/371)	23.8%(72/303)	1.212	0.2709
Myocardial damage	1.9%(13/674)	1.9%(7/371)	2.0%(6/303)	0.00769	0.9301
Hospitalization	44.2%(306/691)	42.1%(159/378)	47.0%(147/313)	1.667	0.1966

Notes: *Shows the difference between the two groups has a statistical significance as $P < 0.05$.

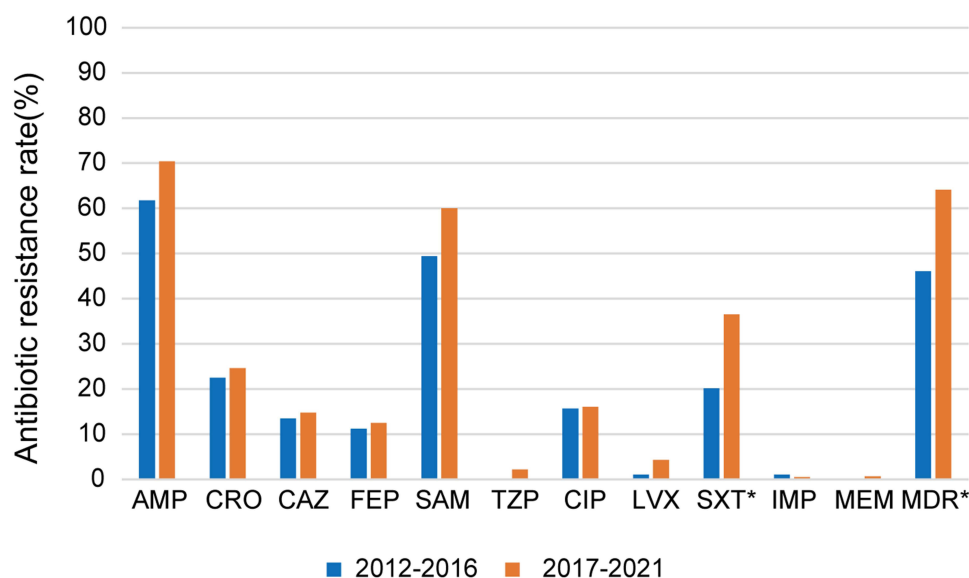


Figure 3 Antibiotic resistance of *Salmonella* spp. isolates from children <14 years old, during the periods 2012–2016 and 2017–2021, Fuzhou, China.

Notes: *Shows the difference between the two groups has a statistical significance as $P < 0.05$. SXT: $\chi^2 = 9.146$, $P = 0.0025$. MDR: $\chi^2 = 10.7$, $P = 0.0011$.

Abbreviations: CAZ, Cefazidime; FEP, Cefepime; CRO, Ceftriaxone; SXT, Trimethoprim/sulfamethoxazole; AMP, Amoxicillin; MEM, Meropenem; CIP, Ciprofloxacin; LVX, Levofloxacin; TZP, Piperacillin/tazobactam; SAM, Ampicillin sulbactam; IMP, Imipenem; MDR, multidrug-resistance.

Antimicrobial Resistance

During this 10-year study period, 691 NTS isolates were identified and 415 infections (60.1%) were MDR. The MDR rate during the last 5 years (2017–2021) was significantly higher than that during the first 5 years (2012–2016) of the study. The drug resistance of almost all drugs and MDR increased during the last 5 years of the study, mainly the resistance to trimethoprim/sulfamethoxazole increased significantly (Figure 3). The NTS isolates were highly resistant to amoxicillin (69.3%) and ampicillin sulbactam (59.0%). Notably, resistance to third-generation cephalosporins, such as ceftriaxone and ceftazidime, was detected in 24.5% and 14.6% of isolates, respectively, whereas resistance to fluorquinolones, such as ciprofloxacin, was observed in 15.8% of samples and 53.3% of isolates presented reduced susceptibility to ciprofloxacin ($n=368$). Only 13 isolates were resistant to piperacillin/tazobactam, and only four isolates were resistant to imipenem (Table 3).

We compared the antimicrobial resistance of *S. Typhimurium* with that of non-*S. Typhimurium* and found that the resistance of *S. Typhimurium* to all antibiotics, including amoxicillin and ampicillin sulbactam, ceftriaxone, ciprofloxacin and trimethoprim/sulfamethoxazole, was significantly higher than that of non-*S. Typhimurium*. More *S. Typhimurium* isolates compared to non-*S. Typhimurium* isolates were resistant to first-line agents (Table 3). The rate of MDR associated with *S. Typhimurium* isolates was higher than that associated with non-*S. Typhimurium* isolates, particularly during the last 2 years of this study (2020 and 2021) (Figure 4).

Discussion

During our study, we summarized NTS infections among children <14 years old in Fuzhou, Fujian, China, during 2012 to 2021 and found that *S. Typhimurium* was the dominant serotype and increased sharply. Meanwhile, our data indicated the difference of clinical symptoms, laboratory test results, and drug resistance between *S. Typhimurium* infection and non-*S. Typhimurium* infection. We found that *S. Typhimurium* infection was commonly occurred in children younger than 3 years and most of them are gastrointestinal infection while non-*S. Typhimurium* infection more often observed in older children and associated with extra-intestinal infection. The rate of multidrug-resistant with *S. Typhimurium* isolates was significantly higher than that of non-*S. Typhimurium* isolates, especially during the last 2 years of this study (2020 and 2021).

Fuzhou is located on the southeast edge of Eurasia and southeast coast of China (25°15'–26°39'N, 118°08'–120°31'E); It has a typical subtropical monsoon climate, with an average annual temperature of 20°C to 25°C, the hottest temperatures occur from July to September, with an average temperature of 33°C to 37°C. The annual relative humidity

Table 3 Antimicrobial Resistance Among *S. Typhimurium* and Non-*S. Typhimurium* Isolates from Children <14 Years Old, Fuzhou China, 2012–2021

Antibiotic	NTS Isolates (n=691)	<i>S. Typhimurium</i> Isolates (n=378)	Non- <i>S. Typhimurium</i> Isolates (n=313)	χ^2	P
Ampicillin	69.3%(479/691)	85.2%(322/378)	50.2%(157/313)	98.77	<0.0001*
Ceftriaxone	24.5%(169/691)	29.9%(113/378)	17.9%(56/313)	13.35	0.0003*
Ceftazidime	14.6%(101/691)	16.1%(61/378)	12.8%(40/313)	1.547	0.2136
Cefepime	12.4%(86/691)	14.6%(55/378)	9.9%(31/313)	3.392	0.0655
Ampicillin sulbactam	59.0%(408/691)	72.8%(275/378)	42.5%(133/313)	64.83	<0.0001*
Piperacillin tazobactam	1.9%(13/691)	2.1%(8/378)	1.6%(5/313)	0.2498	0.6172
Imipenem	0.6%(4/691)	0.5%(2/378)	0.6%(2/313)	0.03592	0.8497
Meropenem	0.6%(4/691)	0.5%(2/378)	0.6%(2/313)	0.03592	0.8497
Ciprofloxacin	15.8%(109/691)	19.3%(73/378)	11.5%(36/313)	7.862	0.0050*
Levofloxacin	3.5%(27/691)	3.7%(14/378)	4.2%(13/313)	0.0922	0.7614
Trimethoprim/sulfamethoxazole	34.4%(238/691)	43.7%(165/378)	23.3%(73/313)	31.34	<0.0001*
Class level					
0 class (no resistant)	13.6%(94/691)	5.6%(21/378)	23.3%(73/313)	45.99	<0.0001*
1 class	16.2%(112/691)	8.7%(33/378)	25.2%(79/313)	34.36	<0.0001*
2 classes	10.1%(70/691)	15.6%(59/378)	3.5%(11/313)	27.51	<0.0001*
3 classes	19.2%(133/691)	19.0%(72/378)	19.5%(61/313)	0.02144	0.8836
≥4 classes	40.8%(282/691)	51.1%(193/378)	28.4%(89/313)	36.28	<0.0001*
MDR	60.1%(415/691)	70.1%(265/378)	47.9%(150/313)	35.12	<0.0001*
First-line agents					
0 agent (no resistant)	14.2%(98/691)	5.8%(22/378)	24.3%(76/313)	47.95	<0.0001*
1 agent	24.7%(171/691)	20.1%(76/378)	30.4%(95/313)	9.651	0.0019*
2 agents	20.5%(142/691)	22.0%(83/378)	18.8%(59/313)	1.013	0.3142
3 agents	30.8%(213/691)	39.7%(150/378)	20.1%(63/313)	30.71	<0.0001*
4 agents	9.7%(67/691)	12.4%(47/378)	6.4%(20/313)	7.144	0.0075*

Notes: First-line agents (ampicillin, ceftriaxone, ciprofloxacin, trimethoprim/sulfamethoxazole). *Shows the difference between the two groups has a statistical significance as $p < 0.05$.

is approximately 77%. In this study, *Salmonella* infection increased in the warm seasons, especially in summer. Stronger research evidence indicated that *Salmonella* infections are elevated in warm climates.^{27,28}

In our study, *S. Typhimurium* was the most predominant serotype in children <14 years old and greatly increased annually. Other studies performed in China also showed that *S. Typhimurium* was the most common serotype in children.^{14,22,29} However, some studies have shown that *S. Enteritidis* was the most common serotype in China.^{30,31} According to our results, the next most common serotypes were *S. Enteritidis* and *S. Stanley*. In some countries, most human clinical cases are dominated by one serotype, such as *S. Typhimurium* in Australia or *S. Enteritidis* in Brazil and Europe.^{32–34} However, other countries have a more balanced distribution of cases associated with each serotype, such as *S. Enteritidis*, *Salmonella* Newport, and *S. Typhimurium* in the United States, and *S. Enteritidis*, *S. Stanley*, and

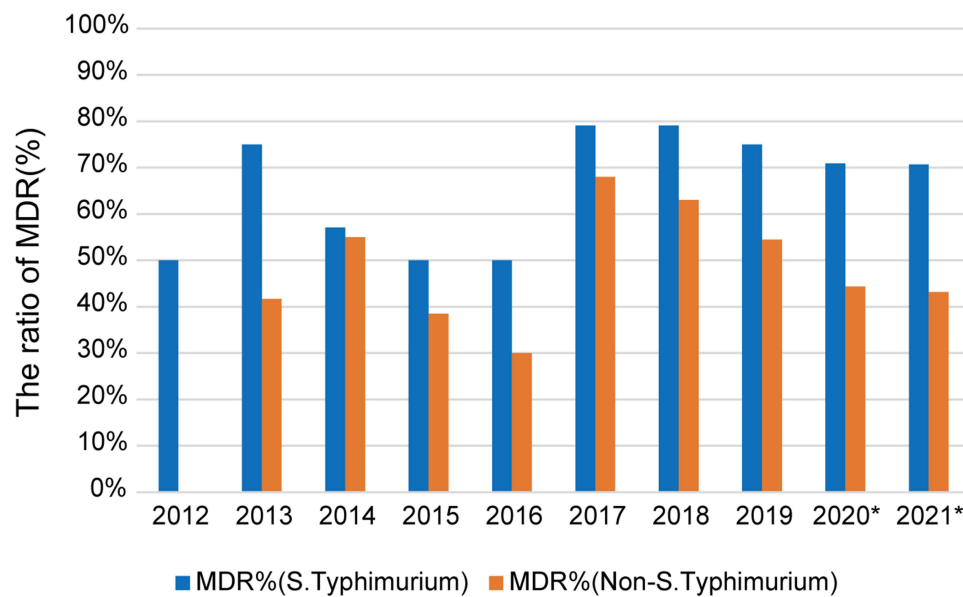


Figure 4 Change of drug resistance and MDR (%) in past ten years, Fuzhou, China.

Notes: *Shows the difference between the two groups has a statistical significance as $P < 0.05$. 2020: $\chi^2 = 10.6$, $P < 0.001$; 2021: $\chi^2 = 16.13$, $P < 0.0001$.

Salmonella Weltevreden in Thailand.^{35,36} Despite the discrepancy in the rates of illness in each geographic region, *S. Typhimurium* and *S. Enteritidis* have been consistently reported as the serotypes that contribute to the highest rates of clinical human salmonellosis worldwide.^{22,29–32,37} The variation in serotype distribution in a region may be associated with the presence of a local animal reservoir especially pets like turtles³⁸ or food source mainly come from eggs and poultry.²¹ Meanwhile, the cause of the increase in *S. Typhimurium* infections with children annually is not clear. This trend was also happened in other areas in China like Hangzhou,³⁹ Chongqing,¹⁴ Ningbo²² and so on. Data from the European Food Safety Authority (EFSA) showed that outbreaks caused by *S. Typhimurium* were mainly attributed to pork.²¹ Also a study investigating meat derived from livestock revealed that *S. Typhimurium* was the dominant serotype in China from 2018 to 2020.⁴⁰ Another investigation in China revealed the most prevalent *Salmonella* serotypes were *S. Typhimurium* in retail meats and eggs.⁴¹ *S. Typhimurium* has had the main ecological role in regional food production systems, such as poultry and egg, which has been successfully occupied by *S. Typhimurium* and has become a reservoir for its further transmission through contaminated food products. To prioritise interventions, it is important to evaluate the sources and trends of salmonellosis outbreaks. We recommend monitoring food safety to reduce the risk of the infection of *S. Typhimurium*.

In our study, *S. Typhimurium* infection was commonly occurred in children younger than 3 years and most of them are gastrointestinal infection, while non-*S. Typhimurium* more often observed in older children and associated with extra-intestinal infection. This could be because it is customary for Chinese parents to feed congee mixed with cooked minced pork and steamed egg during the weaning of infants, and *S. Typhimurium* infections are mostly attributed to pork and egg.^{21,41} The result was similar to the other study.^{14,22} Other studies has showed that nontyphoidal *Salmonella* serotypes are diverse in their host range and epidemiology and vary in their propensity to cause bloodstream infection and severe human disease.²³ In our study, a significantly higher number of patients with *S. Typhimurium* infections had diarrhea than non-*S. Typhimurium*. Our findings were not entirely consistent with investigation from a large survey conducted at the same time in Zhejiang province, which may result from differences in the selection of population.⁴² The group we had choose was children confirmed by positive culture test results including medical and surgical patients while they choose all groups with bacterial foodborne diseases. However, invasive infections, especially blood infections, were observed significantly more often with non-*S. Typhimurium* than with *S. Typhimurium*. This phenomenon was similar to that reported by others both here and abroad.^{23,43} It has been reported that *Salmonella Typhimurium* is considered to have a modest likelihood of causing NTS infections, while other less common serotypes, such as Heidelberg, Choleraesuis,

and Dublin, are more likely to cause invasive disease.⁴³ We found that *Salmonella* Saintpaul could easily cause invasive infections; therefore, further research will be performed in the future. Virulence mechanisms, genetic differences in serotypes, and the host immune status contribute to the diversity of clinical symptoms.

Gastroenteritis and fever were the most common clinical symptoms of infected patients. Among the 691 cases of salmonella infections, a significantly higher number of patients with *S. Typhimurium* infections had diarrhea. *S. Typhimurium* is an invasive bacterium that invades intestinal mucosal epithelial cells, causes mucus, pus, and blood in the stool, and produces enterotoxin, thereby enhancing intestinal mucosal secretion and leading to diarrhea.⁴⁴ Routine fecal analyses were often performed to assess the functional status of the gastrointestinal tract. Mucus, pus, and red blood cells were commonly observed with bacterial enteritis. Among those with diarrhea, significantly more children with *S. Typhimurium* had feces containing mucus compared to those with non-*S. Typhimurium*. *S. Typhimurium* results in more efficient host cell invasion and is likely to contribute to a strong inflammatory response and higher infiltration of neutrophils and other inflammatory cells.⁴⁵ Fever is also a common clinical symptom of infection. In general, the rates of vomiting and bloody stools were not high. Because the age of onset was approximately 3 years, the symptoms of abdominal pain could not be accurately evaluated clinically. In addition to digestive tract symptoms, respiratory tract infections were relatively common in children infected with salmonella, with an incidence close to that of children infected with *S. Typhimurium* in the Xiamen area.¹³ Another concomitant symptom was convulsions. Convulsions were complicated by high fevers, and their rates are similar to those of febrile convulsions.¹⁸ It is considered that convulsions are secondary to high fevers. Salmonella infections some cause myocardial damage. Laboratory examinations of white blood cells, neutrophils, and C-reactive protein levels were commonly performed to evaluate the degree of the inflammatory response. For children with diarrhea and bloody stools accompanied by fever and increased white blood cells and C-reactive protein levels, it is necessary to perform a fecal culture test as soon as possible to clarify the diagnosis and guide treatment.

The resistance to the most antibiotics and the rate of MDR of *S. Typhimurium* was significantly higher than that of non-*S. Typhimurium*, consistent with domestic report in China.^{46,47} Our findings demonstrated a high rate of ampicillin resistance among *S. Typhimurium* isolates. The result was similar to the nationwide average.⁴⁸ These results suggest that ampicillin is not appropriate for the treatment of *S. Typhimurium* in the region where this study was performed. Additionally, fluoroquinolones have not been approved by the Food and Drug Administration for those younger than 18 years of age, and they are not recommended unless the benefits of therapy outweigh the potential risks of drug administration.⁴⁹ Therefore, third-generation cephalosporins are considered alternative drugs for the treatment of salmonellosis in infants.⁵⁰ But our study revealed a high rate of resistance to third-generation cephalosporins, such as ceftriaxone that was similar to the nationwide average.⁴⁸ Therefore, the rapid increase in the resistance to third-generation cephalosporins in infants is considered a warning signal. The proportion of multidrug-resistant isolates reached 70.1%, thus surpassing that of *Salmonella* spp. This finding is consistent with that of Ke et al,⁵¹ who found that the rate of MDR associated with *S. Typhimurium* was very high and increased yearly, with even higher rates observed for infants. Therefore, the increase in multidrug-resistant salmonella isolates, particularly those resistant to ciprofloxacin and third-generation cephalosporins, may lead to the failure of human infection treatments. Colistin is a last-line antibiotic used for the clinical treatment of multidrug-resistant Enterobacteriaceae infections. Unfortunately, a 10-year study involving continuous surveillance and a genomic study performed in Guangdong, Southern China, revealed that the emergence of and relatively high prevalence of the mobilised colistin resistance (*mcr-1*) gene have spread throughout the entire human health system, thereby threatening the usage of colistin in the clinical setting.⁵² During our study, most isolates were sensitive to piperacillin/tazobactam, indicating that it can be considered an alternative for treating infections caused by third-generation cephalosporin-resistant strains or multidrug-resistant salmonella isolates in infants, thus reducing the use of carbapenem antibiotics. Careful surveillance of salmonella and its microbial resistance patterns is important to the prevention and control of the increase of multidrug-resistant clones.⁵³

Limitations

This retrospective study had some limitations. First of all, the case data were collected through the electronic medical records, some information was either missing or incomplete such as the etiology and food categories, settings, etc.

because the physicians focus on the diagnosis and treatment of the disease, the etiology often is ignored, so the conclusions might not be representative. Second, lack of cognition and limited detection capacity, we did not carry out the detection of monophasic isolates clinically. Due to the absence of the strain, we were unable to retest to differentiate *S. Typhimurium* typical strains and monophasic variants. Further case surveillance should focus on the etiology and food, and make efforts to carry out the test to differentiate *S. Typhimurium* typical strains and monophasic variants clinically.

Conclusion

In summary, our current data described the epidemiology characteristics of NTS infections among children in Fuzhou city for the first time over the past 10 years. *S. Typhimurium* was the dominant serotype and greatly increased. There are some significant differences in clinical symptoms, laboratory test results, and drug resistance between *S. Typhimurium* and non-*S. Typhimurium*. Understanding the differences which might benefit the prevention and treatment of NTS infection. Meanwhile, the rapid increase in the resistance of *S. Typhimurium* is considered a warning signal. It is necessary to carry out drug resistance analysis and whole genome sequencing of *Salmonella* cases, and further explore its biological mechanism. An overall assessment of *Salmonella* infection in residents by strengthening surveillance, source attribution and burden estimation is a matter of great urgency and more efforts should be directed toward conducting comprehensive assessments for specific public health policy formulation.

Abbreviations

MDR, *S. Typhimurium*, non-*S. Typhimurium*.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Fujian Maternity and Child Care Hospital (No. 2023KY001). Informed consent was obtained from all the participants prior to enrollment. Our study was carried out followed the principles outlined in the Declaration of Helsinki.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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