

Clinical features and drug resistance analysis of non-typhoidal *Salmonella* infection in children

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Abstract

Introduction: There is limited information on non-typhoidal *Salmonella* (NTS) infections among children in China. The aim of this study was to explore the clinical features, strain serotypes, and drug resistance patterns of NTS infection in children.

Methodology: A retrospective study of children with NTS admitted to three tertiary hospitals between January 2015 and December 2024 was conducted. The clinical features and drug resistance were compared among the patients.

Results: Out of a total of 131 patients, 94 cases (71.76%) visited the hospital between June and September, and 82 cases (62.60%) were aged 6 months to 2 years. The main clinical manifestations were fever and diarrhea, with 94 cases (71.76%) presenting high fever ($> 39^{\circ}\text{C}$) and 129 cases (98.50%) experiencing diarrhea. Stool consistency was predominantly loose paste or watery. Regarding serotypes, *Salmonella* Typhimurium was the most common (96 cases, 73.28%), while *Salmonella* Dublin ranked second (12 cases, 9.16%). The study revealed an increasing resistance rate to ceftriaxone. High resistance rates ($> 80\%$) were observed for ampicillin, cefazolin, and gentamicin; whereas high sensitivity ($> 90\%$) was noted for ceftazidime, piperacillin-tazobactam, and carbapenems. The rate of sensitivity to ceftazidime was linearly correlated with age ($p = 0.03$).

Conclusions: NTS predominantly occurred in summer and autumn among children aged 6 months to 2 years. The clinical features were primarily fever and diarrhea. Given the rising resistance to ceftriaxone, ceftazidime may be prioritized for empirical treatment.

Key words: *Salmonella*, non-typhoidal, manifestation, drug resistance, children.

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Introduction

Salmonella, a genus of Gram-negative bacilli, was reported to be a leading global foodborne pathogen in 2019 [1]. The bacterium is transmitted via contaminated foods such as fruits, meat products, eggs, and dairy; and is a significant global public health burden [2]. Non-typhoidal *Salmonella* (NTS) was reported to be the major pathogen causing an estimated 94 million illnesses annually [3], predominantly affecting children under 5 years of age [4], but associated with the death of children aged 5–14 years [5].

The principal manifestation of NTS infection is diarrheal enterocolitis, and it can lead to serious invasive NTS infection, which may result in severe complications such as bacteremia, meningitis, and osteomyelitis. Children who have lower immune defenses are more susceptible to severe complications. Studies have shown the significant, and often overlooked, impact of NTS in Asia [6]. Moreover,

although there is increased recognition worldwide, little data on NTS infection among children is available in China; and the clinical features of pediatric patients at greater risk of NTS disease, along with the relevant antimicrobial treatment practices, remain insufficiently explored.

With the increase in the number of children with NTS and the widespread use of antibiotics in recent years, the prevalence of resistance in NTS has increased [7]. Therefore, it is important to pay attention to NTS infection in children, and administer timely treatment and appropriate antibiotics to avoid adverse outcomes. Therefore, this study explored the clinical features and drug resistance patterns of pediatric NTS infections in three tertiary hospitals located in China to better understand the epidemiology of NTS infections among children and to provide information for appropriate clinical management.

Methodology

Study subjects

A total of 130 strains of NTS were obtained from blood samples of hospitalized children in three tertiary A hospitals (the highest level of hospital classification within mainland China) located in Sichuan Province, China between January 2015 and December 2024. This study was approved by the Ethics Committee of The First Affiliated Hospital of Chengdu Medical College (2024CYFYIRB-BA-Nov07). Informed consent was obtained from the parents of all participants. Written informed consent was provided by the participants' guardians.

Although *Salmonella* Typhimurium is the most common pathogen, it is not clear whether there are differences in the disease caused by different NTS in children. Therefore, NTS were grouped based on whether the disease was caused by *Salmonella* Typhimurium ($n = 96$) or other serotypes ($n = 35$).

The inclusion criteria were (1) age < 18 years; (2) mucus and blood in stools, along with more frequent bowel movements; (3) stool test revealed numerous white blood cells, pus cells, and different levels of red blood cells; (4) stool test showed positive results for NTS strains; and (5) clinical diagnosis suggested acute invasive bacterial gastroenteritis, conforming to the diagnostic criteria for infectious gastroenteritis according to the "Guidelines for the Diagnosis and Treatment of Acute Infectious Diarrhea in Children" (2020 Edition) [8].

The exclusion criteria were (1) incomplete laboratory data; (2) incomplete treatment course; and (3) non-infectious gastrointestinal conditions (such as allergic enteritis, gastrointestinal malformations, and inflammatory bowel disease). A total of 6 cases were excluded (including 2 incomplete records, 1 incomplete treatment, 3 non-infectious gastrointestinal conditions).

Antibiotic resistance was defined as intermediate or resistant minimum inhibitory concentration. Therapeutic efficacy was defined as the resolution or improvement of the patient's clinical symptoms; or some clinical examination indicators like routine blood tests, C-reactive protein (CRP), or stool culture results returned to essentially normal levels. Multi-drug resistance (MDR) was defined as resistance to ≥ 3 structurally distinct antibiotic classes

Materials

Equipment for *Salmonella* culture included Gram-negative bacteria identification antimicrobial susceptibility composite plate and identification culture medium, antimicrobial susceptibility culture medium

(BD Company, New Jersey, USA), Kirby-Bauer (K-B) antimicrobial susceptibility paper (OXOID, Basingstoke, UK); SS agar (Britt Biotechnology Company, Zhengzhou, China), PhoenixTM-100 automatic bacterial identification/antimicrobial susceptibility analysis system (BD Company, New Jersey, USA), Gram-negative identification/susceptibility panels and broths (BD Company, New Jersey, USA), K-B susceptibility discs (OXOID, Basingstoke, UK), and *Salmonella-Shigella* agar (Britt Biotechnology Company, Zhengzhou, China).

Fecal culture for *Salmonella* was performed according to the National Guide to Clinical Laboratory Procedures (3rd Edition) [9] and the Ministry of Health industry standard (WS 271-2007 Diagnostic Criteria for Infectious Diarrhea) [10]. Suspicious colonies were isolated and inoculated onto *Salmonella-Shigella* agar medium. *Salmonella* was suspected if typical black colonies grew on the SS agar after overnight incubation. Following preliminary identification of the colonies, the *Salmonella* genus was identified using the PhoenixTM-100 fully automated bacterial identification system. Antimicrobial susceptibility testing was performed using the K-B disk diffusion method. Susceptibility categories (susceptible, intermediate, resistant) were determined based on the diameter of the inhibition zones; isolates falling within the intermediate range were not considered susceptible. The procedures and interpretation of results adhered to the standards of the Clinical and Laboratory Standards Institute (CLSI 2016) [11]. Serotyping was performed based on the results of the NTS diagnostic serum agglutination test (Ningbo Tianrun Bio-pharmaceutical, Zhejiang, China), and cross-referenced with the Kaufmann-White scheme for *Salmonella* antigen classification.

Data collection

The collected data included demographics; clinical signs and symptoms including fever, vomiting, diarrhea, abdominal pain; laboratory findings including white blood cell count (WBC), neutrophil percentage (N%), lymphocyte percentage (L%), hemoglobin (Hb), platelet count (PLT), CRP, stool routine, culture/antibiotic susceptibility test results; antibiotics used; and information on treatment. All data entry was verified for accuracy and double-checked.

Statistical analysis

All data were analyzed by using the SPSS 22.0 software (IBM, Armonk, NY, USA). Categorical data were presented as counts (percentages) and compared

using χ^2 tests. Normally distributed continuous data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm S$) and compared using Student t-tests. Non-normally distributed data were expressed as median (interquartile range, IQR), and compared using the Mann-Whitney test. A significance level of 5% was applied to show the significance of the variables. In addition, the Cochran-Armitage trend test was used to evaluate the correlation between a dichotomous variable and an ordered categorical variable.

Results

Demographic and clinical observations

The study included 131 patients, comprising 79 males (60.3%) and 52 females (39.7%). The majority were aged between 6 months and 2 years. Most cases were reported from June to September ($n = 94$, 71.8%), with a decline thereafter (Figure 1).

The primary symptoms were fever ($n = 122$, 93.1%) and diarrhea ($n = 129$, 98.5%). Among them, 91 cases (74.0%) had a body temperature $> 39^\circ\text{C}$. Diarrhea was severe in 32 cases (24.4%), exceeding 10 times/day, with 4 cases exceeding 20 times/day. Stool characteristics were primarily yellow, watery, or loose paste, with "egg-drop" stools in 12 cases (9.2%). Mucus was present in 84 cases (64.1%), while blood streaks or fresh blood were found in 42 cases (32.1%), and mucopurulent bloody stools in 21 cases (16.0%) (Table 1). There were significant differences in the presence of mucus ($p = 0.016$) and mucopurulent stool ($p = 0.038$) prevalence across infant (< 1 year), toddler ($\geq 1, < 3$

years), and preschool/school-age (≥ 3 years) groups (Table 2).

Laboratory indicators

A total number of 68 patients (51.9%) presented with elevated WBC counts ($> 10 \times 10^9/\text{L}$), 9 patients exceeding $20 \times 10^9/\text{L}$. CRP levels were high ($> 8 \text{ mg/L}$) in 109 patients (83.2%), and 16 patients had levels above 100 mg/L. Fecal occult blood tests were positive in 121 cases (92.4%). Microscopic examination revealed WBC counts greater than 10/HPF in 79 patients (60.3%), and pus cells were noted in 34 patients (26.0%). No significant differences ($p > 0.05$) in laboratory results were found among the serotype groups (Table 1).

Figure 1. Distribution of frequency and the age of infection according to the months.

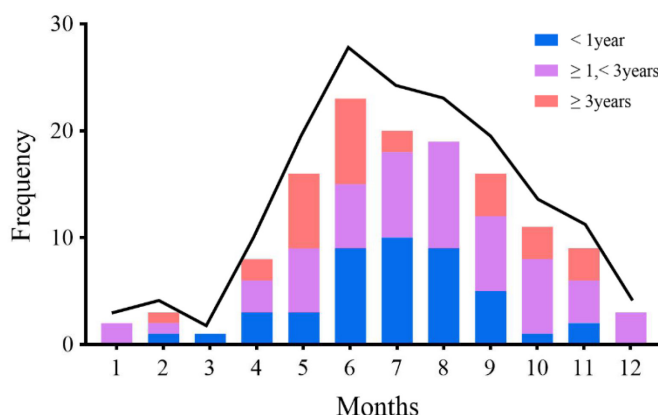


Table 1. Clinical characteristics of children with non-typhoidal *Salmonella* (NTS) infection.

Variables	<i>Salmonella</i> Typhimurium group (n = 96)	Non-Typhimurium <i>Salmonella</i> group (n = 35)	p	Total (n = 131)
Gender (n, %)				
Male	57 (59.38)	22 (62.83)	0.72	79 (60.31)
Female	39 (40.62)	13 (37.14)		52 (39.69)
Age (n, %)				
Infant (< 1 year)	32 (33.33)	12 (34.29)	0.89	44 (33.59)
Toddler (1–3 years)	41 (42.71)	16 (45.71)		57 (43.51)
Preschool/school-age (< 18 years)	23 (23.96)	7 (20.00)		30 (22.90)
Clinical presentation (n, %)				
Fever	39.38 $\pm$ 0.67	39.31 $\pm$ 0.89	0.94	39.50 $\pm$ 0.51
Diarrhea	94 (97.90)	35 (100.00)	0.39	129 (98.50)
Vomit	25 (26.04)	11 (31.43)	0.54	36 (27.50)
Bloody purulent stool	16 (16.70)	5 (14.28)	0.74	21 (16.01)
Sepsis	13 (13.54)	3 (8.57)	0.44	16 (12.21)
Respiratory tract infections	24 (25.00)	11 (31.42)	0.46	35 (26.72)
Myocardial damage	3 (3.13)	2 (5.71)	0.45	5 (3.82)
Febrile seizures	6 (6.25)	2 (5.71)	0.91	8 (6.11)
Blood routine				
WBC ($\times 10^9/\text{L}$)	11.27 (7.32, 14.62)	12.67 (7.94, 12.28)	0.59	11.61 (7.73, 15.05)
Hb (g/L)	123.07 (115.00, 126.50)	121.12 (110.50, 130.50)	0.56	123.05 (114, 130)
N (%)	64.42 $\pm$ 13.84	66.28 $\pm$ 16.26	0.60	63.97 $\pm$ 15.38
L (%)	25.56 $\pm$ 11.62	25.07 $\pm$ 13.58	0.56	26.50 $\pm$ 12.85
CRP (mg/L)	40.79 (11.25, 52.63)	48.10 (11.26, 66.90)	0.34	40.52 (10.82, 53.70)

Normally distributed continuous data are expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$), non-normally distributed data are expressed as median (interquartile range, IQR). WBC: white blood cells; Hb: hemoglobin; N: neutrophil; L: lymphocyte; CRP: C-reactive protein.

Table 2. Clinical characteristics of different age groups of children with non-typhoidal *Salmonella* (NTS) infection.

Variables	Infants (n = 44)	Toddlers (n = 57)	Other ages (n = 30)	p
Male (n, %)	26 (59.09)	35 (61.40)	18 (60.00)	0.97
Female (n, %)	18 (40.09)	22 (38.60)	12 (40.00)	
Fever (n, %)	39.08 ± 0.79	39.49 ± 0.61	39.50 ± 0.76	0.06
Vomit (n, %)	9 (20.45)	15 (26.32)	12 (40.00)	0.18
Diarrhea (n, %)	44 (100)	56 (98.25)	29 (96.67)	0.51
Mucous stool (n, %)	36 (81.82)	32 (57.14)	16 (55.33)	0.02
Bloody stool (n, %)	19 (43.19)	16 (28.07)	7 (23.33)	0.17
Bloody purulent stool (n, %)	12 (27.27)	5 (8.77)	4 (13.33)	0.04
Sepsis (n, %)	5 (11.36)	7 (12.28)	4 (13.33)	0.97
Mixed other pathogens (n, %)	2 (4.55)	5 (8.77)	3 (10.00)	0.62
Respiratory tract Infection (n, %)	9 (20.45)	18 (31.58)	8 (26.67)	0.46
CRP (mg/L)	37.83 (11.67, 57.16)	38.84 (10.65, 49.90)	39.91 (3.42, 52.13)	0.61
Typhimurium (n, %)	32 (72.73)	41 (71.93)	23 (76.67)	0.89

Infants include age < 1 years old, toddlers include children who are between 1 years old and < 3 years old. The others age group includes age ≥ 3 years but < 18 years old. Normally distributed continuous data are expressed as mean ± standard deviation ($\bar{x} \pm s$), non-normally distributed data are expressed as median (interquartile range, IQR). Mixed other pathogens: co-infection with other pathogens besides respiratory pathogens, such as rotavirus and norovirus. CRP: C-reactive protein.

Serotypes and antimicrobial susceptibility

All the children in this study were effectively treated by antibiotic therapy. *S. Typhimurium* was the most common among the 131 isolates, comprising 96 cases (73.3%); followed by *S. Dublin* (12, 9.2%), *S. Enteritidis* (6, 4.6%), and single cases of *S. Agona*, *S. Derby*, and *S. Cholerae Suis* (0.8% each); along with 14 isolates that could not be typed (10.7%). The isolates exhibited high resistance (over 80%) to ampicillin, cefazolin (first-generation cephalosporin), and gentamicin; while showing high sensitivity (over 90%) to ceftazidime, ertapenem, imipenem, and piperacillin-tazobactam. Moderate sensitivity (over 70%) was noted for ceftriaxone and cefotaxime (third-generation cephalosporins). *S. Dublin* demonstrated greater sensitivity (over 80%) to quinolones (ciprofloxacin, levofloxacin) and piperacillin-tazobactam compared to other serotypes. There were 7 MDR isolates; and 1 of them belonged to *S. Enteritidis* and was resistant to third-generation cephalosporins, penicillins, imipenem, and ertapenem, but was sensitive to piperacillin-tazobactam (Table 3).

A total of 114 patients were treated with third-generation cephalosporins. The rate of effectiveness of

third-generation cephalosporins was 97.37%. Additionally, there was a statistically significant difference among the different age groups in the sensitivity to ceftazidime (Table 4). Cochran-Armitage Trend Test was used to evaluate the difference and it was found that the rate of sensitivity to ceftazidime among the children was linearly correlated with age ($p = 0.03$).

Discussion

In this study, NTS primarily occurred in infants, especially in patients aged between 6 months and 2 years. This finding is consistent with other research results [12]. Relatively few patients were aged 0–6 months, and this may be related to the presence of specific antibodies acquired from the mother. Besides, most cases were reported from June to September. Sichuan is located in a basin where the summer temperature ranged between 28–37 °C and the air is humid. These conditions are suitable for *Salmonella* breeding.

The clinical manifestations of NTS infection are not specific. In this study, fever and diarrhea were the predominant symptoms among pediatric patients.

Table 3. Antimicrobial susceptibility of 131 non-typhoidal *Salmonella* (NTS) isolates.

Antimicrobials	<i>Salmonella typhimurium</i> (n = 96)			<i>Salmonella Dublin</i> (n = 12)			Other serotypes of <i>Salmonella</i> (n = 23)		
	Resistant	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant	Sensitive	Intermediate
Ampicillin (n, %)	83 (88)	11 (11)	0 (0)	8 (67)	4 (33)	0 (0)	12 (57)	9 (43)	0 (0)
Ceftazidime (n, %)	7 (7)	87 (92)	1 (1)	0 (0)	12 (100)	0 (0)	1 (5)	20 (90)	1 (5)
Ciprofloxacin (n, %)	9 (10)	49 (53)	34 (37)	0 (0)	10 (91)	1 (9)	1 (5)	14 (67)	6 (28)
Ceftriaxone (n, %)	23 (24)	73 (76)	0 (0)	2 (17)	10 (83)	0 (0)	4 (17)	19 (83)	0 (0)
Cefotaxime (n, %)	21 (20)	72 (77)	3 (3)	3 (25)	9 (75)	0 (0)	2 (10)	19 (90)	0 (0)
Ertapenem (n, %)	0 (0)	86 (100)	0 (0)	0 (0)	12 (100)	0 (0)	1 (5)	19 (95)	0 (0)
Imipenem (n, %)	0 (0)	93 (99)	1 (1)	0 (0)	12 (100)	0 (0)	1 (6)	17 (94)	0 (0)
Levofloxacin (n, %)	5 (5)	49 (53)	38 (42)	0 (0)	10 (83)	2 (17)	1 (5)	13 (62)	7 (33)
Piperacillin, tazobactam (n, %)	1 (1)	85 (97)	2 (2)	0 (0)	12 (100)	0 (0)	1 (5)	19 (95)	0 (0)
MDR (n, %)		5 (5)			0 (0)			2 (2)	

MDR: multi-drug resistant.

Table 4. Distribution of antibiotic performance in different age groups (n = 131).

Antimicrobials	Infants (n = 44)			Toddlers (n = 57)			Others ages (n = 30)			p
	Resistant	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	Resistant	Sensitive	Intermediate	
Ampicillin (n, %)	33 (77)	10 (23)	0 (0)	47 (86)	8 (14)	0 (0)	23 (79)	6 (21)	0 (0)	0.65
Ceftazidime (n, %)	0 (0)	44 (100)	0 (0)	4 (7)	51 (90)	2 (3)	5 (17)	24 (83)	0 (0)	0.02
Ciprofloxacin (n, %)	0 (0)	28 (68)	31 (32)	9 (16)	29 (52)	18 (32)	1 (4)	16 (59)	10 (37)	0.96
Ceftriaxone (n, %)	6 (14)	38 (86)	0 (0)	14 (25)	43 (75)	0 (0)	9 (30)	21 (70)	0 (0)	0.83
Cefotaxime (n, %)	5 (12)	37 (86)	1 (2)	13 (24)	42 (76)	0 (0)	6 (21)	21 (72)	2 (7)	0.43
Ertapenem (n, %)	0 (0)	44 (100)	0 (0)	1 (2)	56 (98)	0 (0)	0 (0)	30 (100)	0 (0)	0.84
Imipenem (n, %)	0 (0)	44 (100)	0 (0)	1 (2)	56 (98)	0 (0)	0 (0)	30 (100)	0 (0)	0.84
Piperacillin, tazobactam (n, %)	0 (0)	41 (100)	0 (0)	1 (2)	50 (96)	1 (2)	1 (4)	25 (93)	1 (4)	0.58

However, there were significant differences in stool characteristics across different age groups, with younger children exhibiting a higher likelihood of mucoid bloody stool. This could be because *Salmonella* adheres to the intestinal wall after entering the intestine. Next, it directly invades the small or colonic wall by utilizing the type III secretion system encoded by *Salmonella* Pathogenicity Island-1 and Pathogenicity Island-2 to invade intestinal mucosal epithelial cells. The bacterium replicates within these cells and produces enterotoxins, triggering inflammatory cell infiltration that results in exudative diarrhea [13]. This leads to the presentation of mucoid and bloody stools. Alternatively, it could be because it is associated with the immature development of intestinal function and incomplete establishment of the gut microbiome in young children [14]. Therefore, blood culture, and stool routine and culture should be performed as soon as possible, before the use of antibiotics, when clinical fever with gastrointestinal symptoms occurs.

S. Typhimurium remained the predominant serovar in this study, consistent with the findings of Zhang *et al.* [15]; *S. Dublin* ranked second. This differs from studies conducted in Jiaxing [16] and Liaoning [17] where *S. Dublin*, primarily hosted by cattle, was mainly transmitted through consumption of contaminated raw milk or dairy products. The prevalence of *S. Dublin* may be related to local dietary habits and the prevalence of *Salmonella* in animals, although this correlation requires further investigation. In this study, the clinical features and antimicrobial susceptibility of *S. Typhimurium* infection were compared to those of other *Salmonella* serovars and revealed no significant differences between the two groups. Other serovars, such as *S. Enteritidis* and *S. Derby*, were similarly less common in this study compared to Hu *et al.*'s research [18] showing no significant increase.

The resistance rate of NTS to antimicrobial agents increased year by year. The antimicrobial resistance monitoring report of the US Centers for Disease Control and Prevention showed that the resistance rate of NTS

to ceftriaxone increased from 2.5% in 1996 to 2007 to 5% in 2003 to 2013. Song *et al.* reported that the resistance rate of NTS to ceftriaxone in China from 2016 to 2018 was 9.9% [19]. This study concluded that resistance to ceftriaxone and cefotaxime exceeded 20%, and the susceptibility rate of NTS to carbapenems was 99.24%. Susceptibility rates exceeded 90% for both ceftazidime and piperacillin-tazobactam. Resistance rates exceeded 60% for ampicillin, ampicillin-sulbactam, and co-trimoxazole. Besides, the resistance rates of NTS to ceftriaxone (23.96%), cefotaxime (19.85%), and ceftriaxone (22.14%) showed a slight increase compared to the resistance rates reported in local studies by Jiang *et al.* [20]; while resistance to ceftazidime (6.10%) was similar. This suggests a gradual rise in resistance to some third-generation cephalosporins, aligning with recent reports of increasing *Salmonella* resistance and MDR strains [21]. Given the rising resistance to some third-generation cephalosporins, switching to ceftazidime could potentially slow the increase in resistance rates to other cephalosporins in this class.

The present study revealed a significant difference in sensitivity to ceftazidime across various age groups. The ceftazidime sensitivity rate in children was linearly correlated with age ($p = 0.03$). This variation may be associated with factors such as autoimmune status, local antibiotic usage patterns, and the resistance profiles of NTS. However, the specific relationship between age and antibiotic sensitivity requires further investigation. *S. Typhimurium* exhibited resistance rates exceeding 85% to cefazolin and ampicillin but remained sensitive to third-generation cephalosporins, piperacillin, and carbapenems, and showed relatively good sensitivity to cefotaxime. This pattern is consistent with the findings of Zhang *et al.* [15]. *S. Typhimurium* showed slightly higher resistance to third-generation cephalosporins compared to other *Salmonella* serovars. Ceftazidime is suggested as the preferred empirical agent to preserve cephalosporin sensitivity, considering the increasing resistance rates to ceftriaxone and cefotaxime,

combined with the resistance patterns observed in this study. If ceftazidime proves ineffective, piperacillin-tazobactam sodium, which shows higher sensitivity, can be used.

Limitations

There are some limitations of this study. This is a single-region retrospective study with a relatively small sample size which limits the strength of conclusions regarding regional epidemiological characteristics. The number of non-Typhimurium serovars included was insufficient for analyzing the prevalence of other serovars. In addition, resistance gene detection was not performed. Future studies should aim to collect larger datasets, conduct multicenter research, analyze long-term trends in NTS resistance, and incorporate genotype testing of resistant strains to better guide clinical treatment.

Conclusions

NTS infections predominantly occurred in summer and autumn, affecting children aged 6 months to 2 years. The clinical presentation of NTS was primarily characterized by fever and diarrhea. Clinical features showed little variation across different *Salmonella* serovars. Early stool culture and antimicrobial susceptibility testing are crucial. Ceftazidime is recommended for empirical therapy. Antibiotic selection could be adjusted based on the susceptibility results, when available.

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Ethical considerations

This study was approved by the Ethics Committee of The First Affiliated Hospital of Chengdu Medical College (2024CYFYIRB-BA-Nov07). Informed consent was obtained from the parents of all participants. Written informed consent was provided by the participants' guardians.

Authors' contributions

Conceptualization: YS, LQ; methodology: GL, ZY, CX, HC, CQ, XM, YS, LQ; investigation: GL, XM, HC; data curation: GL, ZY, CX, HC, CQ, XM, YS, LQ; formal analysis: GL,

ZY, CQ, HC, YS, LQ; visualization: YS, LQ; validation: GL, CQ, YS, LQ; writing—original draft: GL, CQ, YS, LQ; writing—review and editing: GL, ZY, CX, HC, CQ, XM, YS, LQ; project administration: GL, CQ, YS, LQ; resources: CQ, YS, LQ; supervision: CQ, YS, LQ.

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Conflict of interest

No conflict of interest is declared.

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