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ORIGINAL RESEARCH

Epidemiology, Serotype and Resistance of *Salmonella* Isolates from a Children's Hospital in Hangzhou, Zhejiang, China, 2006–2021

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Purpose: This research investigated the dynamics of antibiotic resistance in *Salmonella* and the epidemiology of *Salmonella* infection in children. These data can aid in the prevention and control of the *Salmonella* epidemic and the diagnosis and treatment of salmonellosis.

Methods: In this study, we retrospectively reviewed and analysed data regarding epidemiology, clinical symptoms, *Salmonella* serotypes, and antibiotic resistance from the medical records of patients with *Salmonella* infections in Hangzhou Children's Hospital from April 2006 to December 2021.

Results: A total of 2099 *Salmonella* isolates were identified during the 16-year study period, and 98.6% (2069) of the isolates were isolated from stool. About 84.5% (1773/2099) of the total *Salmonella* isolates were detected from May to October. The median age of the 2099 children with *Salmonella* infection was 1.4 years (17 months) (IQR: 0.9–2.8 years). In 1572 (74.9%) patients, the course of the disease was limited to uncomplicated gastroenteritis. *S. Typhimurium* (805/2099, 38.4%) was predominant, followed by *S. Enteritidis* (290/2099, 13.8%). The total number of serotypes and the number of less common serotypes are increasing. Nontyphoid *Salmonella* that cause invasive infections, including *S. Typhimurium, S. Stanley*, and *S. Choleraesuis*, accounted for 60.0% (18/30). The *Salmonella* strains were resistant to ampicillin, ampicillin-sulbactam, trimethoprim-sulfamethoxazole, ceftriaxone, and ciprofloxacin at percentages of 71.5%, 51.5%, 36.5%, 22.4%, and 14.7%, respectively. No imipenem-resistant strains were identified. 24.8% of the isolates exhibited multidrug resistance (MDR).

Conclusion: *S. typhimurium* and *S. enteritidis* were the dominant serotypes in children (<2 years) with *salmonella*-infected arrhoea in Hangzhou, China. Ongoing serotype monitoring should be necessitated and dynamic changes in serotypes should be carefully examined to prevent the sudden outbreak of foodborne illness. *Salmonella* exhibits a higher rate of resistance to common antibiotics, and the risk of multidrug resistance should not be ignored. Therefore, clinicians should administer antibiotics judiciously according to the results of drug sensitivity tests.

Keywords: *Salmonella*, serotype, antibiotic resistance, children; epidemiology

Introduction

Salmonella, a gram-negative bacillus belonging to the Enterobacterales family, is a major foodborne pathogen worldwide. The genus *Salmonella* consists of only two species: *S. enterica* and *S. bongori*. *Salmonella enterica* is divided into the following six subspecies: *S. enterica* subsp. *enterica, S. enterica* subsp. *salamae, S. enterica* subsp. *arizonae, S. enterica* subsp. *diarizonae*, S. enterica subsp. *houtenae* and *S. enterica* subsp. *indica*. The White-Kauffmann-Le Minor scheme is used to serotype *Salmonella* isolates based on the identification of surface O (somatic) and H (flagellar) antigenic epitopes. Over 2600 serotypes have been reported; *S. enterica* subsp. *enterica* comprises more than 1500 serotypes[1,2] and is responsible for more than 99% of human salmonellosis cases,[3] such as those caused by *Salmonella Typhi, Salmonella Paratyphi, Salmonella Typhimurium*, and *Salmonella Enteritidis*.

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Salmonella isolates with different serotypes vary in pathogenicity. *S. Typhi* and *S. Paratyphi*, classified as typhoidal *Salmonella*, can cause typhoid and paratyphoid and are usually associated with higher mortality.[4] Other serotypes, known as nontyphoidal *Salmonella* (NTS), usually cause self-limited acute gastroenteritis; however, they can cause invasive infections in immunocompromised infants and young children with malnutrition.[5] The report entitled "WHO Estimates of the Global Burden of Foodborne Diseases" shows that in 2010, the primary cause of nondiarrhoeal foodborne disease resulting in death was *Salmonella Typhi* (52,000). Most deaths due to foodborne diarrhoeal disease agents were due to nontyphoidal *S. enterica*, accounting for 59,000 deaths, and included 22,000 deaths due to invasive disease caused by this bacterium.[6] In recent years, the incidence of invasive nontyphoidal *Salmonella* infections (iNTSs) has increased annually. The serotypes most commonly associated with iNTS are *S. Typhimurium, S. Enteritidis*, and *S. Dublin*, and the serotype with the highest degree of invasiveness was found to be *S. Dublin*.[7,8] Therefore, knowledge regarding the distribution of *Salmonella* serotypes is helpful for physicians to better grasp a patient's condition.

The current recommendations for antimicrobial therapy for *Salmonella* infections include extended-spectrum cephalosporins and fluoroquinolones, and third-generation cephalosporins are the drugs of choice for the treatment of severe salmonellosis in children. With the widespread use of antibiotics in various fields, resistance to cephalosporins and fluoroquinolones along with first-line antimicrobial agents is increasing at an alarming rate, and some studies have found that antimicrobial-resistant NTS is associated with an increased risk of invasive illness or death.[9,10] Therefore, surveillance of *Salmonella* antimicrobial resistance is important for physicians to formulate effective therapeutic plans to reduce the occurrence of complications.

In this study, we review the epidemiology of *Salmonella* infection, distribution of *Salmonella* serotypes and antimicrobial resistance of *Salmonella* among children infected with *Salmonella* from April 2006 to December 2021 to provide a basis for designing prevention and control strategies and reducing the incidence of infection by antimicrobial-resistant *Salmonella*.

Materials and Methods
Source of Data
From April 2006 to December 2021, patients aged younger than 18 years and culture positive for *Salmonella* (repeated sampling was excluded) were identified from the records of the clinical microbiology laboratory at Hangzhou Children's Hospital. The available information on age, sex, specimen source, clinical manifestations, *Salmonella* serotypes, and antimicrobial susceptibility was retrospectively reviewed and analysed. The calculation of age was based on the days from the date of birth to the date of presentation to the hospital divided by 365. In addition, the number of children who underwent stool culture for *Salmonella* during 2006–2021 was counted, repeated sampling was excluded, and the *Salmonella* isolation rate from stool was calculated.

Culture, Identification and Antibiotic Susceptibility Testing
Fresh faecal samples were inoculated on SS agar plates at 35 °C for 18–48 h, and suspicious colonies were inoculated on Kligler iron agar and chromogenic agar for biochemical identification. Whole blood (1 mL to 5mL) for bacterial culture was collected and inoculated into a paediatric bottle (BACT/ALERT PF, BioMérieux, France), and the culture was incubated in an automatic blood culture system (BACT/ALERT 3D) for 5 days or until it was rated positive. A colony from the positive blood culture was inoculated on blood agar and incubated at 36 °C for 18–24 h. Pus samples were cultured directly on blood agar at 36 °C for 18–48 h.

The identification and antibiotic susceptibility testing of *Salmonella* was performed using the VITEK 2 COMPACT automatic analysis system (BioMérieux, France), employing the GN and AST GN13 panels (BioMérieux, France), respectively. The susceptibility breakpoints that were used were those recommended by the Clinical and Laboratory Standards Institute (CLSI) guidelines for isolates subsequently obtained. The breakpoint criteria that were set in the analysis system were used to interpret the AST results, and the breakpoint criteria were updated in a timely manner when the CLSI guidelines changed. Standard strains (ATCC700323, ATCC25922, ATCC700327, and ATCC29213) were used for microbiological quality control. Isolates identified as the genus *Salmonella* were further investigated to detect the

somatic (O) antigen and flagellar (H) antigen by slide agglutination with commercial antisera (Ningbo Tianrun Bio-Pharmaceutical Co., Ltd., Ningbo, China), and the serotype was determined according to the White-Kauffmann-Le Minor scheme. Normal saline was used as a control.

Definitions

We defined "non-invasive" cases as those in which *Salmonella* had been isolated from stool 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 other extraintestinal sites.

Multidrug resistance (MDR) was defined as resistance to three or more antibacterial 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).

Statistical Analysis

All data were entered into Microsoft Excel. SPSS 22.0 software was used for the statistical analysis. A chi-square test or Fisher's exact test was used to analyse categorical data, and the multiple comparisons for percentages were verified based on Bonferroni methodology. Results with a p value of < 0.05 were considered statistically significant.

Results

Demographics, Monthly Prevalence and Clinical Presentation

A total of 2099 *Salmonella* isolates were identified from April 2006, to December 2021; 2069 (98.6%) isolates were isolated from stool, 28 (1.3%) from blood and 2 (0.1%) from pus samples. The ward-to-outpatient ratio was 1:2.1 (ward, 667; outpatient, 1432). *Salmonella* isolation rates exhibited a 1.3:1 ratio for males to females (males, 1196; females, 903). The median age of the 2099 children with *Salmonella* infection was 1.4 years (17 months) (IQR: 0.9–2.8 years; range: 17 days-16.1 years). The number of *Salmonella* isolates detected increased with age before 1 year and decreased after 1 year. A total of 1400 children (66.7%) were < 2 years old, of whom 66.4% (929/1400) were 0.6–1.3 years (7–16 months) old. Invasive *Salmonella* infection was most common in children under 1.3 years (16 months) old (73.3%, 22/30) (Figure 1). The number of *Salmonella* isolates detected was highest in August, followed by July, June, September, May and October, accounting for 84.5% (1773/2099) of the total (Figure 2).
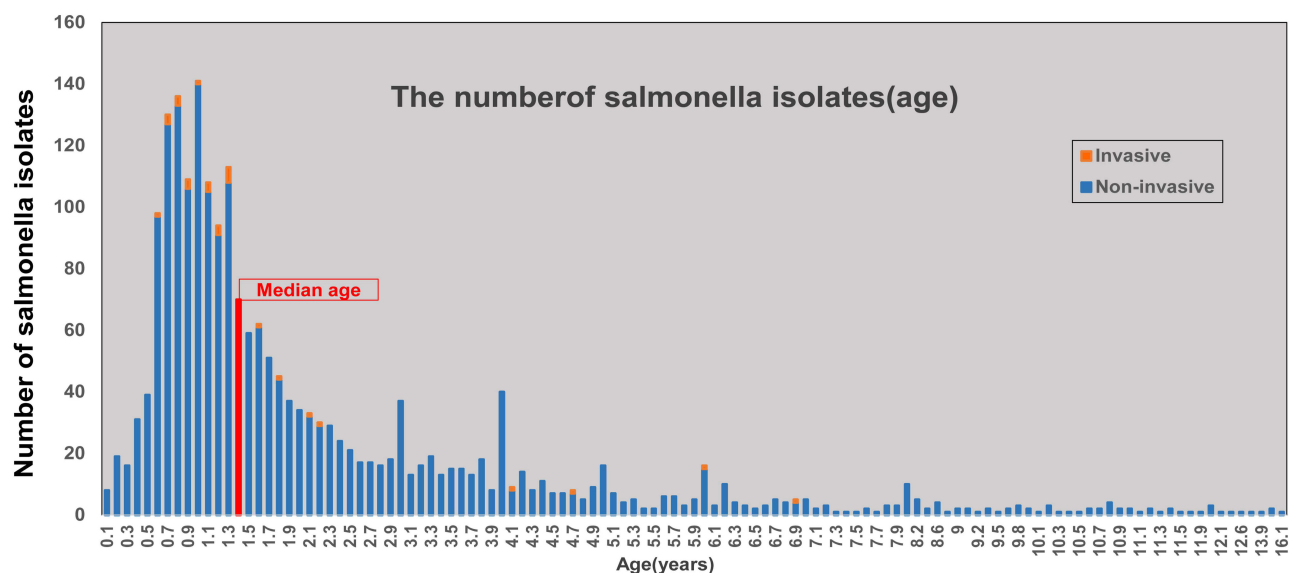

Figure 1 The number of *Salmonella* isolates from patients of different ages. The bar chart shows the number of *Salmonella* infection cases and the invasive or non-invasive status of infections among various age groups of patients in Hangzhou from April 2006 to December 2021. Red bar: The median age.
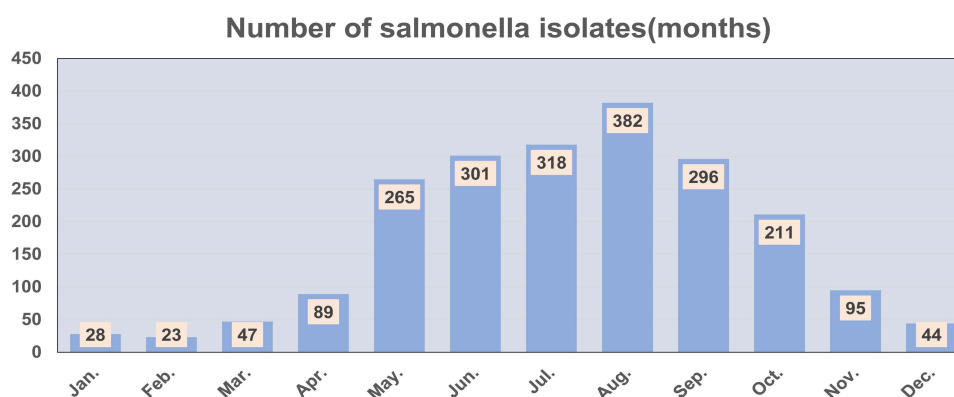
Number of salmonella isolates(months)

Figure 2 Distribution of 2099 *Salmonella* isolates by month from April 2006 to December 2021.

The disease course in 1572 (74.9%) patients was limited to uncomplicated gastroenteritis. A total of 10.1% (213/2099) of patients exhibited sepsis. Respiratory infections and convulsions were noted in 7.7% (162/2099) and 1.1% (23/2099) of patients, respectively. We compared the clinical presentation of invasive infection cases with that of non-invasive infection cases. The children with invasive infections were more likely to present with symptoms of respiratory infection and convulsions than the 2069 children with non-invasive infections (Table 1).

The Detection Rate of *Salmonella* Isolates from Stool

As 98.6% (2069/2099) of *Salmonella* isolates were detected in stool, an analysis of the annual *Salmonella* isolation rates from stool was performed. This analysis suggested that there was a sudden increase in the number of *Salmonella* isolates starting in 2014. The average detection rate from 2006 to 2013 was 3.77%, whereas that from 2014 to 2021 was 12.03%. The detection rates in the two periods were significantly different (χ^2=464.796, P<0.001) (Table 2).

Characteristics of *Salmonella* Serotype Distribution

Of the 2099 *Salmonella* isolates, 2070 were *Salmonella enterica* subsp. *enterica* (55 serotypes from 12 serogroups were identified), one was *Salmonella enterica* subsp. *diarizonae* and 28 were in the genus *Salmonella* but untyped. Group B (1248/2099, 59.46%) was the dominant serogroup, followed by Group D (427/2099, 20.34%).

The number of cases of Group B infection increased rapidly with age from 0.5 years (6 months) old and decreased from 0.8 years (10 months) old until 5 years old, which was followed by a plateau. The incidence of Group D infection was far lower than that of Group B before 2 years of age, but after 4 years of age, it was higher than that of Group B (Figure 3 and Table 3).

S. Typhimurium (805/2099, 38.4%) from Group B was the most prevalent serotype, and the proportion per year ranged from 18.7% (40/214) to 56.0% (75/134) between 2006 and 2021. *S. Enteritidis* (290/2099, 13.8%) from Group D, another common serotype, increased in prevalence significantly starting in 2013, and the average detection rate was 1.5% (3/202) from 2006 to 2012 (2 isolates in 2006 and 1 in 2012) and 15.1% (287/1897) from 2013 to 2021 (Figure 4). The

Table 1 Clinical Presentation of Children with Invasive Infections and Non-Invasive Infections

Clinical Presentation	Invasive Infections (n = 30)	Non-Invasive Infections (n = 2069)	χ^2	P
Gastroenteritis	11 (36.7%)	1781 (86.1%)	53.935	<0.001
Sepsis	1 (3.3%)	212 (10.2%)	0.885	0.347
Respiratory infections	10 (33.3%)	152 (7.3%)	24.509	<0.001
Convulsion	3 (10.0%)	20 (1.0%)	14.711	<0.001

Table 2 The Annual Rates of *Salmonella* Isolation from Stool

Year	No. of Stool Samples	No. of *Salmonella* Isolates From Stool	Rate (%) of *Salmonella* Isolation From Stool	Total Stool Samples	Total *Salmonella* Isolates	Average Rate (%)	χ^2	*P*
2006	231	15	6.49	8931	337	3. 77	464. 796	0. 000
2007	209	14	6.7					
2008	244	15	6.15					
2009	699	21	3					
2010	1036	34	3.28					
2011	1399	47	3.36					
2012	1703	48	2.82					
2013	3410	143	4.19					
2014	799	108	13.52	14,399	1732	12. 03		
2015	1330	156	11.73					
2016	1063	134	12.42					
2017	1703	194	11.39					
2018	1848	210	11.36					
2019	2028	240	11.83					
2020	2518	316	12.55					
2021	3110	374	12.03					

differences in distribution by age between *S. Typhimurium* and *S. Enteritidis* isolates were similar to those between Group B and Group D isolates (Figure 3 and Table 3).

The rate of the detection of partially typed and untyped *Salmonella* isolates also increased; 25.0% (525/2099) of all *Salmonella* isolates were partially typed or untyped, and this percentage increased sharply starting in 2017, and the percentage ranged from 0–5.9% from 2006 to 2016 and rose to 28.3–46.7% from 2017 to 2021. The number of different kinds of serotypes increased, and less-common serotypes, such as *S. Jangwani, S. Havana, S. Chandans, S. Meleagridis, S. Weltevreden, S. Aberdeen, S. Pomona, S. Irumu, S. Muenchen, S. Reading, S. Ndolo, S. Goldcoast, S. Concord*, and *S. Kentucky*, were also identified (Figure 4).

The *Salmonella* serogroups in 30 cases of invasive *Salmonella* infection were mainly *Salmonella* Group B (30.0%, 9/30) and *Salmonella* Group D (26.7%, 8/30). The *Salmonella* serotypes were dominated by NTS, including *S. Typhimurium, S. Stanley, S. Choleraesuis*, etc, which accounted for 60.0% (18/30); *S. Typhi* and *S. Paratyphi* accounted for 10.00% (3/30); and 30.00% (9/30) were untyped (Table 4).

Antibiotic Susceptibility of *Salmonella* Isolates

The antibiotic for which *Salmonella* had the highest rate of resistance was ampicillin (71.5%, 594/831), followed by ampicillin-sulbactam (51.5%, 425/826), trimethoprim-sulfamethoxazole (36.5%, 303/830) and ceftriaxone (22.4%, 155/692), and no imipenem-resistant isolates were identified. There was a rise in MDR and resistance to ampicillin, ampicillin-sulbactam, ceftriaxone, ceftazidime, cefepime, aztreonam, ciprofloxacin, and levofloxacin but a decline in resistance to trimethoprim-sulfamethoxazole and piperacillin-tazobactam from 2006 to 2021. Resistance to ciprofloxacin significantly increased in 2013, and the average rates of resistance to ciprofloxacin were 5.5% from 2009 to 2012 and 16.1% from 2013 to 2021 (Figure 5).
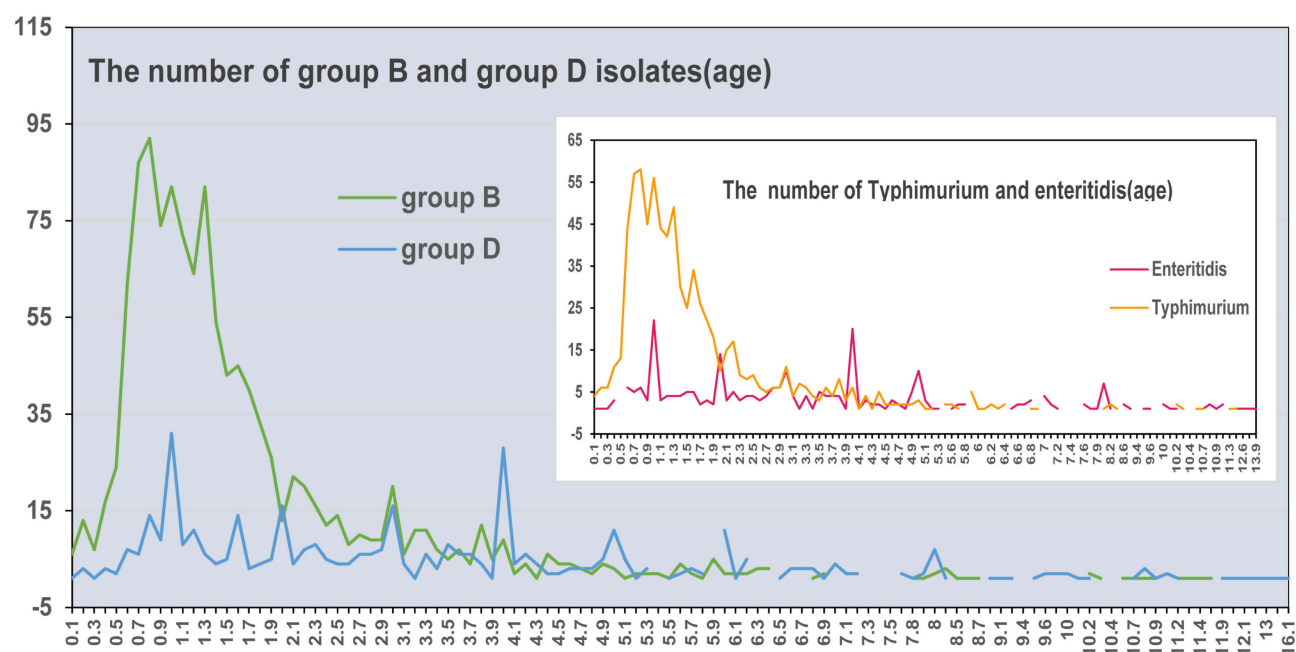
Figure 3 The number of *Salmonella* Group B and Group D isolates by age in Hangzhou, China, from April 2006 to December 2021. The inset shows the number of *S. Typhimurium* and *S. Enteritidis* isolates by age.

The antibiotic resistance profiles of the four main serotypes (Typhimurium, Enteritidis, Stanley, Dublin) were analysed and compared. We found that the four serotypes had the greatest rate of resistance to ampicillin, with resistance rates of 82.3%, 84.7%, 52.9%, and 87.5%, respectively, but the resistance rate of Stanley isolates was significantly lower than those of Typhimurium, Enteritidis, and Dublin isolates. The rates of ampicillin-sulbactam resistance were followed by the rates of ampicillin resistance in the four serotypes, which were 55.9%, 70.9%, 41.2%, and 54.2%, respectively; among them, the resistance rate of Enteritidis isolates was significantly higher than those of Typhimurium and Stanley isolates. The rates of resistance to trimethoprim-sulfamethoxazole in the Typhimurium, Stanley, and Dublin isolates were 44.4%, 34.3%, and 24.0%, respectively, while that in the Enteritidis isolates was 8.2%, which was significantly lower than those of Typhimurium and Stanley isolates. The rates of resistance to ciprofloxacin in the four strains were 19.6%, 1.8%, 8.6%, and 0.0%, respectively, and there were statistically significant differences between the rates in the Typhimurium and Enteritidis isolates. Compared to Enteritidis, Stanley, and Dublin, there were more Typhimurium isolates with MDR, but no significant difference was found among them (Table 5).

The number of *Salmonella* isolates with MDR and rates of resistance to ceftriaxone, ceftazidime, cefepime, ampicillin, ampicillin-sulbactam, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, aztreonam, ciprofloxacin, and levofloxacin observed in non-invasive isolates were higher than those observed in invasive isolates, but there were only statistically significant differences for ampicillin and ampicillin-sulbactam resistance (Figure 6).

Table 3 Comparison of the Proportion of Group B and Group D and of *S. Typhimurium* and *S. Enteritidis* Isolates Before and After 4 Years of Age

Variables	≤4 Years	>4 Years	χ^2	p
Group B	80.1% (1153/1440)	40.4% (95/235)	167.169	<0.001
Group D	19.9% (287/1440)	59.6% (140/235)		
Typhimurium	20.4% (190/933)	61.7% (100/162)	121.3	<0.001
Enteritidis	79.6% (743/933)	38.3% (62/162)		

Salmonella	Group	Type	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
Salmonella enterica subsp. *enterica*	A	Paratyphi A			2											1			3
	B	Typhimurium	4	7	4	5	7	10	18	41	47	83	75	54	40	101	122	187	805
		Group B							1	1	2			48	53	45	68	30	248
		Stanley	3	2	3	7	4	2	7	17	2	8	7	5	11	3	3	9	93
		Paratyphi B	1	1	2			2	3	2	3		3	2	4		1	1	25
		Abony										1		2	15	1			19
		Saintpaul							10	4		2		1				1	18
		Agona				1				4		2	2	2	4	2		1	18
		Reading							6					1					7
		Heidelberg				2	3												5
		Limete														3	1	1	5
		Paratyphi B var. Java														2	1		3
		Chester												1					1
		Eko	1																1
	C1	Group C1								2	1	4	1	10	19	13	26	27	103
		Infantis								2	1	6	8	1		1	2		21
		Choleraesuis	1		3	2	4	3	4		1				2				20
		Thompson				1				2	2	2		1	5	1		1	15
		Braenderup						1	6	4	2								13
		Paratyphi C						2		4				1					7
		Rissen										1		1	1	2	1		6
		Virchow										1	1	1					3
		Tennessee										1			1				2
		Potsdam						1					1						2
		Papuana															1		1
		Choleraesuis var. Kunzendorf	1																1
		Concord											1						1
		Irumu						1											1
		Moneterideo																1	1
	C2	Group C2							1	1	1	5	1	9	5	10	18	22	73
		Newport	2	2		1	2			3			4	2			1		17
		Goldcoast										1		1	2	5		1	10
		Bovismorbificans				1				1		1	1	1	2				7
		Kottbus								4	1								5
		Muenchen								1		2		1					4
		Manhatan														1	1		2
		Hadar												1					1
		Limete															1		1
	C3	Group C3														1		3	4
		Kentucky															1		1
	D	Enteritidis	2						1	25	31	28	22	26	7	32	57	59	290
		Dublin	1	1	2	4	10	10	4	1		1	1	6	15	1			57
		Group D											1	7	13	10	7	3	41
		Derby				3	3	3	4	2	1	2	2	2					22
		Typhi				1	4		2		4		2						13
		Gallinarum		1					1										2
		Blegdam												1					1
		Ndolo										1							1
	E1	Group E1													3	1	5	16	25
		London					1		1	2	1	1	1	3				2	12
		Anatum					2	1			1	2							6
		Nchanga																3	3
		Weltevreden									2				1				3
		Muenster													2				2
		Give														1			1
		Meleagridis													1				1
	E4	Senftenberg					1	3	4		1								9
		Group E4															1		1
	F	Group F														1		1	2
		Aberdeen					1												1
		Chandans												1					1
	G	Havana														1			1
	J	Jangwani															1		1
	M	Pomona										1							1
Salmonella enterica subsp.		*Salmonella* subspecies *diarizonae*															1		1
Salmonella	untyped	*Salmonella*					1	1		1		1	2	1	7	3	7	4	28
Total			16	14	17	22	36	47	50	145	109	156	134	196	214	241	324	378	2099

Figure 4 Distribution of serogroups and serotypes by year. The different colours represent different serotypes. The figure shows the number of isolates.

Table 4 Distribution of Serogroups, Serotypes and NTS in Invasive Infection Cases

Group (No.)	Serogroup	Serotype	No.
NTS (18)	B[#]	Typhimurium	3
	B[#]	Stanley	3
	C1[#]	Choleraesuis	3
	C2	Group C2*	3
	D[#]	Enteritidis	2
	D[#]	Derby	1
	D[#]	Dublin	1
	E1	Group E1*	2
Typhoidal (3)	A	Paratyphi A	1
	B[#]	Paratyphi B	1
	D[#]	Typhi	1
Untyped (9)	B[#]	Group B*	2
	C1[#]	Group C1*	1
	D[#]	Group D*	3
		Salmonella	3
Total			30

Notes: [#]The total number of Group B isolates was 9, the number of Group D isolates was 8, and the number of Group C1 isolates was 4. *Because *Salmonella* Group C2 and Group E1 do not contain typhoid *Salmonella*, they belong to NTS. While *Salmonella* Groups B, C1 and D included typhoid *Salmonella*, they could not be identified as NTS or typhoid, so they belonged to the untyped group. **Abbreviation**: NTS, nontyphoidal *Salmonella.*

Discussion

The current study was conducted over a period of fifteen years and nine months. *Salmonella* was detected in more than 2000 patients. Nearly one-third of the patients were admitted, as reflected by the ward-to-outpatient department ratio. Gastroenteritis was more common in children with non-invasive *Salmonella* infection, while respiratory infections and convulsions were more likely to be present in children with invasive infections. Nonspecific presentations, such as sepsis and respiratory symptoms, are frequently present in children; in such circumstances, health care workers may commence inappropriate treatment, which may result in delayed or ineffective antimicrobial treatment.[11,12]

Children under five years of age are at particular risk of developing *Salmonella* infection, especially when children are under 2 years of age.[7] The case fatality ratio among cohorts of children with iNTS disease across Africa has been reported to be 20 to 28% and is highest among children <2 years of age.[12] The majority of *Salmonella* infections in this study were observed in infants aged <2 years and were concentrated in those aged 7–16 months, with the peak number of infections occurring in those aged 1 year. Invasive *Salmonella* infection is more common in infants under 16 months of age. Potential reasons for increased susceptibility to *Salmonella* infections include numerous factors, such as gastric hypoacidity, immature endogenous bowel flora, immature gut-associated lymphoid tissue or a lack of serogroup-specific maternal antibodies; other factors include switching from breast feeding to bottle feeding and adding supplementary food, such as meat and eggs, to the diet in addition to crawling habits and the tendency of children to place their fingers or fomites inside the mouth.[13,14]
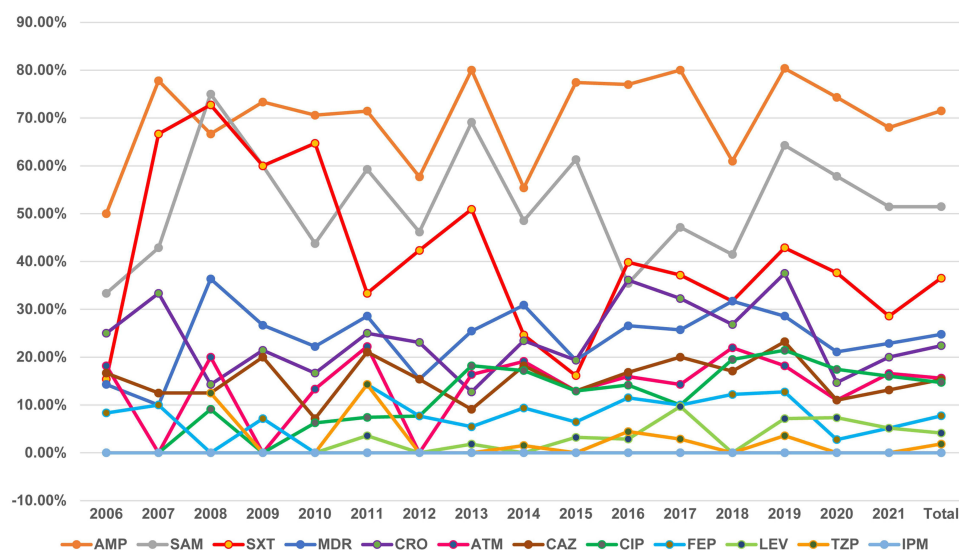
Figure 5 Changes in antimicrobial resistance by year.
Abbreviations: MDR, multidrug resistance; AMP, ampicillin; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; CRO, ceftriaxone; CAZ, ceftazidime; FEP, cefepime; ATM, aztreonam; IPM, imipenem; SXT, trimethoprim-sulfamethoxazole; CIP, ciprofloxacin; LEV, levofloxacin.

Consistent with the results of other reports,[14–18] the proportion of boys infected with *Salmonella* was found to be higher than that of girls, and the majority of *Salmonella* cases occurred in summer and autumn. There is no definitive reason for this phenomenon. One of the possible reasons why boys are more likely to be exposed to pathogens than girls is because they are more active. The association between season and infection is biologically plausible because *Salmonella* growth occurs between 5.2 and 46.2 °C and within an ideal temperature range of 35–43 °C.[19] In the summer, the hot and humid climate facilitates microbial proliferation, so food is more vulnerable to bacterial contamination.

Table 5 The Antibiotic Resistance Profiles of Four Serotypes

Antibiotic	Typhimurium	Enteritidis	Stanley	Dublin	χ^2	P
CRO	27.11% (77/284)	20.88% (19/91)	10.71% (3/28)	22.22% (4/18)	4.624	0.2
FEP	8.94% (32/358)	7.27% (8/110)	8.33% (3/36)	12.00% (3/25)	0.8815	0.83
CAZ	22.56% (81/359)	23.85% (26/109)	8.57% (3/35)	22.22% (4/18)	3.974	0.26
AMP	82.27% (297/361)[a]	84.68% (94/111)[a]	52.94% (18/34)[b]	87.50% (21/24)[a]	19.509	<0.001[c]
SAM	55.87% (200/358)[b]	70.91% (78/110)[a]	41.18% (14/34)[b]	54.17% (13/24)[a,b]	12.288	0.01[d]
TZP	2.54% (9/354)	0.91% (1/110)	5.88% (2/34)	0.00% (0/23)	2.9022	0.32
SXT	44.38% (158/356)[b]	8.18% (9/110)[a]	34.29% (12/35)[b]	24.00% (6/25)[a,b]	49.768	<0.001[e]
ATM	16.91% (57/337)	20.00% (22/110)	12.90% (4/31)	15.79% (3/19)	1.045	0.79
CIP	19.61% (70/357)[b]	1.83% (2/109)[a]	8.57% (3/35)[a,b]	0.00% (0/23)[a,b]	26.782	<0.001[f]
LEV	4.63% (13/281)	1.10% (1/91)	0.00% (0/22)	0.00% (0/18)	2.4349	0.43
MDR	29.83% (108/362)	18.92% (21/111)	13.89% (5/36)	12.00% (3/25)	11.013	0.012[g]
IPM	0.00% (0/275)	0.00% (0/82)	0.00% (0/33)	0.00% (0/24)	–	–

Notes: [a,b]Each subscript denotes a subset of serotype categories. [c]Statistically significant, comparing Stanley versus Typhimurium, Enteritidis and Dublin. [d]Statistically significant, comparing Enteritidis versus Typhimurium and Stanley. [e]Statistically significant, comparing Enteritidis versus Typhimurium and Stanley. [f]Statistically significant, comparing Typhimurium versus Enteritidis. [g]Pairwise comparisons of the four serotypes did not reveal statistical significance based on corrected p values.
Abbreviations: CRO, ceftriaxone; FEP, cefepime; CAZ, ceftazidime; AMP, ampicillin; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; SXT, trimethoprim-sulfamethoxazole; ATM, aztreonam; CIP, ciprofloxacin; LEV, levofloxacin; MDR, multidrug resistance; IPM, imipenem.

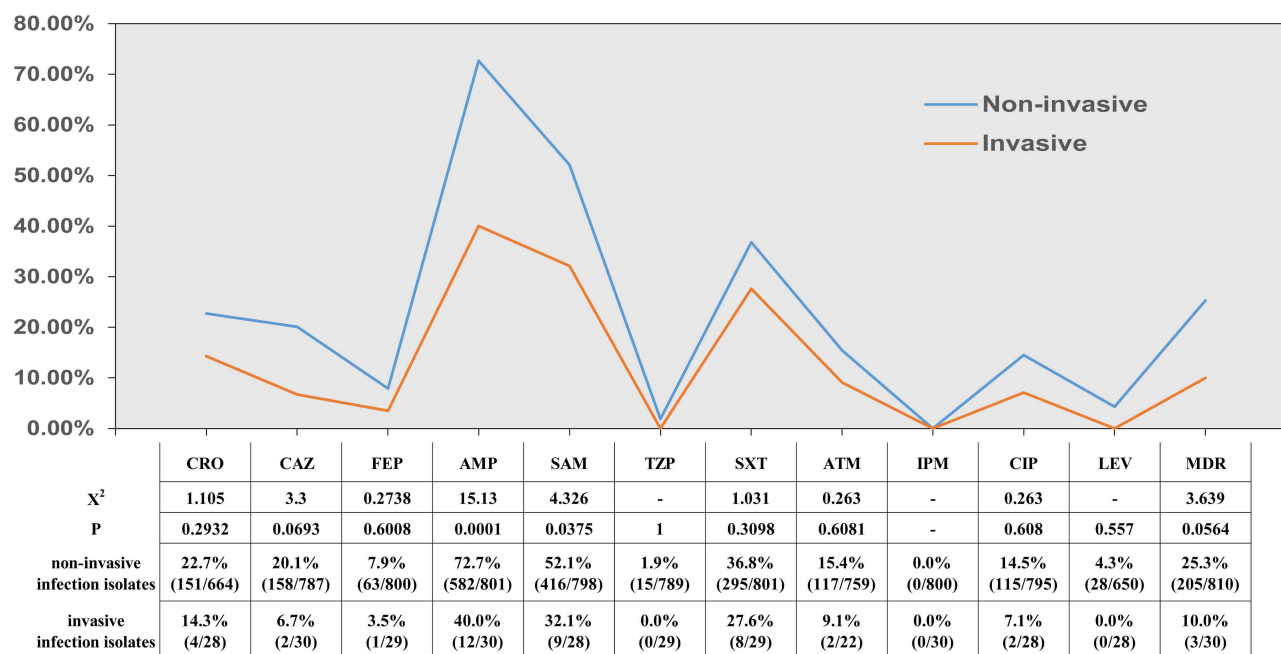## Antibiotic resistance between invasive and non-invasive infection isolates

	CRO	CAZ	FEP	AMP	SAM	TZP	SXT	ATM	IPM	CIP	LEV	MDR
X²	1.105	3.3	0.2738	15.13	4.326	-	1.031	0.263	-	0.263	-	3.639
P	0.2932	0.0693	0.6008	0.0001	0.0375	1	0.3098	0.6081	-	0.608	0.557	0.0564
non-invasive infection isolates	22.7% (151/664)	20.1% (158/787)	7.9% (63/800)	72.7% (582/801)	52.1% (416/798)	1.9% (15/789)	36.8% (295/801)	15.4% (117/759)	0.0% (0/800)	14.5% (115/795)	4.3% (28/650)	25.3% (205/810)
invasive infection isolates	14.3% (4/28)	6.7% (2/30)	3.5% (1/29)	40.0% (12/30)	32.1% (9/28)	0.0% (0/29)	27.6% (8/29)	9.1% (2/22)	0.0% (0/30)	7.1% (2/28)	0.0% (0/28)	10.0% (3/30)

Figure 6 Analysis of antibiotic resistance in invasive and non-invasive infection isolates.
Abbreviations: CRO, ceftriaxone; CAZ, ceftazidime; FEP, cefepime; AMP, ampicillin; SAM, ampicillin-sulbactam; TZP, piperacillin-tazobactam; SXT, trimethoprim-sulfamethoxazole; ATM, aztreonam; IPM, imipenem; CIP, ciprofloxacin; LEV, levofloxacin MDR, multidrug resistance.

In addition, people prefer to eat raw and cold food in summer. All of these factors may increase the risk of *Salmonella* infection.

In our study, we found that the detection rate of *Salmonella* in stool increased sharply in 2013, and the annual detection rate was similar through 2021 and much higher than that from 2006 to 2012. In patients with *Salmonella* infection, stool testing typically demonstrates the presence of leucocytes.[20] Since 2013, physicians in our hospital have referred to the results of stool testing to determine whether it is necessary to perform stool culture. Therefore, the detection rate was greatly improved.

The dynamics of the *Salmonella* Group B and Group D isolation rates among different age groups of patients were similar to those observed in a previous report.[11,21] In our study, children younger than 4 years were more likely to have Group B strain infection than older children were, and infections caused by Group D strains were more common than those caused by Group B strains in patients older than 4 years. Furthermore, *S. Typhimurium* (Group B) and *S. Enteritidis* (Group D) infections showed the same trend, which was similar to the result of another previous study.[22] However, *S. Typhimurium* remains the most prevalent serotype, and its prevalence rises annually; many reports are in concordance with our findings, such as those in Ningbo, Zhejiang, China,[23] southern India,[24] Africa,[25] Australia,[16] Thailand and Laos provinces.[26] However, studies from Shanghai, China,[27] and the United States[28] reported that *S. Enteritidis* was more common than *S. Typhimurium*. A study from Kolkata, India, showed that *S. Guorthington* was the predominant serotype, followed by *S. Enteritidis* and *S. Typhimurium*. The variation in serotype distribution in a region may be associated with the presence of a local animal reservoir or food source.

In our report, *S. Enteritidis* incidence increased significantly starting in 2013, whereas there were only three isolates observed from 2006 to 2012. The reason for this increased incidence may be that some isolates were misidentified as other serotypes due to use of commercial antisera or other factors from 2006 to 2012.[29] The less common serotypes, such as *S. Goldcoast*[30] and *S. Hadar*,[31] have gradually increased in incidence in recent years. The most frequently isolated *Salmonella* serotypes in European countries, such as *S. Java*, *S. Jangwani*, *S. Manhattan*, and *S. Pomona* are associated with exotic pets,[32] which could be due to international travel, human migration, and food, animal feed, and livestock trade.[33] In addition, the number of partially typed and untyped *Salmonella* isolates also increased. This result may be due to the quality of commercial

antisera, the lack of flagellar antigens in *Salmonella* isolates, and the increase in the incidence of less common serotypes.[29] To solve this problem, we took different measures, such as increasing the use of commercial antisera from different manufacturers, using soft agar plates to induce flagellum expression, and training staff members.

The rising prevalence of iNTS disease has become acutely apparent in recent decades, and the *Salmonella* serotypes most commonly associated with iNTS are *S. Typhimurium, S. Enteritidis*, and *S. Blin*.[7] In our study, the *Salmonella* serogroups in 30 cases of invasive *Salmonella* infection were mainly Group B and Group D. The *Salmonella* serotypes were dominated by NTS, but there was no dominant serotype in iNTS infection. We will continue to focus on these strains that develop invasive infections and study them in-depth by genome sequencing methods.

The results of our report revealed higher rates of antimicrobial resistance to conventional antibiotics (ampicillin, ampicillin-sulbactam and trimethoprim-sulfamethoxazole), which were similar to the rates observed in other regions of China[15,22,23,34–36] but higher than those in Vietnam,[37] Kolkata,[14] the United States and Europe,[38] and Addis Ababa.[39] Due to the high rate of resistance, first-line antibiotics are no longer used for the treatment of *Salmonella* infections,[12] which may be related to the declining trend of antimicrobial resistance to trimethoprim-sulfamethoxazole that was observed in our study.

Third-generation cephalosporins are the standard antimicrobial option for invasive *Salmonella* infections in children. A worrisome development in children is the increased resistance to third-generation cephalosporins in China. A report showed that the rate of resistance to ceftriaxone has increased from 9.1% to 20.4% in recent years.[40] Our study revealed that the rate of resistance to ceftriaxone was 22.4%. The highest rate of resistance to ceftriaxone was found to be 34.9% in nearby regions.[23] The main mechanisms underlying resistance to third-generation cephalosporins in *Salmonella* have been attributed to extended-spectrum β-lactamase (ESBL) genes obtained via horizontal transfer, and CTX-M enzymes include the most common ESBLs that are prevalent worldwide.[41] A previous study by our team showed that the rate of ESBL gene detection in our hospital was 16.38%, and CTX-M was the most common ESBL gene.[42]

Our report suggested a continuous and slow increase in the rate of resistance to some antimicrobial agents, with only a significant increase in the rate of resistance to ciprofloxacin in 2013 because the CLSI lowered the ciprofloxacin susceptibility breakpoints in 2013, with the new MIC being applied only to *Salmonella* spp. From 2013 to 2016 in our hospital, the rate of drug resistance to ciprofloxacin was 16.1%; this rate was higher than those observed in other studies. Although fluoroquinolones are not recommended for use in children due to their adverse effects on cartilage,[43] the higher rate of resistance to ciprofloxacin reported among paediatric *Salmonella* isolates in China should not be ignored.[44] The increasing frequency of ciprofloxacin resistance has been associated with an increasing prevalence of plasmid-mediated quinolone resistance (PMQR), which provides only low-level resistance that, by itself, does not exceed the clinical breakpoint for susceptibility but nonetheless facilitates the selection of microbes with higher-level resistance and renders infections by pathogens containing PMQR harder to treat.[45] In addition, there is an interesting finding derived from the data shown in the figure displaying the changes in antimicrobial resistance by year (Figure 5): the rates of resistance to all antibiotics in 2020 were lower than those in 2019, and whether this was related to the coronavirus disease 2019 (COVID-19) pandemic is unknown.

Carbapenems remain one of the last resorts for the treatment of severe *Salmonella* infections. Although all isolates were observed to be sensitive to imipenem in this study, NDM-1-producing *Salmonella* has been isolated from a child in China.[46] Continuous surveillance of resistance to carbapenems is necessary to preserve their efficacy in the treatment of NTS and other infections.

The resistance profiles differed among different serotypes. We compared the antibiotic resistance profiles of the four main serotypes (Typhimurium, Enteritidis, Stanley, and Dublin), and the results showed that *S. Typhimurium* had higher resistance to some antibiotics than other serotypes, whereas the serotypes showed no significant difference in resistance to ceftriaxone, which was similar to the results of previous studies.[15,47]

A study in the United States reported that blood isolates were more likely to be resistant to a first-line antimicrobial agent.[28] Therefore, we compared the antibiotic resistance of stool isolates and nonstool isolates. Non-invasive isolates were more abundant than invasive isolates, but there were no statistically significant differences except for in the rates of resistance to ampicillin and ampicillin-sulbactam. Although MDR/hyper pathogenic phenotypes have emerged, such as *Salmonella enterica* serotype *Typhimurium* phage type DT104 (DT104)[48] and *Salmonella Typhimurium* ST313,[49,] the relationship between the virulence and antibiotic resistance of *Salmonella* is worth further study.

Our study showed that the number of *Salmoenlla* isolates with MDR increased from 14.3% in 2006 to 22.86% in 2021. It may not be possible to compare different regions because antibiotic use may vary, but the prevalence of isolates with MDR has steadily risen worldwide. Hence, the emergence of isolates with MDR and increasing resistance to important antibiotics suggest that prevention measures and ongoing surveillance of antibiotic resistance are needed to control infections.

Conclusion

In conclusion, the most common symptom of *Salmonella* infection was diarrhoea caused by nontyphoid *Salmonella* in children (mainly under two years old) in Hangzhou, China. Routine stool results obtained from children with diarrhoea are recommended to determine the need for *Salmonella* testing.

S. Typhimurium and *S. Enteritidis* were the dominant serotypes in children (<2 years) with *salmonella*-infected diarrhoea. Therefore, more care should be taken to ensure children's food safety, especially during the summer and fall. Furthermore, the prevalence of less common serotypes has gradually increased in recent years, so we should continue to strengthen the surveillance of *Salmonella* serotypes and pay attention to the dynamic changes in serotypes to prevent the sudden outbreak of foodborne illness.

The antibiotic resistance rates of *Salmonella* to third-generation cephalosporins and fluoroquinolones showed an upwards trend. Ceftriaxone in particular, with a resistance rate of 22.4%, may not be suitable for empirical use until the sensitivity is established. In addition, the rate of MDR is more than 20%, suggesting that prevention measures and ongoing surveillance of antibiotic resistance are needed to control infections.

There were some shortcomings to this study. First, only one isolate typing method was used, and many isolates failed to be typed, which had some influence on the analysis of the results. Methods based on molecular typing techniques will be used in the next study. Second, not all isolates underwent antibiotic sensitivity testing, and there was no investigation of the mechanisms underlying resistance; this will be our next focus and direction of research.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and obtained approval from the Medical Ethics Committee at Hangzhou Children's Hospital, China. All isolates were the result of regular laboratory procedures, and no patient-identifiable information was acquired. Therefore, informed consent was not needed.

Disclosure

The authors report no conflicts of interest in this work.

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