

Antibiotic Resistance Patterns of Salmonella Typhi and Non-Typhi in North-Central Nigeria: A Cross-Sectional Study

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ABSTRACT

Antimicrobial resistance significantly threatens global health, especially in treating *Salmonella* infections in developing countries. In sub-Saharan Africa, inadequate water, sanitation, and limited diagnostic and treatment capabilities exacerbate the issue. This study addresses the lack of data on enteric fever and drug susceptibility patterns of *Salmonella* in Nigeria. The objective of the study was to identify *Salmonella* isolates from febrile patients in Karu Local Government Area, Nasarawa State, Nigeria, and determine their antibiotic resistance patterns. Secondary objectives included characterizing the demographics and clinical profiles of infected patients. This cross-sectional study was conducted in four health facilities. Research assistants recruited individuals clinically diagnosed with enteric fever and with temperatures above 37.4°C. Blood samples were collected and cultured using the BD Bactec™ FX automated system. Isolates were identified through morphology, Gram stain, and chemical methods. Antibiotic susceptibility was tested using the modified Kirby-Bauer method, interpreted per CLSI guidelines. The data was analyzed using Statistical package for the Social Sciences (version 24) The results showed out of 818 febrile patients, bacterial pathogens were isolated in 46 cases (5.6%). The majority were gram-negative bacteria, with *Salmonella* spp.

leading (43.5%). *Salmonella* Typhi accounted for 23.9%, and non-Typhi *Salmonella* 19.6%. Both *S. Typhi* and non-Typhi *Salmonella* showed over 60% resistance to Trimethoprim/Sulfamethoxazole and chloramphenicol. Cephalosporin resistance was also high, whereas fluoroquinolone resistance was low. Notably, interesting resistance patterns were observed to Imipenem, Streptomycin, and Gentamicin. The study highlights the high prevalence of *Salmonella* infections and significant antibiotic resistance in the region. Health facilities can enhance diagnostic capabilities, routine antimicrobial surveillance, and antibiotic stewardship. Health authorities and communities should partner to improving water, hygiene, sanitation, to mitigate the impact of these infections and combat antimicrobial resistance.

Keywords: *Salmonella* infection, Typhoid fever, Drug resistance, Antimicrobial resistance.

INTRODUCTION

Antimicrobial resistance (AMR) is emerging and spreading globally which is putting the achievements of modern medicine at risk and threatens the effective control and treatment of a range of infections worldwide [1,2]. AMR is a major issue in *Salmonella* infection worldwide especially in developing countries [3-5]. Where morbidity and mortality caused by *Salmonella* infection in sub-Saharan Africa can be drastically reduced by the provision of clean water and good sewage systems, coupled with prompt diagnosis and treatment [6-9]. The right choice of antibiotic against infectious microorganisms is essential, because of the evolving threat of antimicrobial resistance across the globe [2]. World Health Organization (WHO) in 2019 estimated that 9 million cases and 110,000 typhoid-related deaths occur annually worldwide [10]. In Nigeria, reliable data from which to estimate the burden of enteric fever or determine the drug susceptibility pattern of *salmonella* pathogens are difficult to obtain [6,11]. Since national, regional, or routine antimicrobial surveillance systems are rare or non-existent, [12] most patients especially with enteric fever are diagnosed using a single Widal test and subsequently treated or treated empirically following clinical diagnosis. Furthermore, many health facilities cannot carry out blood culture for laboratory diagnosis [6, 7]. Diagnosis presently in Nigeria is mostly clinical, but the need for microbiological laboratories and clinicians to ensure that culture results inform the choice of antibiotics given to patients is essential. Even though the commonly diagnosed febrile illnesses in patients presenting to health facilities in Nigeria are malaria and typhoid. [6-8,13] Availability and use of rapid test kits for prompt management of malaria is increasing, but that of typhoid diagnosis is usually a Widal test or stool culture, though outdated blood culture methods [8]. These will pose a challenge for data comparison with other countries in sub-Saharan Africa where several etiologic studies of bacteremia utilized modern culture techniques [7]. Hence, using BD Bactec™ blood culture techniques we aim to identify *salmonella* isolates from febrile patients and determine the drug susceptibility pattern.

METHODOLOGY

Study Area and Study Design

Nasarawa state is located in the middle belt region of Nigeria with Lafia as the capital city. It lies between latitude 7° 45' and 9° 25' N of the equator and longitude 7° and 9° 37' E of the Greenwich meridian. It shares a boundary with Kaduna state to the north, Plateau state to the east, Taraba and Benue states to the south, to the west are Kogi and the Federal Capital

Territory (FCT). It has a total land mass of 26,256 km², a population of approximately 2,886,000 with a density of 109.9/Km². Karu Local Government Area (LGA) is one of the thirteen LGAs in the state. It is contiguous with the FCT contributing to the high population density of the area. The study was carried out in selected health facilities in urban slums of Karu Local Government Area (LGA) of Nasarawa State. It was a hospital based cross-sectional study design, carried over 12 months at Bingham Health Clinic, Auta Balefi; PHC Kodape; Masaka PHC and Uke General Hospital.

Sample Size Estimation and Method of Sampling

The sample size for the study was calculated using the Leslie and Kish formula¹⁶ for estimating sample size for cross-sectional study; $n = (Z\alpha^2pq)/d^2$. The prevalence of typhoid fever in Abuja, Nigeria which was 2.4%.¹⁷ Therefore, $n = 1.96^2 \times 0.024 \times (1-0.024) / 0.05^2$. $n=361$. 10% was added for non-response giving 397. A design effect to 2 was further applied to the sample size, the sample size of 794 was calculated. The respondents that meet the inclusion criteria were recruited for the study consecutively until the required sample size was reached.

Data Collection

Research assistants were placed at the selected health facilities, and they recruited individuals clinically diagnosed with enteric fever and having a temperature above 37.4°C or suspected to have enteric fever. Four (1 per health facility) research assistants were involved in the study. The recruited research assistants were Community Health Extension Workers (CHEWs) who could speak the local languages and are trained on the criteria for enrolment into the study, completion of the questionnaire, and standard procedures for collection and handling of blood samples. In addition, training was also held for clinical and laboratory staff at the health facilities on the purpose, nature, and protocol of the study. Trained health workers at the health facilities worked with the research assistants to screen patients and recruit eligible ones for enrolment. A patient in whom a blood culture has been requested by the consulting clinician was assessed to see if they fulfilled the study entry criteria. The inclusion criterion includes a patient resident in the study communities, greater than 1 year of age and consent to participate in the study, and the exclusion criteria is age less than 1 year old or decline to give consent to participate. The study was explained to the patient, or their relative, parent or guardian. If they consent to participate in the study a signed (or thumbprint) witnessed consent form was completed. Patients were asked to fill a standardized questionnaire. The following data was collected and recorded in the study questionnaire: Information about the clinical history (including age, other demographic data, socioeconomic status, detail of presenting illness, past medical history, and recent medication history including any antibiotics taken recently), physical examination findings (including body weight and an assessment of nutrition status) and results of relevant investigations from microbiology.

Sample Collection Procedure

After consent, a blood sample for blood culture was taken from the respondent. Blood for blood culture was collected into BD Bactec™ blood culture bottles for adults and pediatric BD Bactec™ blood culture bottles for children, by the trained CHEWs before antibiotics were commenced even though, the impact of prior antibiotic exposure on culture yield was minimized using the Bactec™ culture system with culture bottles containing an antibiotic-removing device (resins). For children, 1–3 mL of blood was collected and placed into a BACTEC Ped Plus/F blood culture bottle. For adults, 8–10 mL of blood was collected, which was placed

into a BACTEC Plus/F (for adults) bottle. Blood culture was not done when the amount of blood collected was less than the desired volume (most specimens are); however, isolation rates did not vary by volume of blood cultured.

Blood cultures were cultured on a BD Bactec™ FX automated system for 5 days. Bottles that signal positive were examined by Gram stain and cultured on standard media and an aliquot of the blood culture broth was stored at -80°C. Bacteria were identified by a combination of morphology, Gram stain, and chemical methods. Drug susceptibility tests were performed by modified Kirby-Bauer method against relevant locally available antibiotics discs with Ciprofloxacin, Perfloracin, Sparfloxacin, Ofloxacin, Ceftazidime, Cefuroxime, Streptomycin, Gentamycin, Amoxicillin, Augmentin, Chloramphenicol, Imipenem and Trimethoprim/Sulfamethoxazole which were interpreted according to current CLSI guidelines (13).

Data Analysis

Ethical Considerations:

Both written and oral informed consent was obtained from the respondent. They were asked to sign the consent form, the form read to uneducated respondents, and they were requested to apply their fingerprints to the forms, Ethical clearance was obtained from Bingham University, Karu, Abuja. Patients received normal medical care by the clinic medical staff and Initial treatment followed routine practice following current guidelines. The results of the study investigations were communicated to physicians as soon as possible. The treatment was at the discretion of the Clinic's Medical staff.

Data Storage and Security:

The study questionnaire was stored in a locked cabinet at Bingham University. The anonymized data was entered and stored in a password-protected database on study computers. Specimens were stored in a - 80°C freezers in Zankli Research Centre (ZRC), Bingham University laboratory. Only authorized researchers had access to the specimens in the laboratory.

RESULTS

The isolates identified in the study are depicted in Figure 1. It shows that Blood cultures were performed for the assessment of 818 acutely ill febrile patients. Bacteria were isolated from the bloodstream of 46 (5.6%) while 772 (94.4%) had no bacterial pathogens in the blood culture. The majority (65.2%) of the positive blood culture is gram-negative bacteria in which *Salmonella spp* was the leading cause of bacteremia (43.5%) with salmonella typhi predominating 11 (23.9%) and non-typhi salmonella 9 (19.6 %). Other organisms isolated are *Pseudomonas spp* accounted for 8.7% while *K. Pneumoniae* and *E. coli* accounted for 4.3% and 2.2% respectively. Also, gram-positive isolates cultured are *Staphylococcus spp* and *Streptococcus* which constitute 32.6% and 2.2% respectively.

Table 1 shows the characteristics of participants in the study in relation to the S. Typhi, S. Non-Typhi, and other pathogens isolated. The mean age (SD) was 15.2 (11.6%) for S. Typhi, 12.3 (9.0%) for S. Non-Typhi, and 21.0 (11.3%) for other pathogens with age group 5-10 years predominating (64%) for S. Typhi and age group 10-20 years having a majority (56%) for S. Non-Typhi, even though age group 5-10 had 22%. Interestingly, *Salmonella spp* was not isolated in the age group 40-60 years. In terms of gender, most *Salmonella spp* isolates are from

male participants: *S. Typhi* (64%) and *S. Non-Typhi* (56%) whereas the other pathogens are mostly (69%) from female participants. While *S. Typhi* (73%) and *S. Non-Typhi* (78%) were cultures from students with only 9% and 11% from housewives respectively and single participants in the study had 91% for *S. Typhi* and 89% for *S. Non-Typhi* whereas married participants had 9% and 11% for *S. Typhi* and *S. Non-Typhi* respectively. In addition, most participants with typhoid fever had only a primary level of education, 64% for *S. Typhi* and 56% for *S. Non-Typhi* and they are from Kodape, Masaka, and Uke settlements.

The antibiotic resistance pattern of *S. Typhi* and *S. Non-Typhi* is shown in Table 2 with over 60% resistance to Trimethoprim/Sulfamethoxazole and chloramphenicol. Also, *S. Typhi* had more than 50% resistance and *S. Non-Typhi* had more than 75% resistance to ceftazidime and cefuroxime. Whereas *S. Typhi* isolate resistance pattern with the fluoroquinolones is 0% for pefloxacin, ciprofloxacin and ofloxacin both had only 1 (9%) and sparfloxacin had 2 (18%) resistance. That of *S. Non-Typhi* shows 0% for ofloxacin, ciprofloxacin, and sparfloxacin, with pefloxacin having 1 (11%) resistance. Penicillin (Amoxicillin and Augmentin) showed a mixed resistance pattern to *S. Typhi* (27% and 46%) and *S. Non-Typhi* (67% and 22%). The pattern for *S. Typhi* and *S. Non-Typhi* isolate resistance to Imipenem (9% and 22%), Streptomycin (46% and 44%) and Gentamicin (9% and 0%) are very interesting.

DISCUSSION

In this study, blood cultures done on 818 acutely ill febrile patients, identified bacterial pathogens in 46 cases [5.6%]. Thus, the incidence of bacteremia is similar to (7.5%) in a large surveillance report among children in the north-central region of Nigeria [7]. This slight difference may be due to the settings (primary and secondary health facilities) or patient health-seeking behavior lining towards secondary facilities. The study provides additional insights into the characteristics and antibiotic susceptibility patterns of *Salmonella* in Nigeria which are seen in other studies [5,6,8,13]. *Salmonella* infections are common in densely populated areas with poor hygiene and sanitation, contributing to high typhoid fever rates among infants, children, and adolescents, like observations in Asia [14-16].

Participant characteristics varied by the type of pathogen isolated. The mean age for those with *Salmonella Typhi* was 15.2 years, while for non-Typhi *Salmonella* was 12.3 years. For other pathogens, the mean age was higher at 21.0 years. The age group most affected by *Salmonella Typhi* was 5-10 years (64%). This suggests that younger children are particularly vulnerable to *S. typhi* infections, which could be attributed to factors such as low immunity, hygiene practices, and close contact in school environments with infected persons (16). Whereas, the 10-20 years age group predominated for non-Typhi *Salmonella* (56%), which indicates that teenagers are more frequently affected by it, potentially due to differences in dietary habits and risky behaviors [3, 17].

Interestingly, *Salmonella* spp. was not found in patients aged 40-60 years. This may be that older persons have developed immunity due to prior exposure or have a reduced risk of infection due to the environment [18]. Gender distribution showed that males were more frequently infected with *Salmonella* spp. (*S. Typhi* 64%, non-Typhi 56%), while other pathogens were more common in females (69%). Additionally, most *Salmonella* infections were among students and single participants, with a significant portion having only a primary level of education and residing in Kodape, Masaka, and Uke settlements. This suggests that low

educational levels might correlate with higher infection rates, possibly due to a lack of knowledge and awareness about proper hygiene practices [17].

The antibiotic resistance patterns for *Salmonella* Typhi and non-Typhi revealed significant resistance to common antibiotics. Both showed over 60% resistance to Trimethoprim/Sulfamethoxazole and chloramphenicol. This high level of resistance poses a challenge as these antibiotics are frontline drugs for the treatment of salmonella infection. The resistance may be attributed to widespread use and often misuse leading to the development of resistant strains, especially in developing countries where regulations are weak [12,19-23]. Resistance to ceftazidime and cefuroxime was also high, with *S. Typhi* showing over 50% resistance and non-Typhi more than 75%. These third-generation cephalosporins are important in the treatment of severe infection, with option limited which may indicate a potential crisis in managing severe infection [24]. Fluoroquinolone resistance was low, with *S. Typhi* showing no resistance to pefloxacin and minimal resistance to ciprofloxacin (9%) and sparfloxacin (18%). Non-Typhi *Salmonella* showed no resistance to ofloxacin, ciprofloxacin, and sparfloxacin, and only 11% resistance to pefloxacin. This low resistance level is promising, as fluoroquinolone are often used as second-line drugs when the first-line drugs fail [25,26]. The penicillin resistance pattern was mixed, with *S. Typhi* showing 27% resistance to amoxicillin and 46% to Augmentin, while non-Typhi showed 67% and 22% resistance respectively. This variability in resistance can be attributed to the presence of beta-lactamase enzymes produced by some *s. typhi* strains, which can degrade penicillin and make it ineffective [27].

The study confirms that *Salmonella* spp. are the leading cause of bacteremia in the country, with *Salmonella* Typhi more prevalent than non-Typhi *Salmonella*. Antibiotic susceptibility varied, with fluoroquinolones and gentamicin showing the least resistance [28]. Augmentin had a 46% resistance rate for *S. Typhi*, comparable to a 47% rate reported in another study [29]. Chloramphenicol and Septrin showed the highest resistance, suggesting the need to revise first-line treatments for typhoid fever due to high resistance rates among common *Salmonella* isolates [30]. The distinct disease epidemiology, influenced by the study locations, aligns with findings from other studies on children, despite the lack of routine typhoid vaccination in the country due to insufficient data on disease burden [31].

Previous studies show these microbes have higher prevalence in the northern part of Nigeria, potentially due to lower education levels and poor sanitary practices [32]. Further phylogenetic analysis of these isolates is needed to determine their genome and resistance patterns, particularly concerning the presence of resistant gyrase genes [33].

The study underscores the critical issue of antibiotic resistance in treating bacteremia caused by *Salmonella* spp. and other pathogens. The high resistance rates to commonly used antibiotics like Trimethoprim/Sulfamethoxazole, chloramphenicol, and cephalosporins highlight the need for ongoing surveillance and the development of more effective treatment protocols. The low resistance to fluoroquinolones suggests they remain a viable treatment option, although continuous monitoring is essential to prevent the emergence of resistance. The findings also emphasize the importance of targeted interventions for specific demographics, particularly younger age groups and males, who are more frequently affected by *Salmonella* infections. Education and awareness campaigns, especially in the identified settlements, could help in

early detection and appropriate treatment, potentially reducing the prevalence and impact of these infections.

CONCLUSIONS

Salmonella spp. was the leading cause of bacteremia, affecting younger participants, with males being more frequently infected by Salmonella spp. compared to females. The antibiotic resistance patterns showed high resistance of both Salmonella Typhi and non-Typhi to Trimethoprim/Sulfamethoxazole and chloramphenicol, as well as varying resistance to cephalosporins and fluoroquinolones, and interesting resistance trends to imipenem, streptomycin, and gentamicin. There is therefore an urgent requirement for health facilities to begin the implementation of modern diagnostic techniques and the establishment of routine antimicrobial surveillance systems to guide appropriate antibiotic use.

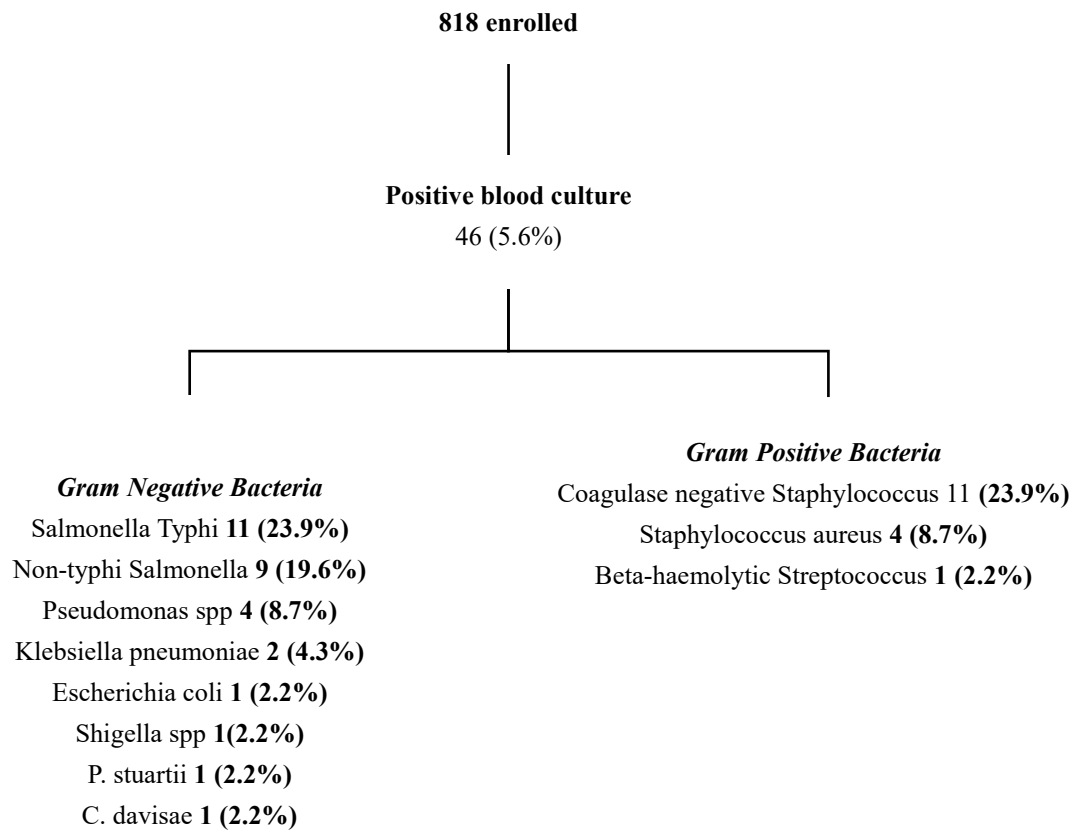


Figure 1: Isolates Identified in the Study

Table 1: Characteristics of participants by pathogen

Variable		S. Typhi n= 11 (%)	S. Non-Typhi n = 9 (%)	Others n = 26 (%)
Age (Years)	Mean (SD)	15.2 (11.6)	12.3 (9.0)	21.0 (11.3)
Group	0-5	0 (0)	1 (11)	2 (8)
	5-10	7 (64)	2 (22)	4 (15)
	10-20	1 (9)	5 (56)	6 (23)
	20-40	3 (27)	1 (11)	13 (50)

	40-60	0 (0)	0 (0)	1 (4)
Sex	Female	4 (36)	4 (44)	18 (69)
	Male	7 (64)	5 (56)	8 (31)
Occupation	Housewife	1 (9)	1 (11)	6 (23)
	Student	8 (73)	7 (78)	11 (42)
	Civil servant	1 (9)	0 (0)	1 (4)
	Trader	1 (9)	0 (0)	5 (19)
	Artisan	0 (0)	0 (0)	1 (4)
	Unemployed	0 (0)	0 (0)	1 (4)
	Others	0 (0)	1 (11)	1 (4)
	Married	1 (9)	1 (11)	11 (42)
	Single	10 (91)	8 (89)	14 (54)
	widowed	0 (0)	0 (0)	1 (5)
Education	None	0 (0)	1 (11)	2 (4)
	Primary	7 (64)	5 (56)	8 (31)
	Secondary	3 (27)	3 (33)	12 (46)
	Tertiary	1 (9)	0 (0)	4 (15)
Settlement	Bingham	0 (0)	0 (0)	1 (4)
	Kodape	7 (64)	0 (0)	8 (31)
	Masaka	3 (27)	4 (44)	7 (27)
	Uke	1 (9)	5 (56)	10 (38)

Table 2: Antibiotics resistance patterns of Salmonella Typhi and Non Typhi Salmonellas

	Trimethoprim/ sulfamethoxazole	Chloramphenicol	Ceftazidime	Cefuroxime	Sparfloxacin	Ciprofloxacin	Ofloxacin	Pefloxacin	Imipenem	Amoxicillin	Augmentin	Streptomycin	Gentamicin
Isolate	Salmonella Typhi												
1	R	R	R	R	S	S	S	S	R	R	R	R	S
2	R	R	R	R	S	S	S	S	S	S	R	S	S
3	R	R	R	R	S	S	S	S	S	S	R	S	S
4	R	R	S	R	S	S	S	S	S	R	S	R	S
5	S	R	R	S	R	R	S	S	S	R	S	S	S
6	S	S	R	R	S	S	S	S	S	S	S	S	S
7	R	S	S	R	S	S	S	S	S	S	R	S	S
8	S	R	R	S	R	S	S	S	S	S	S	S	S
9	R	S	S	S	S	S	S	S	S	S	R	S	R
10	S	S	S	S	S	S	R	S	S	S	S	R	S
11	R	R	S	S	S	S	S	S	S	S	S	S	S
Resistant (%)	7 (64)	7 (64)	6 (55)	6 (55)	2 (18)	1 (9)	1 (9)	0 (0)	1 (9)	3 (27)	5 (46)	3 (27)	1 (9)
	Non-Typhi Salmonella												
1	R	R	R	R	S	S	S	S	R	R	R	R	S
2	R	R	R	R	S	S	S	S	S	R	R	R	S
3	R	R	R	R	S	S	S	S	S	R	S	R	S
4	R	R	R	R	S	S	S	S	R	R	S	S	S
5	R	R	R	R	S	S	S	S	S	R	S	S	S

6	S	R	R	R	S	S	S	R	S	R	S	S	S
7	R	S	S	R	S	S	S	S	S	S	S	R	S
8	S	S	R	R	S	S	S	S	S	S	S	S	S
9	S	S	S	S	S	S	S	S	S	S	S	S	S
Resistant (%)	6 (67)	6 (67)	7 (78)	8 (89)	0 (0)	0 (0)	0 (0)	1 (11)	2 (22)	6 (67)	2 (22)	4 (44)	0 (0)

Table 3: The Incidence of Multidrug Resistance (MDR) For Salmonella

Salmonella type	Isolate	No of Salmonella isolates	No. of MDR Salmonella isolates	% of MDR Salmonella isolates
S. Typhi		11	9	81.8%
Non-Typhi Salmonella		9	7	77.7%

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