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**ORIGINAL RESEARCH**

# EPIDEMIOLOGY AND CHARACTERISTICS OF RESISTANT TYPHOIDAL SALMONELLA STRAINS PREVALENT IN LAFIA, NIGERIA

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**Abstract**

Resistance to antibiotics by pathogens is a burden to disease management. The study characterized Salmonella species in patients with fever and determined their antibiotic susceptibility patterns in Dalhatu Araf Specialist Hospital Lafia, Nigeria. Faecal samples were collected from 400 patients, and Salmonella species were isolated. The isolates were rested against ten antibiotics to determine their multi-drug and extensively drug-resistant capabilities, after which molecular characterization was done. Male patients between the ages of 21 to 30 years had the highest prevalence of 17(44.7%) of the pathogen, and they were the most susceptible among those who regularly drank water from boreholes (19(50.0%)). Augmentin with 44(73.0%) Salmonella susceptibility was the most effective antibiotic, while gentamycin, ampicillin, chloramphenicol, and cotrimoxazole had the isolates obtaining resistance of 60(100%), 59(98.0%), 57(95.0%), and 56(93.4%) respectively. Only six of the 60 Salmonella isolates were not multidrug-resistant, while 25 were extensively drug-resistant. Isolates S9 and S25 with staG genes were the only Salmonella typhi found in the study; others with ttr genes were of the Salmonella genera. The study concludes that the first-line antibiotics administered to patients with typhoid fever are no longer effective; hence, proactive measures should be put in place to surmount the observed challenge.

**KEYWORDS:**

Antibiotics, Lafia, Pathogen, Prevalence, Resistance, Typhoidal Salmonela

## 1 | INTRODUCTION

Salmonella enterica serotypes Typhi, and Paratyphi A, B, and C are responsible for bacteremic illnesses referred to as typhoid and paratyphoid fever and collectively as enteric fever. The burden of Salmonella diseases is a major health concern responsible

for most infectious diseases in developing countries where there are problems with sanitation and portable drinking water[1]. Serovars of Salmonella typhi and S. paratyphi A, B, and C cause enteric fever, while other strains, such as S. typhimurium and S. enteric Enteritidis, cause salmonellosis. Pathogenic bacteria remain the leading cause of death in the world, and worldwide surveillance data showed an increase in antibiotic resistance caused by Salmonella species[2]. Resistance to drugs by Salmonella species differs among species based on geographical locations and serotypes[3].

The World Health Organization (WHO) reported in 2020 that resistance to antibiotics is now a pandemic, and there is a need for urgent solutions. Antibiotic resistance has become a global challenge because pathogens continue to resist common antibiotics[4]. Disease burdens have increased, showing the poor activity of antibiotics against recently discovered resistant microorganisms. Resistant Salmonella species are responsible for complications associated with bacteremia, intestinal perforations, morbidity, and death in Nigeria, making the country one of the highest cases of intestinal perforations[5]. Typhoid and paratyphoid are endemic diseases in Nigeria, and there are gaps in the accurate identification and characterization of the causative agents, making treatment difficult. This study was to characterize Salmonella isolates and determine their antibiotics susceptibility pattern in Lafia, Nasarawa State.

## 2 | PREVIOUS RESEARCHES

Due to the ease with which they develop resistance to recognized antibiotics, gram-negative bacteria of the Enterobacteriaceae family are a concern. Extended-spectrum β-lactamase (ESBL) producing Enterobacteriaceae causes significant morbidity, and the associated burden on individuals and healthcare facilities is huge[6, 7]. Due to inadequate access to healthcare facilities, hospital overcrowding, poverty, poor hygiene standards, ignorance, inappropriate use of antibiotics, and consumption of animal products, the threat posed by bacteria that produce extended-spectrum-lactamases in Nigeria and other developing countries is inadequately quantified. These elements contribute to the spread of multidrug-resistant bacteria, particularly those that produce ESBLs. Typhoid fever frequently results in intestinal perforation in Nigeria[5]. The pathogen (Salmonella enterica serovar Typhi, Paratyphi A, and C) and its associated infection incidence are linked to unclean water and poor sanitation. Typhoid fever is brought on by Salmonella enterica serovar Typhi, Paratyphi A, and C.

Salmonella infections are endemic in Nigeria, with complications resulting from MDR-Salmonella strains. Several authors in Nigeria reported high disease prevalence rates, including 80.00% in Abeokuta, 13.00% in Kano, 45.00% in Jos, 16.89% in Lafia, 42.00% in Oweri, and 67.00% in Niger State[8–11]. Other effects of infection include high mortality rates, the development of severe salmonellosis, the failure of empirical therapy, and an increased risk of intestinal perforation. Typhoid perforations are common, and the fatality rate can reach 23%, according to studies done in Yobe State in northern Nigeria[12]. Unpublished data from Dalhatu Araf Specialist Hospital in Lafia shows that, on average, 23 cases of intestinal perforation are reported monthly. Rapid and accurate sub-typing of Salmonella is required to monitor outbreaks, identify them, and win the war against resistance. The benefit of whole genome sequencing (WGS) is that it offers a clear understanding of the pathogen by supplying strain- or clone-specific fingerprints that can be used to exclude cross-infection, clarify bacterial transmission patterns, and also to locate reservoirs or sources of infection in humans[13, 14].

Drug resistance is a significant financial burden, extending the course of an illness, exposing patients to infections that are difficult to cure, increasing death rates and posing hazards to the public and healthcare professionals, and having a detrimental impact on the patient and the community. The United Nations recently forecast that antimicrobial resistance might push over 23 million people into extreme poverty[15]. If nothing is done soon, the world and Nigeria, in particular, will soon succumb to the catastrophic effects of antimicrobial resistance, particularly Salmonella-related infections. The globe is already facing ineffective antibiotics' negative health and economic effects. The absence of pertinent epidemiological data necessary for tracking outbreaks and infection sources in this region of the nation is a significant setback in the fight against Salmonella-related infections.

## 3 | MATERIAL AND METHOD

### 3.1 | Ethical Clearance and Sample Collection

Dalhatu Araf Specialist Hospital Lafia, Nasarawa State's Ethics and Research Committee, gave ethical approval for the study. Four hundred stool samples were collected in sterile containers from patients with fever symptoms in the hospital's different

wards from March 2020 to June 2021. All patients who gave their consent were given a pre-labeled sterile sample container into which they collected about 15 g of their stool sample. All those who did not consent were excluded from the research.

## 3.2 | Isolation and Identification of Salmonella Species

About 5 g of the stool was inoculated in 10 ml of Selenite F broth incubated at 37°C for 24 h using a sterile wire loop; it was subcultured into Salmonella Shigella Agar (SSA) and incubated for another 24 h at 37°C. The growing colonies were purified on Nutrient agar by picking a single colony, streaking it on the agar, and incubating it for another 24 h. Identification was based on gram reaction and morphological and biochemical tests[16].

## 3.3 | Antibiotic Susceptibility Test of Isolates

Antibiotic susceptibility testing was done using the disk diffusion method on Muller-Hinton agar following the Clinical and Laboratory Standards Institute (CLSI) guidelines. The most prescribed antibiotics in treating enteric fever in the hospital were the drugs of choice in the study. Five classes of antibiotics, namely penicillin, Cephalosporin, Quinolones, aminoglycoside, Sulfonamides, and chloramphenicol[16], were used in the test. The 10 antibiotic drugs are amikacin (10 µg), amoxicillin/clavulanic acid (30 µg), ampicillin (10 µg), ceftriaxone (30 µg), chloramphenicol (30 µg), ciprofloxacin (30 µg), gentamycin (10 µg), cefotaxime (30 µg), trimethoprim/sulfamethoxazole, and ceftazidine (30 µg). A colony from the pure culture of the isolate was picked from the culture plate with a wire loop and inoculated into the McFarland standard solution. A suspension of 103 cells was streaked on the Mueller Hinton agar plate.

After a 5 min incubation at room temperature, antimicrobial discs were carefully placed on each plate and incubated at 37°C for 18 - 24 h. Zones of inhibition were measured to determine if isolates were resistant or susceptible based on the antibiotics disc diffusion zone interpretation guide. Multiple drug-resistant (MDR) isolates resist ampicillin, chloramphenicol, and cotrimoxazole. In contrast, an extensively drug-resistant (XDR) isolate is resistant to ampicillin, chloramphenicol, cotrimoxazole, quinolones, and cephalosporins, defined by Klemn et al.[17].

MDR Index = (number of antibiotics to which isolate is resistant)/( total,number of antibiotics tested)

## 3.4 | Molecular Identification of The Isolates

The DNAs of Salmonella typhi genes were isolated by molecular methods described by[18] with minor modifications. Five milliliters of an overnight broth culture of the Salmonella isolate in Luria Bertani (LB) was spun at 14000 rpm for 3 min. The cells were again suspended in 500 uL normal saline and heated at 950C for 20 min. The heated Salmonella typhi suspension was cooled on ice and spun for another 3 min at 14000 rpm. The DNA supernatant was transferred to a 1.5 mL microcentrifuge tube and stored at -20oC for the downstream reactions.

The 16s rRNA region of the rRNA genes of the isolates was amplified using the 21F: 5'-CAGGCCTAACACATGCAAGTC-3' and 18R: 5'-GGGCGGTGTGTACAAGGC-3' primers on an ABI 9700 Applied Biosyst¬ems thermal cycler at a final volume of 50 microlitres for 30 cycles. The PCR mix is made of the X2 Dream Taq Master mix supplied by Inqaba, South Africa (Taq polymerase, dNTPs, MgCl), the primers at a concentration of 0.4M, and the extracted DNA as a template. The PCR conditions were as follows: Initial denaturation, 95ºC for 5 min; denaturation, 95ºC for 30 seconds; annealing, 52ºC for 30 s; extension, 72ºC for 30 s for 30 cycles and final extension, 72ºC for 5 min. The product was resolved on a 1% agarose gel at 120V for 20 min and visualized on a blue light transilluminator.

The amplification of the probes for the ttr gene encoding genus Salmonella and staG encoding S. typhi was done as described by Nair et al.[19]. Primers and probes for ttr and staG genes were designed using the PrimerQuest Tool V8 (https://www.idtdna.com/PrimerQuest/Home/Index) using sequences obtained from the NCBI nucleotide database (https://www.ncbi.nlm.nih.gov/nucleotide/) as shown in Table 1 .

The PCR was performed in an ABI 9700 Applied Biosystems thermal cycler containing a 50 µL reaction mixture. The mixture is made up of 5 µL template DNA, 0.2 µL 18x PCR buffer II, 1.6 µL 1.25 mM mixture of deoxynucleoside triphosphates, 1.6 µL 25 mM MgCl2, 0.1 µL 5 U of AmpliTaq Gold DNA polymerase per µL, 0.2 µM concentration of each primer, and 1 µL of 5 µM probe (supplied by Inqaba, South Africa). Negative control was run with each PCR using 2.5 µL of nuclease-free water for the template, and the following positive controls were used: NCTC 8385 for S. Typhi (ttr and staG) supplied by Inqaba, South

**TABLE 1** The primer and probe sequences for each target gene with the coloured fluorescent dye.

| Genre | Name | Sequence (5'–3') | Amplicon Size | References |
|---|---|---|---|---|
| 16SrRNA | 16S rRNA -F | CAGGCCTAACACATGCAAGTC | 1362 | |
| | 16S rRNA -R | GGGCGGTGTGTACAAGGC | | |
| ttr | $ttr_F$ | CTCACCAGGAGATTACAACATGG | 589 | Nair et al.[19] |
| | $ttr_R$ | AGCTCAGACCAAAAGTGACCATC | | |
| probe | $ttr_P$ | FAM-CACCGACGGCGAGACCGACTTT-BHQ1 | | |
| staG | $staG_F$ | CGCGAAGTCAGAGTCGACATAG | 364 | Nair et al.[19] |
| | $staG_R$ | AAGACCTCAACGCCGATCAC | | |
| probe | $staG_P$ | FAM-CATTTGTTCTGGAGCAGGCTGACGG-BHQ1 | | |

The color of the reporter is related to the spectrum of detection; quenchers are in bold.
FAM=6-carboxyfluorescein; BHQ=black hole quencher; F= forward primer; R= reverse primer; P= probe.

**TABLE 2** The demographic information of participants.

| Demographic Parameters | Total Participants | | Positive Cases | |
|---|---|---|---|---|
| | Male (%) | Female (%) | Male (%) | Female (%) |
| | 257 (64.3) | 143 (35.8) | 38 (63.3) | 22 (33.3) |
| **Age** | | | | |
| 1-10 | 29 (11.3) | 18 (12.6) | 8 (21.1) | 2 (9.1) |
| 11-20 | 43 (16.7) | 27 (18.9) | 6 (15.8) | 8 (36.3) |
| 21-30 | 35 (13.6) | 17 (11.9) | 17 (44.7) | 6 (27.7) |
| 31-40 | 73 (28.4) | 58 (40.6) | 4 (10.6) | 2 (9.1) |
| 41-50 | 72 (28.0) | 14 (9.8) | 2 (5.3) | 3 (13.6) |
| 51-60 | 35 (13.6) | 9 (6.3) | 1 (2.6) | 1 (4.5) |
| **Sources of drinking water** | | | | |
| Borehole | 163 (63.4) | 84 (33.6) | 19 (50.0) | 8 (36.4) |
| Well | 46 (17.9) | 21 (32.2) | 5 (13.2) | 5 (22.7) |
| Stream | 19 (7.4) | 12 (8.3) | 8 (21.1) | 3 (13.6) |
| Other sources | 29 (11.3) | 26 (20.3) | 6 (15.8) | 6 (27.3) |
| **Residence** | | | | |
| Urban | 131 (51.0) | 97 (67.8) | 17 (44.7) | 9 (40.9) |
| Rural | 119 (46.3) | 53 (37.1) | 21(55.3) | 13 (49.1) |

Africa. The conditions for the PCR were an initial activation of 95 °C for 3 min, followed by 40 cycles of denaturation at 95 °C for 30 seconds, annealing at 60°C for 30 seconds, and extension at 72°C for 10 seconds.

Tsaku et al.[18] adopted the agarose gel electrophoretic assay method. An eight microlitre of PCR products stained with ethidium bromide was loaded into 1.0% (wt/vol) agarose gel wells with a molecular marker run concurrently at 120 V for 30 min. The DNA bands were visualized and photographed under UV light at 595 nm.

## 4 | RESULTS AND DISCUSSION

### 4.1 | Demographic Profile of Participants

Age group 21-30 of the demographic parameters examined recorded the highest number of cases, with 17(44.7%) men and 6(27.7%) women testing positive (Table 2 ), followed by the age group 11-20 recording 6(15.8%) positive cases among the participating men, and 8(36.3%) among the women. Age group 41-50 had a relatively low number of positive cases, with the men and women recording 2(5.3%) and 2(9.1%), respectively. Participants drinking water sources showed that those who took boreholes had the highest positive cases, with the male and females obtaining 9(50.00%) and 8(36.3%), respectively. Sixty-seven of the participant used water from a well, of which 3(13.2%) of the male tested positive, and 8(21.1%) men and 3(13.6%) women were positive among the 31 that drank water from a stream.

The setting of the study area showed that samples collected from rural participants had a higher prevalence because of the lack of access to clean drinking water. Age group 21-30 had the highest number of positive cases, which can be adduced to the growing-up period when eating outside among youths is highest. Guard-Petter[20], in their study, obtained the highest number of cases between ages 5-9. The high prevalence recorded among age groups 1-10 is attributed to poor hand washing practice, poor hygiene, and low immunity. Males recorded a higher number of cases than females in this study. This can be attributed to the

**TABLE 3** The susceptibility of the antibiotic drugs on Salmonella species.

| Drug | Number of Resistant | Number of Susceptible | Interpretation of the zone of inhibition (mm) |
|---|---|---|---|
| AN | 26 (43.0) | 34 (57.0) | R<14; S≥17 |
| AMC | 16 (26.3) | 44 (73.0) | R<13; S≥18 |
| AM | 59 (98.0) | 1 (2.0) | R<13; S≥17 |
| CRO | 46 (76.7) | 14 (23.0) | R<14; S≥23 |
| CHL | 57 (95.0) | 3 (5.0) | R<12; S≥18 |
| CIP | 29 (48.0) | 31 (52.0) | R<15; S≥12 |
| GEN | 60 (100) | 0 (0.0) | R<12; S≥15 |
| CAZ | 40 (66.0) | 20 (34.0) | R<14; S≥18 |
| SXT | 56 (93.4) | 4 (6.6) | R<10; S≥16 |
| CTX | 23(38.0) | 37 (62.0) | R<14; S≥23 |

AN = Amikacin, AUG = Amoxicillin/Clavulanic Acid,
AM = Ampicillin, CRO = Ceftriaxion, CHL = Chloramphenicol,
CIP = Ciprofloxacin, GEN = Gentamycin, CAZ = Ceftazidime,
SXT = Cotrimoxazole, CTX = Cefotaxime, R = Resistance, S = Susceptible.

eating habit of men. Females tend to eat at home compared to males since food hawkers have been linked to the transmission of the disease[21]. The report differed from Benue, where the prevalence was higher in females than males[22]. These contradictions can be due to lifestyle and the number of participants in the study. The water source is one of the key factors considered in this study because Salmonella is a waterborne pathogen. Most participants drink water from the borehole, while those drinking from streams share the same drinking water with animals that contaminate the water with waste. Open defecation is common in rural settings, leading to water contamination, especially during the rainy season. Most of the sachet table water hawked has been reported to be contaminated from the water source or during production[23]. Water from boreholes is sold by hawkers who, in the process, contaminate it as they transport it to consumers who buy from them.

## 4.2 | Antibiotic Susceptibility Profile of Salmonella Isolates

In vitro, assay of the antibiotics susceptibility test of 60 Salmonella isolates showed that gentamycin was the most resisted by all the isolates (Table 3 ). The first line drug comprising ampicillin, chloramphenicol, and cotrimoxazole were resisted by 59 (98.2%), 57 (95.0%), and 56 (93.0%) isolates, respectively. Augmentin was the least resisted antibiotic, with 44 (53.0%) isolates susceptible and 16 (26.3%) isolates resistant. Amikacin and cefotaxime gave promising outcomes, with 34 (57.0%) and 37 (62.0%) Salmonella isolates susceptible to the drugs, respectively. The report of the antibiotic susceptibility test further showed that isolates S11 and S39 have a multi-drug resistance index (MDRI) of 1 which means they resisted all the drugs tested on them (Supplementary material 3). Three isolates (S9, S26, and S34) have an MDRI of 0.4, while the remaining isolate has an MDRI of ≥ 0.5. Fifty-four (90.0%) isolates were multidrug-resistant (MDR) Salmonella species, while 25 (46.0%) isolates were extensively drug-resistant (XDR). Six (10.0%) were susceptible to at least one of the hospital's first-line antibiotics in treating Salmonella infection (Supplementary material 1).

The antibiotic susceptibility profile showed that the three first-line drugs used in the treatment of Salmonella were resisted by more than 90% of the isolates. Gentamycin resistance was recorded in all the isolates. The first-line drugs used in treating Salmonella were resisted by more than 90% of the isolate; this can be linked to the fact that most of these drugs are cheap and can be bought without a prescription, so the drugs are misused, creating room for resistance. Amikacin is the drug with the highest susceptibility in this study, possibly because it is expensive and taken parenterally. Fluoroquinolones (ciprofloxacin) were resisted by 29 (48%), which agrees with Kim et al.[24], who related the resistance of fluoroquinolones to qnsS mutation seen among Salmonella species. This study reported that resistance to ciprofloxacin by Salmonella is 29 (48%), which is in line with the finding of Mutai et al.[25], which reported the same number of cases of quinolone resistance in Kenya.

Cefotaxime and ceftriaxone are third-generational cephalosporins most isolates in the study area resisted. Table 3 showed a summary of the resistance pattern showing that quinolones and cephalosporin were highly resisted, which is in agreement with the findings of Lamini et al.[11] that reported the prevalence of extended-spectrum beta-lactamase (ESBL) among Salmonella species in the study area, which can translate to such resistance pattern seen.

This work showed a high distribution of XDR 46% in the study area, which agrees with the findings of Chiou et al.[26], who reported that most Salmonella isolates resisted first. Second-line drugs make them susceptible to only azithromycin. The findings agree with the report of Akinyemi et al.[9], which reported cephalosporin resistance in Lagos to be 49% for ceftazidime, cefotaxime 46%, and 37% for ceftriaxone. Some patients do not even complete their antibiotics, giving room for resistance[27]. The resistance seen in this research could be due to the extensive overuse of antibiotics for medical and agricultural purposes, as earlier pointed out by NARMS[28]. The molecular mechanism of Salmonella resistance to antibiotics is complex, which includes the production of enzymes that degrade the structure of antibiotic molecules, biofilm production, and genetic mutations[3, 9, 29].

### 4.3 | Isolated Salmonella Strains

Sixty samples (prevalence 15%) were positive for the presence of Salmonella species. staG genes specific only to Salmonella typhi were found in two isolates, S9 and S25. In contrast, most isolates contain the ttr gene of the genus Salmonella except isolates S32, S42, S43, S44, S45, S46, S47, S48, S51, S52, S54, S58, S59, and S60 (Supplementary material 2). Molecular diagnostic methods are accurate and reliable in detecting diseases that individuals harbor without apparent symptoms. The presence of the ttr gene in the 60 isolates confirmed that they are of the Salmonella genus. The presence of the staG gene confirmed that the isolates were S. typhi. In 2017, typhoid and paratyphoid cases globally were about 14.3 million, which is high because serology is the diagnostic method most health facilities adopt. The findings in this study showed that molecular detection methods are more reliable surveillance tools for diagnosing symptomatic and asymptomatic enteric fever[30]. The prevalence of Salmonella in the study area stands at 15%, which is lower than the prevalence reported recently from a study carried out in Port Harcourt, Nigeria, among food handlers (30%)[31]. A higher prevalence of 23.50% was reported in a study between 2006 and 2015 in Kano State, Nigeria, and another group reported a prevalence of 57.00%[32]. A lower prevalence of 4.29% was reported from Benue State[22]. The variation in the prevalence of Salmonella can be multifactorial, ranging from differences in the diagnostic methods, level of education, lifestyle, and geographical settings of the patients. The sample collected (stool) has a specificity of 50-70%[33].

## 5 | CONCLUSION

Pathogens resistance coupled with poverty continues to challenge disease management in Africa. Typhoid fever is prevalent and defies treatment as it cuts across all age groups. The study confirmed the ineffectiveness of ampicillin, chloramphenicol, and cotrimoxazole (first-line drugs) in treating the infection. The study further confirmed that while some causal agents are MDR and XDR, only two were Salmonella typhi, and 14 do not belong to the genus Salmonella. The molecular method in this study distinguished Salmonella typhi from other species in the study area. The study reported Salmonella prevalence to be 15% which is high. The antimicrobial susceptibility, resistance profile, and different patterns in the Salmonella strain provided information about the MDR and XDR isolates. This information showed continuous antibiotics and epidemiology surveillance for better treatment outcomes. More studies based on the genetic mechanism of resistance and whole genome sequence will increase our understanding of the population diversity and resistance mechanisms of Salmonella species in the study area.

## CREDIT

**Jebes Lamini Ngolo:** Methodology, Investigation, Resources, and Writing - Original Draft. **Olukayode Olugbenga Orole:** Conceptualization, Resources, Writing - Review & Editing, Supervision. **Aleruchi Chuku:** Resources, Project administration.

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