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Prevalence of Multi-Drug Resistant (MDR) *Salmonella Typhi* from Stool of Patients Attending Tertiary Medical Facilities in Makurdi, Benue State

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Abstract

Typhoid fever has continued to persist as a major health problem and poses emergence of Multi-Drug-Resistant (MDR) *Salmonella typhi* to commonly used antibiotics as a great challenge in its treatment. Transmission occurs by the consumption of contaminated food and water, and has remained endemic in developing countries of Africa and Asia due to poor hygienic and sanitary conditions. The aim of this paper is to investigate the prevalence of MDR *Salmonella typhi* isolated from stool samples of patients attending Benue State University Teaching Hospital (BSUTH) and Federal Medical Centre (FMC), Makurdi. A total of four hundred (400) stool samples were collected from patients. *Salmonella typhi* was isolated using Selenite broth, Salmonella Shigella agar and Xylose Lysine Deoxycholate agar. The isolates were purified on Bismuth Sulfite agar and identified using cultural and biochemical characteristics. Isolation rate of *S. typhi* in the study area was 43.8% (n=175). The antibiotic susceptibility pattern of the *S. typhi* isolates showed that 48% (n=84) were resistant to one or more class (es) of antibiotics. The isolates demonstrated the highest resistance to the fluoroquinolone (ciprofloxacin) (28.6%; n=24) followed by macrolide (azithromycin). All the isolates were however, susceptible to carbapenem (imipenem) and aminoglycoside (chloramphenicol). None showed combined resistance to all the antibiotics at a particular time. Isolates from BSUTH (60.1%) were more resistant to multiple antibiotics than those of FMC. The differences in the occurrence rate of MDR strains with respect to location was statistically significant (χ^2=27.459, df=8, $p < 0.05$). One important finding of this work is the high rate of resistance demonstrated by *S. typhi* to fluoroquinolones (ciprofloxacin) which unfortunately, is the most widely used antibiotic by the health care practitioners among the studied hospitals in the treatment of typhoid fever.

Keywords: *Salmonella Typhi*; Typhoid Fever; Stool; Isolates; Resistant

Abbreviations: MDR: Multi-Drug-Resistant; BSUTH: Benue State University Teaching Hospital; FMC: Federal Medical Centre; CLSI: Clinical Laboratory Standards Institute; PBS: Phosphate Buffered Saline; WHO: World Health Organization

Introduction

Multi-drug-resistant typhoid fever is caused by *S. typhi* strains that are resistant to all the three first-line recommended drugs used for its treatment [1,2] Kelvin et al., 2019. Typhoid fever (enteric fever) is caused by *Salmonella typhi*, a Gram negative, motile, non-spore forming, rod-shaped and facultative anaerobic bacterium [3]. The bacterium is solely a human pathogen with no known animal reservoir [4,5]. It is endemic in the tropical and sub-tropical regions of the world and it has become a major public health problem in developing countries of the world including Nigeria (Kelvin et al., 2019). Its estimated global annual incidence is 540 per 100,000 and 17 million cases worldwide (Kelvin et al, 2019), [6].

Antibiotic therapy is the mainstay for the treatment of typhoid fever; however, the emergence of multi-drug resistance (MDR) has become a major threat to public health [7,2]. Previous researchers have reported occurrence of MDR *S. typhi* strains in recent years in different parts of Nigeria and around the world [3,4 & 8]. *S. typhi* has been reported to be resistant to Amoxicillin/clavulanic

acid, tetracycline, ciprofloxacin, ampicillin, ceftraxoness and cotrinoxazole [7,8]. This suggests that most patients that contract the emerging MDR strains of *S. typhi* will not respond to treatment adequately if placed on one of the drugs, and may lead to high rates of treatment failure as reported by [9].

Chloramphenicol has been the treatment of choice for typhoid fever since its discovery in 1947. Because of the alarming spread of plasmid mediated chloramphenicol resistant *S. typhi* throughout the world, newer antibiotics with good invivo activity against *S. typhi* are needed. Typhoid fever responds slowly to ampicillin, amoxicillin, cotrimoxazole or trimethoprim alone [10]. Among fluoroquinolones, ciprofloxacin, ofloxacin and perfloxacin are most widely used antimicrobial agents. They act by inhibiting bacterial enzymes DNA gyrase which is responsible for division, coiling and supercoiling of bacterial DNA during multiplication. Of the third generation cephalosporins; ceftriaxone, cefotaxime and cefoperazone are effective therapeutic alternative in multidrug resistant *S. typhi* infected cases [11,12] opined that when a strain of microorganism acquires resistance to a drug, another drug must be found to treat the resistant infections effectively. If resistant to second drug develops, a third drug is needed and so on.

The fluoroquinolones (ciprofloxacin and ofloxacin), third generation cephalosporins (ceftriaxone and cefixime), and azithromycin came up as the second line of treatment for multidrug resistant strains. Aztreonam and imipenem are also potential third line drugs that have been used recently in serious infections [13]. The azalide antimicrobial, azithromycin is also an option in the treatment of multidrug resistant enteric fever [14].

Materials and Methods

Ethical approval

Ethical approval was sought and obtained from the ethical committee of the Benue State University Teaching Hospital and Federal medical Centre, Makurdi, Benue State.

Sample collection and inoculation

Four hundred (400) stool samples were collected from patients. Two hundred (200) samples each was collected from Benue State Teaching Hospital and Federal Medical Centre, Makurdi. The samples were examined for the presence of *Salmonella typhi*. The stool specimens were transported to the laboratory in a flask packed with ice for inoculation, isolation and identification.

Each specimen was inoculated into Selenite broth base, a pre-enrichment broth (Oxoid, CM 0395) and incubated at 37°C for 24 h. Loopfuls of the broth was streaked onto Salmonella Shigella Agar (Toxoid, CM 0099), Xylose Lysine Deoxycholate Agar (Oxoid, CM 0469) and Bismuth Sulfite Agar (Oxoid, CM 0201). Inoculated plates were incubated (37°C, 24h) and suspected colonies were sub-cultured repeatedly on media used for primary isolation to obtain pure cultures.

Antimicrobial susceptibility test

The *Salmonella typhi* isolates were subjected to antimicrobial susceptibility test using the standard disc diffusion method as described by [11]. Results were interpreted using the criteria of the Clinical Laboratory Standards Institute (CLSI, 2013). Overnight cultures of each *S. typhi* isolate were inoculated into a test tube containing 5 ml of phosphate buffered saline (PBS). The turbidity of each inoculum was adjusted to 0.5 McFarland standard prepared by mixing given amounts of Barium chloride and sulphuric acid.

The standardized culture was evenly spread over the entire surface of Mueller-Hinton agar (Oxoid, CM 0337) plates using sterile swab stick. Sterile forceps was used to carefully pick and gently place the antibiotic discs of known concentrations on the dried but inoculated surface of the Mueller-Hinton agar plates. The discs were gently pressed onto the medium surface with a sterilized forceps to ensure firm contact. The plates were incubated at 37°C for 24h.

The antibiotic impregnated discs (Oxoid Ltd) used were Amoxicillin/clavulanic (30µg), ceftazidime (30µg), ceftriaxone (30µg), amoxicillin (10µg), sulphamethoxazole/trimethoprim (25µg), chloramphenicol (30µg), ciprofloxacin (5µg), azithromycin (15µg), gentamycin (30µg) and imipenen (10µg). Diameters of zones of inhibition (if any) around the antibiotic disc were measured to the nearest millimetre using a ruler.

Result

From the total samples collected and analysed, FMC had a higher rate of isolation (46.8%; n=111), while BSUTH had isolation rate of 39.3% (n=64). The differences in isolation rate of *Salmonella typhi* with respect to location is statistically significant (χ^2=54.293, df=1, $p < 0.05$). Out of 175 confirmed *S. typhi* isolates, 48% (n=84) were resistant to one or more classes of antibiotics (Table 1). The isolates demonstrated highest resistance to fluoroquinolone (ciprofloxacin) (28.6%; n=24). This was followed by azithromycin (a Macrolide) (25.0%; n=21). All the isolates were however susceptible to imipenem (carbapenem), chloramphenicol and gentamycin (aminoglycosides) (Table 2). The multidrug resistance profile of *S. typhi* with respect to age is as presented in (Table 3). Resistance to AML, AZM and AMC occurred most frequently. Though, there are differences in the resistance pattern across different age groups, the differences were not statistically significant (χ^2=101.241, df=16, $p>0.05$).

Table 4 shows MDR profile of *S. typhi* with respect to gender. AML, AZM and AMC occurred most frequently, 11(13.1%) while the least frequent was SXT, AZM, AML and CFT, 1(1.2%). There was no significant difference in the MDR profile of *S. typhi* with respect to gender (χ^2=12.343, df=15, $p>0.05$).

The distribution of multi-drug-resistant *S. typhi* according to locations is as shown in Table 9. Isolates from BSUTH (60.1%, n=39) had a higher rate of multi-drug resistant strains than isolates

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from FMC (40.5%; n=45). The differences in the occurrence rate of MDR strains with respect to location is statistically significant (χ^2=27.459, df=8, p < 0.05).

Table 1: Isolation Rates of *Salmonella typhi* with Respect to Location.

Locations	Number investigated	Number Positive (%)	Number Negative (%)
BSUTH	163	64 (39.3)	99(60.7)
FMC	237	111(46.8)	126 (53.2)
Total	400	175 (43.8)	225 (56.2)

χ^2 = 54.293, df=1, p = 0.000 (p<0.05)

Table 2: Resistance of *S. typhi* Isolates to Different Classes of Antibiotics.

Antibiotics class (µg)	Resistant Number (n)	Frequency (%)
Fluoroquinolones Ciprofloxacin (5µg)	24	28.6
Macrolides Azithromycin (15µg)	21	25.0
Penicillins Amoxicillin (10µg)	12	14.3
Cephalosporins Ceftriaxone (30µg) Ceftazidime (30µg)	 07 05	 8.3 6.0
Sulfonamides Sulphamethoxazole/Trimethoprin (25µg)	09	10.7
B-lactam/B-lactam inhibitor combinations Amoxicillin-clavulanic acid (30µg)	6	7.1
Aminoglycosides Chloramphenicol (30µg) Gentamycin (30µg)	 0 0	 0 0
Carbapenems Imipenem (10µg)	0	0

84 (48%) of the total isolates (N=175) showed resistance to one or more antibiotic

Table 3: Pattern of Multidrug Resistance among the *S. typhi* Isolates.

Antibiotics	Frequency	Percent
SXT, AZM, AML, CFT	2	2.4
AML, CIP, CFT	3	3.6
CRO, AZM, CIP, CFT	3	3.6
AML, AZM, CIP, AMC, CFT	3	3.6
AML, CRO, CIP, AMC, CFT	4	4.8
CIP, AML, AZM	5	6.0
CRO, CIP, SXT	5	6.0
AML, CRO, SXT, AMC, CFT	5	6.0
CIP, AZM, CFT	6	7.1
SXT, CIP, AML	6	7.1
AML, AZM, CRO, CIP, CFT	6	7.1
AML, AZM, CRO, AMC, CFT	6	7.1
SXT, AMC, CFT	6	7.1
AML, AZM, CRO, CFT	7	8.3
AML, CRO, CIP	8	9.5
AML, AZM, AMC	9	10.7
NO MDR	91	52.0
Total	**175**	**100**

χ^2 = 107.413, df=16, p = 0.000 (p>0.05)

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Distribution of MDR *S. typhi* with respect to age is as presented in (Table 4). Age group ≤10 (68.1%, n=32) exhibited the highest rate of MDR while age group 41-50 (7.1%, n=1) exhibited the least. The difference in the distribution of MDR *S. typhi* with respect to age is not significant (χ^2=8.591, df=6, p>0.05). (Table 5) presents the distribution of MDR *S. typhi* with respect to gender. Isolates from female patients (52.3%, n=23) had higher MDR rate than their male (46.6%, n=61) counterparts. The differences were statistically significant (χ^2=5.662, df=1, p<0.05).

Table 4: Multi-drug Resistance Profile of *S. typhi* with Respect to Age.

	Age (Years)							
Resistance pattern	**≤10**	**Nov-20**	**21-30**	**31-40**	**41-50**	**51-60**	**>60**	**Frequency**
SXT, AZM, AML, CFT	1	0	0	1	0	0	0	2
AML, CIP, CFT	1	1	1	0	0	0	0	3
CRO, AZM, CIP, CFT	1	0	0	2	0	0	0	3
AML, AZM, CIP, AMC, CFT	2	0	1	0	0	0	0	3
AML, CRO, CIP, AMC, CFT	1	1	1	0	0	0	0	3
CIP, AML, AZM	1	1	1	0	1	0	0	4
CRO, CIP, SXT	1	0	2	1	0	0	0	4
AML, CRO, SXT, AMC, CFT	2	0	0	1	0	1	0	4
CIP, AZM, CFT	0	0	3	1	0	0	1	5
SXT, CIP, AML	0	1	4	0	0	0	0	5
AML, AZM, CRO, CIP, CFT	1	2	2	0	0	0	0	5
AML, AZM, CRO, AMC, CFT	2	2	0	1	0	0	0	5
SXT, AMC, CFT	5	1	0	0	0	0	0	6
AML, AZM, CRO, CFT	1	1	2	2	1	0	0	8
AML, CRO, CIP	5	2	3	0	0	0	0	10
AML, AZM, AMC	5	1	4	2	2	0	0	14
Total	29	13	24	11	4	1	1	84

χ^2 = 101.241, df=15, p = 0.000 (p>0.05)

Table 5: Multi-drug Resistance Profile of *S. typhi* with Respect to Gender.

	Gender		
Resistance Pattern	**Male**	**Female**	**Frequency**
SXT, AZM, AML, CFT	0 (0)	1 (1.2)	1 (1.2)
AML, CIP, CFT	1 (1.2)	2 (2.4)	3 (3.6)
CRO, AZM, CIP, CFT	2 (2.4)	1 (1.2)	3 (3.6)
AML, AZM, CIP, AMC, CFT	0 (0)	3 (3.6)	3 (3.6)
AML, CRO, CIP, AMC, CFT	1 (1.2)	2 (2.4)	3 (3.6)
CIP, AML, AZM	1(1.2)	3 (3.6)	4 (4.8)
CRO, CIP, SXT	2 (2.4)	2 (2.4)	4 (4.8)
AML, CRO, SXT, AMC, CFT	0 (0)	4 (4.8)	4 (4.8)
CIP, AZM, CFT	5 (6.0)	0 (0)	5 (6.0)
SXT, CIP, AML	2 (2.4)	3 (3.6)	5 (6.0)
AML, AZM, CRO, CIP, CFT	1 (1.2)	4 (4.8)	5 (6.0)
AML, AZM, CRO, AMC, CFT	0 (6.3)	5 (6.0)	5 (6.0)
SXT, AMC, CFT	2 (2.4)	6 (7.1)	8(9.5)
AML, AZM, CRO, CFT	3 (3.6)	7 (8.3)	10 (11.9)
AML, CRO, CIP	4 (4.8)	6 (7.1)	10 (11.9)
AML, AZM, AMC	4 (4.8)	7 (8.3)	11 (13.1)
Total	**28 (33.3)**	**56 (66.6)**	**84 (100)**

χ^2 = 12.343, df=15, p = 0.000 (p>0.05)

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Discussion

The implication of the high prevalence of *S. typhi* obtained in the present study is that it suggests the existence of a significant public health hazard in the studied area. This finding agrees with results from previous studies in Jos (Raymil et al., 2014) and Nasarawa [15]. Much higher prevalence was, however, reported in Bangladeshs [16] and in Lagos [17]. According to reports of World Health Organization [18], the majority of typhoid fever cases occur in Asia, Africa and Latin America where water-borne diseases are highly prevalent.

FMC had a higher rate of isolation (46.8%; n=111) than BSUTH (39.3%; n=64). This could be attributable to unhygienic practices by the inhabitants of the immediate community (Wadata) where the Federal Medical Centre is located. It is the closest standard health centre to the community which is highly patronized by the inhabitants of the area. Wadata is characterized by poor toilet system, poor sewage disposal system and unavailability of pipe-borne water. These factors may predispose the inhabitants to infection.

Patients within the age range 51-60 years had the highest rate of occurrence (52.9%, n=09) while Subjects above >60 years old had the least rate of occurrence (36.4%; n=04). This could be attributable to suppressed immune system in the elderly while those within the pediatric age range are immunologically naive as opined by [10]. This finding corroborates earlier reports in Makurdi, Central Nigeria [19], Minna [20], Central Ethiopia [21] and Bangladesh [8] although, they reported much higher prevalences. However, the findings of this study disagree with those of [22] in Dhaka City, Bangladesh and [8] in Southern Benue where highest prevalence was reported in the 21-30 years age group with the least prevalence in the age group 50-60 years.

According to [9], there are 21.7 million estimated typhoid cases worldwide annually with more than 700,000 deaths among which infants, children and young adults experienced the greatest burden of the illness. Health education could play an important role in this age group as suggested by [17].

Isolation rate of *S. typhi* showed that male subjects had a higher frequency of isolation (48.0%; n=131) than female subjects (34.6%; n=44). This agrees with the findings of [23,17 & 6] and Adikwu et al. (2022). The findings in other parts of the world also corroborate the result of this study [16,24,21 & 25]. This could be as a result of Benue cultural background where a male is more likely to report to hospital for medical treatment, and also likely to contract infections due to engagement in more outdoor activities. [19,10 & 5] had acknowledged that males usually work outside their homes and may eat hawked foods that are liable to contamination. These habits predispose them to infection. Out of 175 confirmed *S. typhi* isolates, 48% (n=84) were resistant to one or more classes of antibiotics. The isolates demonstrated variable resistance to fluoroquinolone (ciprofloxacin) (28.6%; n=24) and azithromycin (a Macrolide) (25.0%; n=21). All the isolates were however susceptible to imipenem (carbapenem), chloramphenicol and gentamycin (aminoglycosides). This result agrees with the findings of [3,2] but negates the report of [26] that penicillins (e.g., amoxicillin), cephalosporins (ceftriaxone and ceftaxidimess) and fluoroquinolones (ciprofloxacin) are the drugs of choice for the treatment of typhoid fever. The results of this study, however, supported the view of [27] on the use of aminoglycosides (gentamycin and chloramphenicol) in the treatment of typhoid fever and that of [28] on the re-emergence of chloramphenicol in the treatment of typhoid fever.

One important finding of this work is the high rate of resistance demonstrated by *S. typhi* to fluoroquinolones (ciprofloxacin) which unfortunately, is the most widely used antibiotic by the health care practitioners among the studied hospitals in the treatment of typhoid fever. This could be attributable to the abuse of ciprofloxacin in the studied area and individual self-medication. [17,4 & 29] suggested that fluoroquinolones which inhibit the function of the DNA gyrase are the drugs most frequently used in treating typhoid fever globally. The implication of the result of this study is that resistance of *S. typhi* to fluoroquinolones has made treatment more expensive for patients in endemic areas in the midst of challenging clinical evaluations for new and economical typhoid treatment options. A prolonged course of high-dose fluoroquinolone, azithromycin, oral or injectable cephalosporins is required to treat patients diagnosed with typhoid caused by quinolone-resistant Salmonella strains. This includes its attendant cost. [10,27] reported that this expensive treatment, however, are not very clinically effective because of higher faccal carriage rates, ultimately resulting in greater Salmonella transmission potential. Hence, antibiotics must not be abused or used excessively as this imprudent gesture can cause a rapid emergence of antibiotic resistance, rendering patients in high-risk impoverished nations such as India and African countries to be at a brutal disadvantage [10].

Resistant to AML, AZM and AMC occurred most frequently, 09 (10.7%). None showed resistance to all the antibiotics at a particular time. This supports the findings of [23] in Federal Capital Territory, Abuja, Nigeria. The implication of this finding is that patients placed on this antibiotic will not respond adequately to treatment. Amoxicillin is derived from penicillin and categorized under beta-lactam antibiotics. It is degraded rapidly in an acidic environment as suggested by [15]. Of all the beta-lactam antibiotics, carbapenems possess the broadest spectrum of activity and the greatest potency against bacteria. Because of this, they are often reserved for more severe infections or used as "last-line" agents [3,5].

The antibiotic susceptibility test showed a remarkable level of resistance to cephalosporins and macrolides. This corroborates the findings of [26]. Ceftriaxone is an alternative to fluoroquinolone in the treatment of typhoid fever among children

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and is given parenterally [6], Nevertheless, Raymil et al. (2014) are of the opinion that azithromycin is a more preferred drug as the frequency of relapse when azithromycin is administered is zero; relapse frequency was evident with ceftriaxone. This is because azithromycin is rapidly transferred from the blood plasma into the tissues. Therefore, the concentration of azithromvcin is higher in the tissues than in the blood plasma. The prolonged half-life of azithromvcin is related to the extensive uptake of the drug and subsequent liberation of the drug from the tissues. The maintenance of a high concentration of azithromycin in the body cells and tissues allows the effective treatment of typhoid fever. [5] supported the effectiveness of azithromycin by stating that it is used for treatment of both typhoidal and non-typhoidal Salmonellosis. Isolates from age group ≤10 (68.1%, n=32) exhibited the highest rate of MDR while age group 41-50 (7.1%, n=1) exhibited the least. This agrees with the findings of [16], though they reported a higher rate in the paediatric age group.

Results of the study showed that the number of MDR strains is higher in females (66.6%) than in males (33.3%). [16,2] however disagree with this finding. They reported a higher MDR strain in male than females. The rate of MDR demonstrated by *S. typhi* isolates in this study is remarkable and of great concern. Studies by [30,27 & 5] had reported increased prevalence of multi-drug resistance around the globe. This finding suggests that most of the patients will not respond to treatment if placed on one of these drugs [31, 32]. The implication is that patients are likely to have a prolonged fever clearance time and high rates of treatment failure [21].

Conclusion

The study has shown a statistically significant difference in the prevalence of *S. typhi* among the various age groups in the study area. The highest prevalence occurred within the age range 51-60 years. In addition, the rate of *S. typhi* infection showed male preponderance over female subjects. The relevance of the use of carbapenems and aminoglycosides is clearly supported by the current finding as most of the isolates were resistant to one or more antibiotics but all were however susceptible to aminoglycosides (chloramphenicol and gentamycin) and carbapenems (imipenen).

One of the most obvious findings from this study is the high rate of resistance demonstrated by *S. typhi* to fluoroquinolones (ciprofloxacin) which unfortunately, is the most widely used antibiotic in the study area for the treatment of typhoid fever. Another important finding of this research is the re-emergence of chloramphenicol susceptible *S. typhi*. The results showed a statistically significant difference in the prevalence of MDR *S. typhi* among the studied hospitals.

Isolates from females had higher MDR strains than isolates from male subjects. There is no statistically significant difference in the distribution of MDR strains within the different age groups. The study demonstrated that the multi-drug-resistant *S. typhi* isolates harboured bla SHV (codes for resistance to βeta-lactam antibiotics) but lacked Imp A (codes for resistance to carbapenems). The rate of MDR *S. typhi* isolates demonstrated in this study is remarkable and calls for great concern. Based on the findings of this research it is recommended that drugs prescribed for treatment and prevention should be used prudently without abuse in order to slow down the emergence of such resistance and More work should be done on the genes coding for resistance in *S. typhi* in Benue State and Nigeria at large using the findings of this work as a baseline. This will not only provide a data base; it will help in monitoring the occurrence rate within the State and country.

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