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Prevalence of β-lactamase-encoding genes in *Salmonella* Typhi isolates from patients attending secondary healthcare facilities in Benue south senatorial district, northcentral Nigeria

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Abstract:

Background: The emergence of multi-drug resistant (MDR) *Salmonella* Typhi poses a major challenge in the treatment of typhoid fever using commonly available antibiotics. However, in many rural and semi-urban communities of low- and middle-income countries (LMICs), routine surveillance for MDR *S.* Typhi is scarcely undertaken. The aim of this study is to determine the prevalence of β-lactamase genes in MDR *S.* Typhi isolated from patients in nine secondary healthcare facilities in Benue south senatorial district, northcentral Nigeria.
Methodology: MDR *S.* Typhi (n=122) isolated from stool samples of patients initially diagnosed with typhoid fever using the Widal agglutination test in a previous study were used in this study. The isolates were confirmed by standard culture and biochemical identification characteristics. Plasmid DNA was isolated from each MDR isolate and selected β-lactam resistant (*bla*$_{SHV}$, *bla*$_{TEM}$, and *bla*$_{CTX-M}$) and carbapenem resistant (*bla*$_{IMP}$) genes were amplified by conventional simplex PCR assay.
Results: A total of 18 (14.8%) MDR *S.* Typhi isolates contained plasmids while on PCR assay, 5 (4.1%) isolates harbored *bla*$_{SHV}$ and 3 (2.5%) harbored *bla*$_{TEM}$, which encodes resistance to β-lactam antibiotics, while none harbored *bla*$_{IMP}$, which encodes resistance to carbapenems or *bla*$_{CTX-M}$, which encodes resistance to many extended spectrum β-lactam antibiotics.
Conclusion: This finding showed that the strains of MDR *S.* Typhi isolates in the study setting are those that harbored *bla*$_{SHV}$ and *bla*$_{TEM}$, which encode resistance to β-lactam antibiotics while strains that harbor *bla*$_{IMP}$ are apparently rare. A larger study across the entire region is required to confirm this finding.

Keywords: *Salmonella* Typhi, multi-drug resistance, *bla*$_{IMP}$, *bla*$_{SHV}$, *bla*$_{TEM}$, *bla*$_{CTX-M}$, plasmid

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Prévalence des gènes codant pour la β-lactamase dans les isolats de *Salmonella* Typhi provenant de patients fréquentant des établissements de soins secondaires du district sénatorial sud de Benue, dans le centre-nord du Nigéria

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Résumé:

Contexte: L'émergence de *Salmonella* Typhi multirésistante (MDR) pose un défi majeur pour le traitement de la fièvre typhoïde à l'aide d'antibiotiques courants. Cependant, dans de nombreuses communautés rurales et semi-urbaines des pays à revenu faible et intermédiaire (PRFI), la surveillance systématique de *S.* Typhi MDR est rarement mise en œuvre. L'objectif de cette étude est de déterminer la prévalence des gènes de β-lactamases chez les *S.* Typhi MDR isolés chez des patients de neuf établissements de santé secondaires du district sénatorial de Benue Sud, au centre-nord du Nigéria.
Méthodologie: Des souches de *S.* Typhi MDR (n=122) isolées à partir d'échantillons de selles de patients initialement diagnostiqués avec une fièvre typhoïde par le test d'agglutination de Widal lors d'une étude précédente ont été utilisées dans cette étude. Les isolats ont été confirmés par culture standard et identification biochimique. L'ADN plasmidique a été isolé de chaque isolat MDR et les gènes sélectionnés de résistance aux β-lactamines (*bla*$_{SHV}$, *bla*$_{TEM}$ et *bla*$_{CTX-M}$) et aux carbapénèmes (*bla*$_{IMP}$) ont été amplifiés par PCR simplex conventionnelle.
Résultats: Au total, 18 isolats (14,8%) de *S.* Typhi multirésistants contenaient des plasmides. Lors d'un test PCR, 5 isolats (4,1%) étaient porteurs du *bla*$_{SHV}$ et 3 isolats (2,5%) du *bla*$_{TEM}$, codant pour la résistance aux antibiotiques β-lactamines. Aucun n'était porteur du *bla*$_{IMP}$, codant pour la résistance aux carbapénèmes, ni du *bla*$_{CTX-M}$, codant pour la résistance à de nombreux antibiotiques β-lactamines à spectre étendu.
Conclusion: Ce résultat a montré que les souches d'isolats de *S.* Typhi multirésistants étudiées étaient celles qui hébergeaient le *bla*$_{SHV}$ et le *bla*$_{TEM}$, codant pour la résistance aux antibiotiques β-lactamines, tandis que les souches qui hébergeaient le *bla*$_{IMP}$ étaient apparemment rares. Une étude plus vaste couvrant l'ensemble de la région est nécessaire pour confirmer ce résultat.

Mots-clés: *Salmonella* Typhi, multirésistance aux médicaments, *bla*$_{IMP}$, *bla*$_{SHV}$, *bla*$_{TEM}$, *bla*$_{CTX-M}$, plasmide

Introduction:

Salmonellae are Gram-negative, flagellated, non-spore forming facultative anaerobes (1). They belong to the family Enterobacteriaceae and contain more than 2300 serotypes (2). *Salmonella enterica* is one of the most common causes of human gastroenteritis worldwide. Antibiotics such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole have been used for the treatment of enteric fever for many years (3). Later in the 1980s, the resistance of *Salmonellae* towards multiple drugs was reported (1), caused by the increased use of fluoroquinolones such as ciprofloxacin and the extended-spectrum cephalosporins (4).

The βeta-lactam antibiotics are widely used in the treatment of infections caused by *Salmonella* in both animals and humans (5). This has led to widespread resistance of *Salmonella* to different β-lactam drugs (6). Resistance to β-lactams in *S. enterica* is primarily caused by the production of acquired β-lactamases (1). More than 340 β-lactamases have been described and many of these have been identified in *Salmonella* (7). Different plasmid genes such as *bla*$_{SHV}$, *bla*$_{TEM}$, *bla*$_{CTX}$ and *bla*$_{CMY}$ have been found to encode extended spectrum β-lactamases (ESBL) in *Salmonella* (8). Also, a few variants of the *bla*$_{OXA}$ genes have been identified in *Salmonella* belonging to the *bla*$_{OXA-1}$ group (comprising *bla*$_{OXA-1}$, *bla*$_{OXA-4}$, *bla*$_{OXA-30}$, *bla*$_{OXA-31}$ and *bla*$_{OXA-47}$ genes) and *bla*$_{OXA-2}$ group (comprising *bla*$_{OXA-2}$, *bla*$_{OXA-3}$, *bla*$_{OXA-15}$, *bla*$_{OXA-32}$, *bla*$_{OXA-34}$ and *bla*$_{OXA-53}$ genes) (8).

The past few decades have shown the emergence of multiple antibiotic-resistant *Salmonella*, particularly the ESBL-producing strains, which represents a significant challenge for human medicine (9). This has caused great concern since cephalosporins are drugs of choice for the treatment of salmonellosis in Nigeria and specifically in southern Benue (3). The ESBL-producing bacteria carry a broad range of β-lactamases that hydrolyze a wide spectrum of penicillin and cephalosporin antibiotics, but not carbapenems (10). Many β-lactamases are members of TEM (named after the patient Temoneira), sulfhydryl reagent variable (SHV), CTX-M (active on cefotaxime, first isolated at Munich), and OXA (oxacillinase) families (11). The three enzymes TEM, SHV and CTX-M represent the most prevalent types of ESBL enzymes (11).

Recently, another group of β-lactamases named AmpC have been described, which confers resistance to all β-lactam antibiotics except the fourth generation cephalosporins and carbapenems (7). In contrast to ESBL, the AmpC group is not susceptible to β-lactam inhibitors, such as clavulanic acid, sulbactam and tazobactam (8). In addition, the AmpC group can be encoded by genes located on chromosomes or plasmids (12). Tran et al., (13) reported that *Salmonella* resistance to the extended-spectrum cephalosporins were shown to commonly result from the action of the plasmid AmpC *bla*$_{CMY-2}$ gene.

Identical plasmid-mediated β-lactamase genes have been detected in Enterobacteriaceae from different countries, which could indicate plasmid-borne spread of these genes between countries (1). Nonetheless, there is

paucity of information on the detection of β-lactamase genes among *S*. Typhi isolates in southern Benue, Nigeria. This study was hence conducted to investigate the genetic basis of MDR in *Salmonella* Typhi isolated from stool of patients in secondary healthcare facilities in southern Benue, northcentral Nigeria.

Materials and method:

Study area:

This study was conducted in Benue State secondary healthcare facilities within the nine local government areas (LGAs) of Benue south geographical zone, Nigeria. These LGAs include Otukpo (TKP), Ohimini (OHM), Apa (APA), Agatu (GTU), Obi (OBI), Oju (OJU), Ado (ADO), Okpokwu (OKP), and Ogbadibo (OGB). Benue south geographical zone is in Benue State, northcentral region of Nigeria, with a population of about 1,307,647 people in 2006 (14).

Study design and isolates:

This is a laboratory-based study to determine the prevalence of β-lactamase genes in MDR *S.* Typhi isolates. From a previous study by Adikwu et al., (15), 122 MDR *S*. Typhi isolates were collected, purified, and confirmed on Bismuth Sulfite agar, based on cultural morphology. The previous study had isolated 447 *S.* Typhi from 1,022 stool samples of patients with typhoid fever and positive Widal agglutination test, and antibiotic susceptibility test had been performed on them using the standard disc diffusion method of Kirby-Bauer as described by Kolhatkar and Ochei (16), with the results interpreted using the guideline of the Clinical and Laboratory Standards Institute (17). MDR in the *S.* Typhi isolates was defined as resistance to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole (18).

Plasmid DNA extraction:

Plasmid DNA was isolated from pure overnight cultures using Bio Teke's Plasmid MiniPrep Kit (Beijing & Wuxi, China) following the manufacturer's instructions. The purity of the DNA was assessed using the Nanodrop spectrophotometer. Exactly 0.4µl of extracted plasmid DNA was placed on the spectrophotometer and the ratio of the absorbance at 260 nm to 280 determined. The purity of the DNA is reflected in the OD260:OD280 ratio and must be between 1.8 and 2.0. Values less than 1.8 indicate protein contamination while values above 2.0 indicate RNA contamination. The DNA isolates were preserved at -20^{o}C until further use.

Amplification of resistance genes:

Genes encoding resistance to β-lactams (*bla*$_{SHV}$, *bla*$_{CTX-M}$, *bla*$_{TEM}$), and resistance to carbapenem (*bla*$_{-IMP}$) were amplified by conventional simplex PCR using specific primers (Table 1), and the PCR conditions described by Hasman et al., (19). The conditions and volume of the reaction were determined by the Solis BioDyne ready to load master mix (5x) used.

PCR was performed in a 20µl reaction under the following conditions; initial denaturation at 95°C for 5 min, followed by denaturation at 95°C for 30 sec, annealing between 54-66°C for 1 min (the annealing temperature is determined by the primer used), extension at 72°C for 2 min, and a final extension at 72°C for 5 min for a total number of 35 cycles.

Agarose gel electrophoresis:

A check gel was performed on 2% TAE agarose gel and electrophoresed at 70 V for 1 hour to confirm the amplified bands, with 100bp Plus DNA ladder (Transgen Biotech, Cat No. BM 311). The bands were visualized under UV light in a gel documentation system

Table 1: Primers used for study

Target gene	Primer	Sequence	Amplicon Size (bp)	Ref
bla$_{SHV}$	SHV – F	5'- GATGAACGCTTTCCCATGATG -3'	214	(20)
	SHV – R	5' - CGCTGTTATCGCTCATGGTAA -3'		
bla$_{TEM}$	TEM – F	5'- AGTGCTGCCATAACCATGAGTG -3'	431	(20)
	TEM – R	5'- CTGACTCCCCGTCGTGTAGATA -3'		
bla$_{CTX-M}$	CTM-X – F	5'- ATGTGCAGYACCAGTAARGTKATGGC -3'	592	(21)
	CTM-X – R	5'- TGGGTRAARTARGTSACCAGAAYSAGCGG -3'		
	IMP – F	5'– GAAGGCGTTTATGTTCATAC -3'	588	(22)
bla$_{IMP}$	IMP – R	5'- GTATGTTTCAAGAG TGATGC -3'		

Results:

Purity and concentration of plasmids extracted from *Salmonella* Typhi isolates:

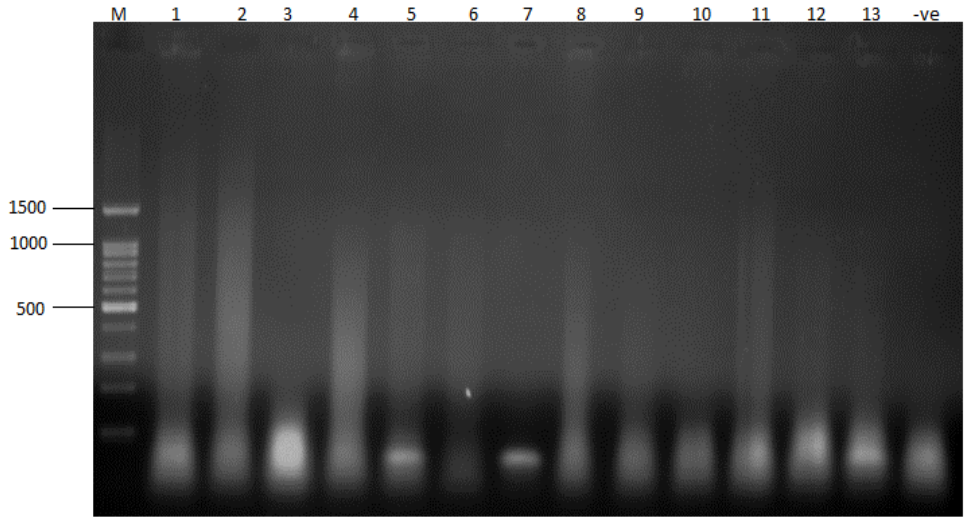
Among the 122 MDR *S.* Typhi isolates, only 18 (14.8%) contained plasmids. The extracted plasmids were pure except for isolate GTU 8 (1.74) as shown in Table 2.

Prevalence of β-lactamase resistance gene in *Salmonella* Typhi isolates:

Among the 122 MDR *S.* Typhi isolates, the β-lactamase resistant genes were detected in 8 of the 18 isolates with plasmids; 0% bla_{IMP} gene (Plate 1), 5 (4.1%) bla_{SHV} gene (Plate 2, 3 and 4), 3 (2.5%) bla_{TEM} gene (Plate 5 and 6), and 0% bla_{CTX-M} gene (Plate 7).

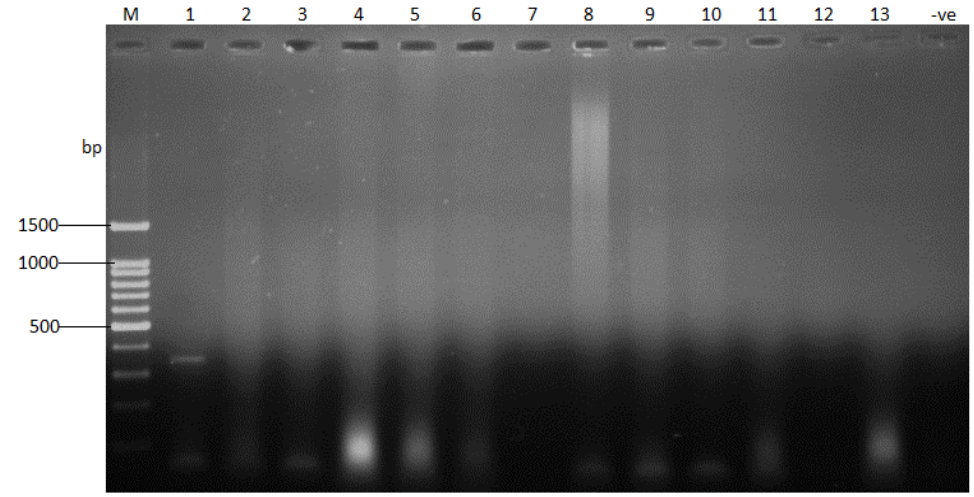
Table 2: Purity and concentration of plasmid DNA extracted from *Salmonella* Typhi isolates

Isolate ID	Nucleic acid concentration (ng/µl)	Absorbance (260:280)
TKP 65	329.1	1.94
TKP 82	833.5	1.98
OHM 27	621.7	1.94
OHM 43	587.3	1.86
APA 5	671.6	1.88
APA 25	661.8	1.95
GTU 8	701.3	1.74
GTU 37	425.6	1.87
OBI 18	393.7	1.96
OBI 38	733.9	1.82
OJU 22	517.8	1.93
OJU 48	658.8	1.97
ADO 16	573.6	1.98
ADO 57	801.7	1.98
OKP 85	606.4	1.88
OKP 100	704.1	1.96
OGB 39	739.6	1.95
OGB 119	583.2	1.99



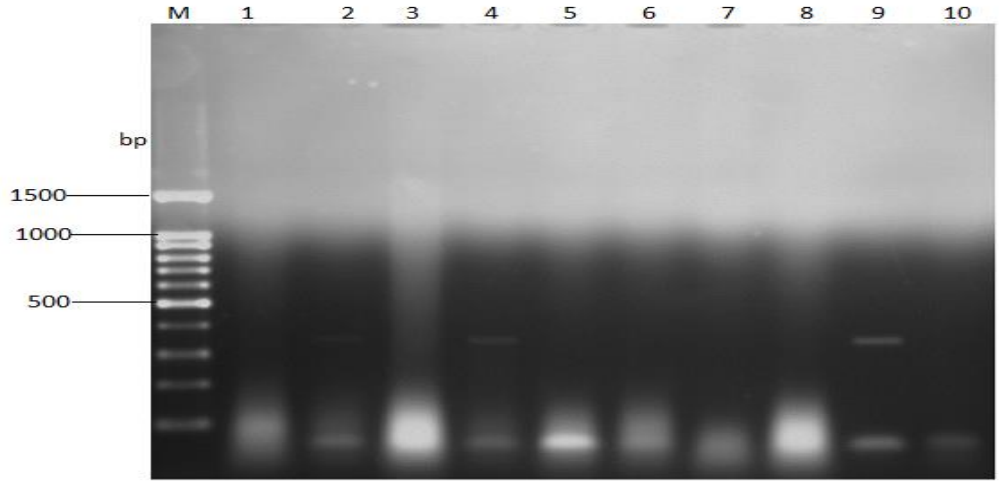
Lane 1 – 13 = Samples; No isolate amplified with bla_{IMP} primer; Lane M: 100bp Molecular DNA ladder; Lane -ve: Negative Control (PCR reaction without DNA); M = Size marker.

Plate 1: Electrophoretograph of amplified bla_{IMP} gene (588bp) in MDR *Salmonella* Typhi isolates



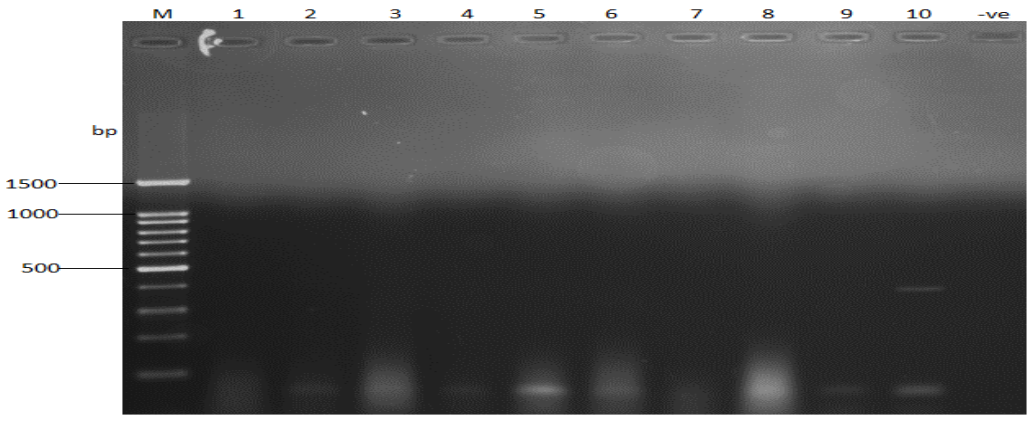
Lane 1 – 13 = Samples; Sample 1 (TKP 46) amplified with *bla*SHV primer; Lane M: 100bp Molecular DNA ladder; Lane -ve: Negative Control (PCR reaction without DNA); M = Size marker

Plate 2: Electrophoretograph of amplified bla_{SHV} gene (214bp) in MDR *Salmonella* Typhi isolates



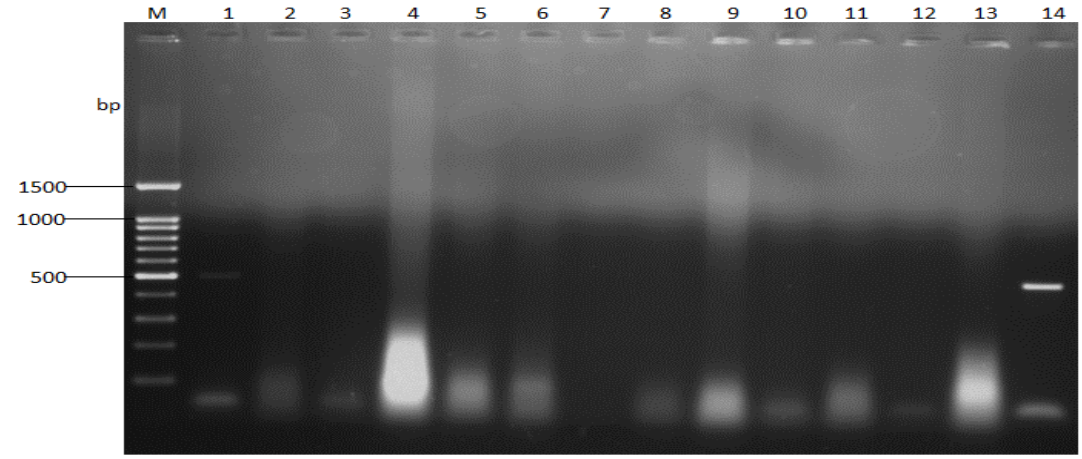
Lane 1 – 13 = Samples; Samples 2 (OBI 66), 4 (OHM 22) and 9 (OJU 51) amplified with bla_{SHV} primer; Lane M: 100bp Molecular DNA ladder; Lane -ve: Negative Control (PCR reaction without DNA); M = Size marker

Plate 3: Electrophoretograph of amplified bla_{SHV} gene (214bp) in MDR *Salmonella* Typhi isolates



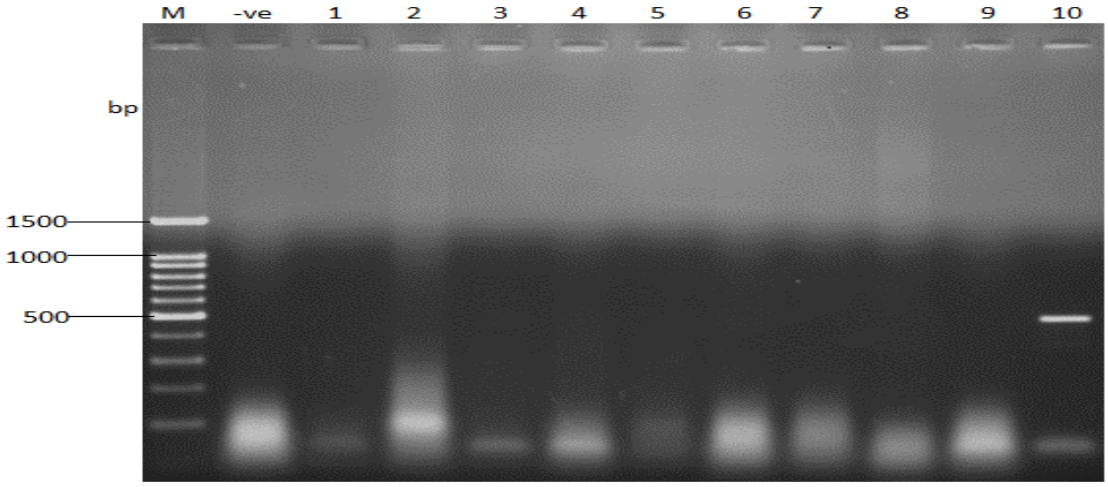
Lane 1 – 13 = Samples; Samples 10 (ADO 7) amplified with bla_{SHV} primer; Lane M: 100bp Molecular DNA ladder; Lane -ve: Negative Control (PCR reaction without DNA); M = Size marker

Plate 4: Electrophoretograph of amplified bla_{SHV} gene (214bp) in MDR *Salmonella* Typhi isolates



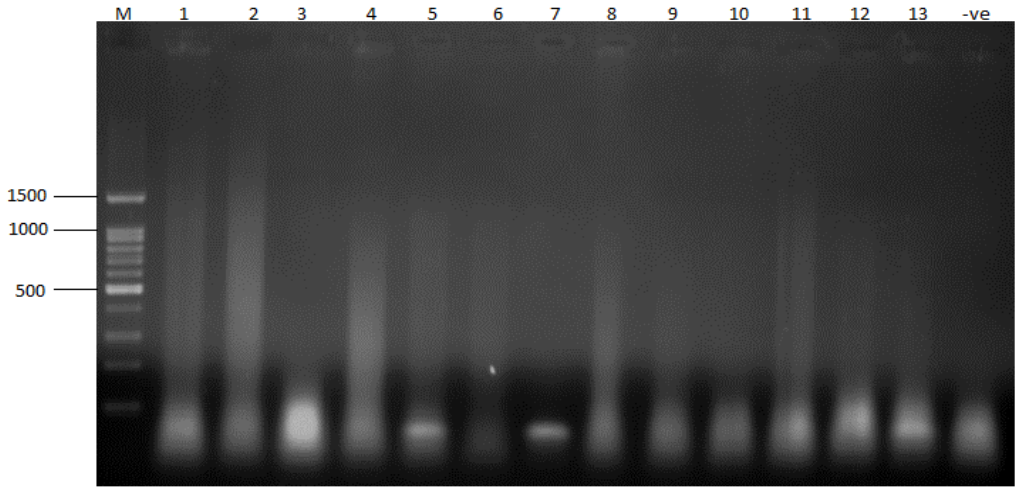
Lane 1 – 13 = Samples; Samples 1 (GTU 5) and 14 (OKP 86) amplified with *bla*$_{TEM}$ primer; Lane M: 100bp Molecular DNA ladder; Lane -ve: Negative Control (PCR reaction without DNA), M = Size marker

Plate 5: Electrophoretograph of Amplified *bla*-$_{TEM}$ gene (431bp) in MDR *Salmonella* Typhi isolates



Lane 1 – 13 = Samples; Sample 10 (OKP 124) amplified with *bla*$_{TEM}$ primer; Lane M: 100bp Molecular DNA ladder; Lane -ve: Negative Control (PCR reaction without DNA). M = Size marker

Plate 6: Electrophoretograph of amplified *bla*$_{TEM}$ gene (431bp) in MDR *Salmonella* Typhi isolates



Lane 1 – 13 = Samples; No isolate amplified with *bla*$_{CTX-M}$ primer; Lane M: 100bp Molecular DNA ladder; Lane -ve: Negative Control (PCR reaction without DNA); M = Size marker.

Plate 7: Electrophoretograph of amplified *bla*$_{CTX-M}$ gene (592bp) in MDR *Salmonella* Typhi isolates.

Discussion:

Enteric fever is endemic due to continued prevalence of *Salmonella* Typhi. The pathogen is transmitted through the fecal-oral route as a result of poor hygiene (1). Antibiotic therapy constitutes the mainstay of the management of enteric fever, however, antibiotic resistance has become a major threat to treatment of enteric fever (15). The purpose of the current study was to detect β-lactamase genes carried by *S.* Typhi isolated from stool of patients.

Amplification of genes by PCR in this study is an indication that some of the MDR isolates harbored bla_{SHV} (4.1%, n=5) and bla_{TEM} (2.5%, n=3) genes which encode resistance to β-lactam antibiotics. They however lacked bla_{IMP} that encodes resistance to carbapenems and bla_{CTX-M}, which encodes resistance to many extended spectrum β-lactam antibiotics. This agrees with the findings of Boisrame-Gastrin et al., (23), Djeffal et al., (24), Eguale et al., (8) and Abdul-Azeez et al., (2). The detection of high resistance rate to β-lactam antimicrobials (27.3%) and the presence of *bla* genes in the present study could be attributed to selective pressure on the commonly used β-lactam antibiotics in the study area. Adikwu et al., (4) reported that amoxicillin and ceftriaxone are frequently employed in the treatment of typhoid fever in Benue South leading to selection pressure. This corroborates the findings of Eguale et al., (8), although they reported a higher detection rate.

The dominant β-lactamase genes detected in the current study were bla_{SHV}. This is consistent with the observed spectrum of resistance to cephalosporin in previous studies (19, 25-27), which all reported resistance to cephalosporins. The finding however disagrees with that of Eguale et al., (8) who reported bla_{TEM} as the dominant beta-lactamase gene. In Africa, bla_{SHV} has been reported from *S.* Typhi isolated from human in Senegal (28), Egypt (29), and children adopted from Mali (23).

Conclusion:

This study showed that some MDR *S.* Typhi isolates harbored bla_{SHV} and bla_{TEM} genes, that encode resistance to β-lactam antibiotics, but lacked bla_{IMP} that encodes resistance to carbapenems. More studies are required to detect other genes encoding resistance to *S.* Typhi in other geographical zones in Benue State in particular and Nigeria at large.

Contributions of authors:

The study was conceptualised and designed by PA, EUU, IOO and CCI; the laboratory acquisition of data was done by PA, DAO, PIA, and MEO; Data analysis was done by PA, DAO, and AAA; the manuscript draft and critical revisions were done by DAO, PA, GAO, GEO, AAA, SOO, MEO, and STS; PA gave the final revision of the manuscript. All authors approved the manuscript submitted for publication.

Conflict of interest:

Authors declare no conflict of interest

Source of funding:

Authors received no external funding

Availability of data:

The data supporting findings of this study are available from the corresponding author upon request.

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