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A Retrospective Study of Multidrug Resistant *Salmonella typhi* in Nigeria

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Abstract

Multi drug resistant *Salmonella typhi* are strains of *S.typhi* that can withstand the therapeutic effects of two or more antibiotics, mostly the first line antibiotics, which include Chloramphenicol, Cotrimoxazole, Streptomycin, Tetracycline, Sulfonamides, Trimethoprim and Ampicillin. This study is basically carried out to expose the detrimental effects of this menace (Multi drug resistance) among most of the populace in Nigeria. Susceptibility tests using various test antibiotics were carried out on *Salmonella typhi* isolated from various clinical samples in Nigeria. The data obtained from the states studied revealed that most of the *Salmonella typhi* isolated were 100% resistant to most of the first line antibiotics. All *S.typhi* isolated in all the states studied were highly susceptible to Ciprofloxacin, except in Niger where 90% of the isolates were resistant to this antibiotic. This study is therefore intended to create awareness on the menace of multidrug resistant *Salmonella typhi* and how the problem can be controlled through measures such as; the production of new antibiotics and vaccines, the acquisition of modern health facilities and techniques for easy detection of multidrug resistant strains and the development of adequate drug storage facilities.

Keywords: *Salmonella typhi*, Multidrug resistant *Salmonella typhi*, Incidence, Nigeria

INTRODUCTION

Salmonella enterica subsp. *enterica* serovar *typhi* (also referred to as *Salmonella typhi*) is a Gram-negative enteric bacillus belonging to the family *Enterobacteriaceae*. It is a facultative anaerobe, catalase positive, oxidase negative non-spore-forming rod shaped bacillus which possess peritrichous flagella (Murray, 1994). The bacterium is restricted to humans and is not known to have a reservoir in animals. Thus, the transmission of *S. typhi* has only been shown to occur from person to person via fecal-oral route. Infection of *S. typhi* leads to the development of typhoid, or enteric fever (Murray, 1994).

Symptoms and Clinical Signs of Typhoid

This disease is characterized by the sudden onset of a sustained and systemic fever, severe headache, nausea, and loss of appetite. Other symptoms include constipation or diarrhea, enlargement of the spleen, possible development of meningitis, and/or general malaise.

Epidemiology

In countries of high endemicity like Indonesia, Pakistan, India and Nigeria a high mortality rate is reported due to typhoid fever ranging from 12 – 32 % in different studies at different times (Khan *et al.,* 2006). These countries seem to share several characteristics including rapid population growth, increased urbanization, inadequate disposal of human waste, decreased water supply and over burdened health care (Crump *et al.,*2004).

Based on the fact that, improved sanitation and hygiene are difficult to implement in many developing countries, and unfortunately, the effectiveness of antimicrobial chemotherapy is also being eroded by the emergence of antibiotic resistance. Antibiotic resistance is increasing among many bacterial species and is rapidly becoming a major world health problem (Crump *et al.,*2004). Generally, resistant *Salmonella typhi*, are well adapted organisms and are usually fitter than a random selection of strains belonging to the same species and they possess the ability to with stand the effect of certain antimicrobial agents (Trung *et al.,* 2007; Oyedum*,* 2015).

Chemotherapy

Treatment of typhoid fever relied mainly on such antibiotics as Chloramphenicol, Ampicillin and Trimethoprim-Sulfamethoxazole (Rowe *et al*., 1997; Trung *et al*., 2007); but in 1980s and 1990s, *S.typhi* developed resistance simultaneously to all drugs used for first line treatment, namely, Chloramphenicol, Ampicillin, Streptomycin, Sulfonamides, Tetracyclines and Trimethoprim-Sulfamethoxazole (Threlfall *et al*., 1992; Trung *et al*., 2007). Thus, the success of most of these antibiotics based therapeutic approach towards *S.typhi* has currently been limited because of the emergence of multidrug resistant strains of *S.typhi, w*hich are also termed multidrug-resistant (MDR) *S.typhi* (Threlfall *et al*., 1992).

Drug Resistance

Multidrug resistance is a prevalent and important problem worldwide (Oyedum, 2015). These infections are more difficult to treat than infections with similar organisms which are susceptible to commonly used agents, and effective therapy is often delayed. Infections with resistant organisms lead to adverse clinical outcomes, increased morbidity and mortality and are costly to the healthcare system. The magnitude of the adverse outcomes relate to the virulence of the organisms, the patient underlying condition, the syndrome, and the delay of appropriate therapy (Trung *et al*., 2007).

Generally, multidrug resistance (MDR) in *S. typhi* strains is often encoded by plasmids (approximately 180 Kb). Of particular interest are the plasmids encoding resistance to most drugs in the first line of treatment, which are; chloramphenicol, ampicillin, trimethoprim, sulfonamides and tetracyclines (Hermans *et al.,* 1996). The immunobiological investigations showed that resistant strains contains less *Vi* antigen (Virulence antigen), and its active and passive mouse protective ability is lower than that of chloramphenicol sensitive Ty 2 strain. Epidemics of different strains of *S. typhi* may coexist in the same geographical area and the rapid emergence of resistance to any antibiotic means that alternative drugs for chemotherapy are also needed (Bhat *et al*., 1998).

Justification and Objectives of the Review

The ills associated with multidrug resistant (MDR) *S. typhi* in Nigeria cannot be overemphasized, based on the fact that the general public is associated with certain factors such as; irrational use of drugs, inadequate diagnosis and improper prescription of drugs (Oyedum, 2015). These encouraged the development and spread of multidrug resistant (MDR) strains of *S. typhi* in Nigeria. Therefore it is imperative that the surveillance of multidrug resistance (MDR) in *S. typhi* of various geo-political zones in Nigeria be carried out continuously to enable the health care providers detect and prevent severe disease and death outbreaks. This study is therefore aimed to review the prevalence of multidrug resistance (MDR) in *S. typhi* of various geo-political zones in Nigeria and to create awareness on the cause of such situation and suggest possible solution to enhance the lives of the entire populace.

Materials and Methods

Study Design

This is a retrospective survey on previous records showcasing studies in various states in Nigeria.

The review basically outlined data acquired from already conducted study utilizing microbiology laboratory records for thirteen years (between 1999 to 2012), from various clinical specimens such as blood and stool in various states in Nigeria. The incidence reviewed in this study spanned across Lagos, Kogi, Oyo, Niger, Adamawa, Imo and Cross-river states. These were said to be regarded as urban settlements with high socio-economic activities that attract influx of populace from nearby surrounding rural areas.

Susceptibility test was carried out using the following; Chloramphenicol (30µg), amoxicillin (25 µg), augmentin (30 µg), ampicillin (30 µg), cotrimoxazole (25 µg), nalidixic acid (30 µg), ciprofloxacin (5 µg),azithromycin (15 µg) and ceftriaxone (30 µg) (Oxoid,UK) (Makunjola, 2009).

Microbiology Data

Microbiology records from these states were reviewed for the purpose of this study. The isolates were recovered from stool and blood clinical samples. The isolates of *S.typhi* tested were those said to be resistant to two or more antibiotics. Specific antibiotics tested on the isolates varied from one state to another. Information regarding the isolate susceptibility pattern for the various states were computed and analysed.

Organism Identification and Susceptibility Testing

Basically all the *S. typhi* isolates mentioned in this review were identified at the various states by standard laboratory methods (Pezzlo, 1992; Reisner *et al*., 1999). Each state performed susceptibility testing according to their own standardized techniques based on current guidelines from National Committee for Clinical Laboratory Standards (NCCLS) (NCCLS, 1997). The Kirby-Bauer disc diffusion method using Nutrient or Mueller-Hinton agar plates, which is the predominant method employed, was mainly used in most of the states reviewed to obtain the required data on the pattern of resistance associated with various isolates. The stool samples were generally streaked on Deoxycholate Citrate agar (DCA) while the blood samples were subjected to blood culture using blood broth to enhance the isolation of the *S.typhi*, all the organisms isolated were then subcultured on Salmonella-Shigella agar (SSA). The plates were all incubated at 37^{o}C for 24 h, after which the cultural and morphological characteristics of the isolates were studied. Identification of isolates was by standard microbiological methods, as described by Cheesbrough (2006).

In Lagos, susceptibility to Ampicillin (25µg) chloramphenicol (30µg), co-trimoxazole (25µg), tetracycline (50µg) and nalidixic acid (30µg), ciprofloxacin (20µg) and Ofloxacin (20µg) was determined for all isolates obtained (Akinyemi *et al.,* 2007).

From Adamawa, the susceptibility testing results were pooled from ampicillin (10µg), chloramphenicol (30µg), ciprofloxacin (10µg) and cotrimoxazole (10µg), which are commercial antibiotic discs, commonly used for the treatment of typhoid fever (Doughari *et al*., 2007).

In owerri, all isolates were subjected to antimicrobial susceptibility testing using 8 different antibiotics. The antibiotic discs used were as follows: Cotrimoxazole (25 µg), Nitrofurantoin (30 µg), Gentamicin (10 µg), Nalixidic acid (30 µg), Ofloxacin (30 µg), Augmentin (30 µg), Tetracycline (30 µg) and Amoxicillin (25 µg) (Kalu *et al.* 2008).

Nkang *et al.* 2009, on the other hand, determined antibiotic susceptibility test on isolates obtained from clinical samples in Calabar by disc diffusion method using antibiotics such as Ampiclox (10µg), Chloramphenicol (30µg), Tetracycline (25µg), Amoxicillin (25µg), Ciprofloxacin (10µg), Gentamicin (10µg) and Ampicillin (30µg).

In Kogi, the antibiotic discs used for susceptibility testing were manufactured by Optimum Laboratory Nigeria Limited and contain ten different discs at the stated quantities, namely: pefloxacin (PEF) (10µg), ciprofloxacin (CPX) (10µg), augmentin (AUG) (30µg), gentamicin (GEN) (10µg), co-trimoxazole (COT) (30µg), ampicillin (AMP) (30µg), streptomycin (S) (30µg),

nalidixic acid (NA) (30µg), cephalexin (CEP) (10µg) and ofloxacin (OFX) (10µg) (Sule *et al.*,2012).

In Oyo, the susceptibility testing for all the isolates was carried out using antibiotics such as Chloramphenicol (30µg), amoxicillin (25µg), augmentin (30µg), ampicillin (30µg), cotrimoxazole (25µg), nalidixic acid (30µg),ciprofloxacin (5µg),azithromycin (15µg) and ceftriaxone (30µg) (Oxoid,UK) (Makanjuola, 2012).

Also in Niger, the susceptibility testing for all the isolates was carried out using antibiotics such as Ceftriaxone (10µg), Cefuroxime (30µg), Amoxicillin(25µg), Ampicillin (30µg), Ofloxacin (10µg), Chloramphenicol (30µg), Ciprofloxacin (10µg), and Augmentin (10µg) (Adabara *et al.*,2012).

Results

The result from Lagos state showed that in 1997, 70%, 72.4%, 72.4% and 70% of *S. typhi* isolates were resistant to Ampicillin, Chloramphenicol, Tetracycline and Cotrimoxazole respectively. The result also revealed that resistance records of 79.0%, 81.6%, 76.3% and 81.6% as well as 86.5%, 89.2%, 83.8% and 81.1% of the isolates to Ampicillin, Chloramphenicol, Tetracycline and Cotrimoxazole were observed in 2000 and 2003 (Figure 1).

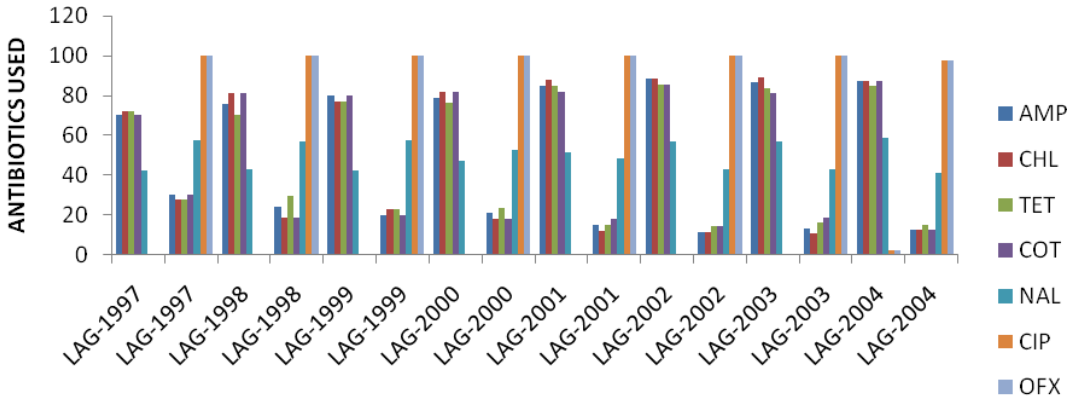

FIG 1 : ANTIBIOTIC SUSCEPTIBILITY PATTERN OF ISOLATES OBTAINED IN LAGOS FROM 1997-2004

The result from Adamawa state showed that in 2007, *S.typhi* isolates were most resistant to Amoxicillin (82.9%), followed by Ampicillin (72.5%), Chloramphenicol (69%) and Cotrimoxazole (56.6%) (Figure 2).

The result from Imo state showed that in 2008, all isolates of *S.typhi* were 100% resistant to three antibiotics namely; Augmentin, Tetracycline and Amoxicillin (Figure 2). The result also revealed that, Ofloxacin and Nitrofuratoin inhibited most of the isolates.

The result from Cross-river state showed that in 2009, all isolates of *S.typhi* were 100% resistant to one of the test antibiotics namely; Amplicox (Figure 2).

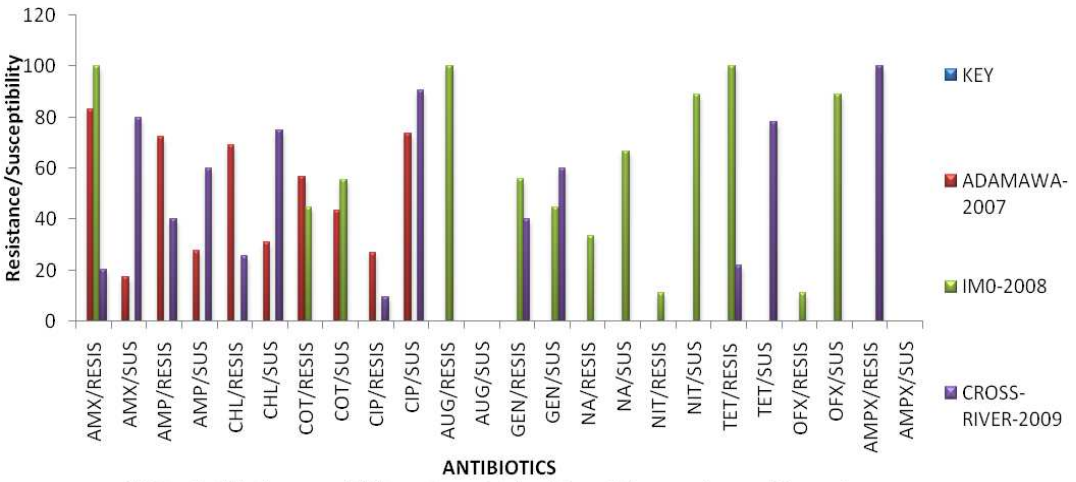

FIG 2: Antibiotic susceptibility pattern obtained from Adamawa,Imo and Cross-river

The result from Adamawa state showed that in 2007, *S.typhi* isolates were most resistant to Amoxicillin (82.9%), followed by Ampicillin (72.5%), Chloramphenicol (69%) and Cotrimoxazole (56.6%). The result also revealed that, in 2001, 62% of the isolates were generally resistant to Amoxicillin, Ampicillin and Chloramphenicol, while in 2002, 45% of the isolates were resistant to Chloramphenicol and Ampicillin (Figure 2).

The result from Kogi state in 2012, showed that, all the *S.typhi* isolates were 100% resistant to six common antibiotics out of the ten antibiotics namely; Pefloxacin, Ciprofloxacin, Augmentin, Gentamicin, Cotrimoxazole, Ampicillin. The result also revealed that resistance ranging from 60–90% was recorded against the remaining four antibiotics namely; Streptomycin, Nalidixic acid, Cephalexin and Ofloxacin (Figure 3).

The result from Oyo state in 2012, showed that, *S.typhi* isolates were most resistant to Cotrimoxazole (67.8%), followed by Chloramphenicol (62.3%) and Ampicillin (61.6%). The result also revealed that, all the *S.typhi* isolates were 100% sensitive to Ceftriaxone (Figure 3).

The result from Niger state in 2012, showed that all the isolates were resistant to Ceftriaxone, Cefuroxime, Amoxicillin, Ampicillin, Ciprofloxacin and Augmentin. The result also showed that all the isolates were sensitive to Ofloxacin and Chloramphenicol (Figure 3).

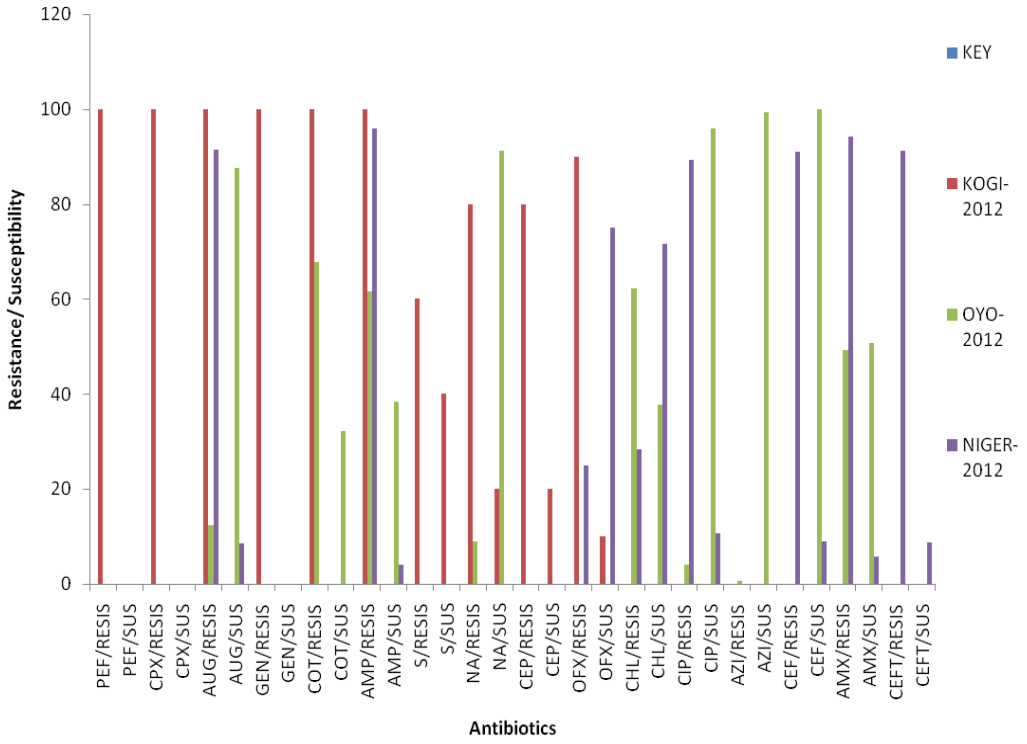

Fig 3: Antibiotic susceptibility pattern obtained from Kogi, Oyo and Niger

DISCUSSION

From the results of the retrospective studies above, it can be clearly observed that emergence of multidrug resistant *S.typhi* in Nigeria is rapid. The rapid development of this multi drug resistance possessed by species of *S.typhi* could be attributed to the irrational and misuse of various antibiotics especially the antibiotics used for the first line treatment. This result agrees with the study of Akinyemi *et al.,* 2007. Apparently, in most poor and developing countries especially Nigeria, due to the inadequate diagnosis carried out by most health workers, establishment of an efficient and effective treatment is usually unattainable. Based on this, the public result to self medication, usually with counterfeit drugs which in most cases lead to increased morbidity and mortality. In addition to this such misuse of antibiotics could also be based on a patient's belief concerning a particular drug. Most people tend to believe that expensive drugs are the most efficient and effective drugs present in the society and in most cases their compliance towards the intake of these drugs allows them practice, intake of incomplete doses of the drugs.

In addition, the high prevalence of MDR *S.typhi* recorded could be attributed to the presence of a particular plasmid, which codes for resistance. Such resistance occurs when plasmids coding for antibiotic resistance are present in *S. typhi*. This agrees with the findings of Pelczar *et al.* (1993), who stated that, plasmid DNA responsible for resistance could be acquired as a result of transmission of resistant genes through conjugation from other organisms like *E. coli* resident in a patient's intestinal tracts. A single plasmid has been observed to code for multi–drug resistance (Doughari *et al.,* 2007). This plasmid belongs to incompatibility group HII and is highly transmissible between similar pathogens. Studies have shown that *S.typhi* usually acquire these plasmids from their environments to increase their abilities of resisting antibiotics (Shrikala, 2004; James and Martin, 2001; Kethleen *et al*., 2002). In the same vein, the prevailing poor hygienic and sanitary conditions, such as;

inappropriate hand washing and contaminated water and food practiced in Nigeria, also enhance the spread of MDR-encoded plasmids between *S. typhi* strains.

Furthermore, the observation of resistance to Nalidixic acid (also known as Quinolone) by *Salmonella typhi* in various states in Nigeria has also been recorded in the above figures, bearing in mind the fact that Quinolones are not drugs commonly prescribed or used by the physicians or public. Based on this, the result could be attributed to the fact that Quinolones as an important antimicrobial agent was indiscriminately used in the production of animal feed and antimicrobial materials used for the humans, such as mouth wash, tooth paste, health and nutritional supplements. Several workers have reported from elsewhere that the use of Quinolones in animals food have led to the rapid emergence of resistant *Salmonella* infections to humans (Threlfall, 2002). Akinyemi *et al.* (2007) also revealed that studies have also shown that antimicrobial agents used in agriculture and closely related agents used in human medicine have been exerting selective pressure (also called selective toxicity) on their target bacteria particularly *Salmonella, Campylobacter* and *Escherichia coli* (Tauxe,1997), a situation that might have arisen in Nigeria.

More importantly, the increasing trends of MDR *S. typhi* may also be due to the spread of these resistant *S. typhi* from one patient to another within cities, towns or states. In most cases, the high prevalence of MDR *S. typhi* may also be due to the spread of these resistant strains of *S. typhi* from one neighboring cities, towns or states in Nigeria that recorded high prevalence of MDR *S.typhi* to those that recorded low prevalence of MDR *S.typhi* through the influx of travelers and animal vectors such as; fly, cockroaches and rodents.

All the figures in this review show that Ciprofloxacin and Ofloxacin are drugs of choice for the treatment of MDR *S. typhi*, based on the fact that the susceptibility of the *S. typhi* to these drugs is high compared to its resistance to it. This could be due to the fact that Ciprofloxacin and Ofloxacin which are Fluroquinolone antibiotics, are still under strict prescription of clinicians and are less abused due to high cost of their procurement in Nigeria (Akinyemi *et al.,* 2007). This review also recorded that MDR-*S. typhi* strains recovered from patients in various states in Nigeria, were all sensitive to Ciprofloxacin and Ofloxacin except in Lagos, Kogi, and Niger in 2004 and 2012 respectively. This could be attributed to the fact that these patients are immunocompromised patients, that is, they had in one way or the other been diagnosed of human immunodeficiency virus – associated acquired immune deficiency syndrome. This agrees with the findings of Akinyemi *et al.,* 2007. Similarly, the recorded result above, also showed that Chloramphenicol was highly resisted in all the states except in Niger state, where most the MDR *S.typhi* were susceptible to it. This could basically be attributed to the fact that the dose and time prescribed by the physicians for the intake of Chloramphenicol in this area was increased, in order to completely eradicate the resistant organisms.

Conclusion and Recommendations

The menace known as multi drug resistance in *S.typhi* is fast gaining grounds in Nigeria, as seen in this retrospective survey. Based on the above figures, effective and continuous surveillance by health workers to detect any case of multi drug resistance in *S.typhi* should be encouraged and practiced using modern health facilities and techniques. The development of new drugs and vaccines against multidrug resistant *S.typhi* should also be encouraged among the populace. In addition, appropriate regulation by the government on the demand and supply of antibiotics in the market and rational use of drugs should be encouraged. In the same vein, awareness on the importance of personal hygiene such as hand washing, use of pesticides and adequate protective measures for food, should be encouraged in the public especially among the rural dwellers to avoid faeco-oral transmission of the etiologic agent of typhoid fever in the countrry.

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