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Review on the Emergence of Quinolone Resistance Against *Salmonella Typhi* in Nigeria

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ABSTRACT

Typhoid fever is a febrile illness caused by *Salmonella species (Enterica serovars typhi*). Typhoid fever is primarily transmitted through contaminated water or food. Quinolones are one of the most commonly prescribed antibacterial classes used for the treatment of different bacterial infections in humans including typhoid fever. Due to the widespread use of these drugs, the number of quinolone-resistant bacterial strains are increasing all the time. *Salmonella* resistance mechanisms to the quinolone antibiotic class have become increasingly complex, attracting global attention. Studies on Salmonella resistance to the quinolone class of antibiotics are not well reported in Nigeria. This information is scanty or completely not covered the Northern parts of Nigeria in the available literature. As a result, this review discusses previous and current research on *Salmonella* resistance to a class of quinolone antimicrobial drugs in Nigeria**.**

Keywords: *Salmonella*; quinolones; Resistance; Typhoid and Antibacterial.

1.0 INTRODUCTION

Salmonella enterica serovars Typhi: Paratyphi A; Paratyphi B, and Paratyphi C are the organisms that cause the acute, feverish, and potentially fatal disease known as typhoid fever. The main way that typhoid fever is spread is through contaminated water or food (Crump *et al*., 2015; Wain *et al*., 2015). It can be difficult to distinguish this systemic infection from other febrile and gastrointestinal infections since it manifests clinically throughout a spectrum of severity with a variety of symptoms and signs, including fever, stomach discomfort, nausea, and vomiting. Worldwide, between 11 to 21 million cases of typhoid fever are reported every year, with 145,000 to 161,000 deaths. The majority of infections are found in South/South-East Asia and sub-Saharan Africa (Akinyemi *et al*., 2021).

Salmonella are facultative aerobic, non-spore-forming, rod-shaped, Gram-negative bacteria. With the exception of *Salmonella pullorum* and *Salmonella gallinarum*, they can move by means of peritrichous flagella (non-motile). Additionally, *Salmonella spp*. are sensitive to heat and frequently die at temperatures of 70°C or higher than that. Hence, they multiply best at temperature between 35° to 37°C and pH of 6.5–7.5. At temperatures below 7°C, pH below 3.8, or water activity below 0.94, complete growth suppression occurs, however the plant may withstand drying for years (Gut *et al*., 2018). Typhoid salmonellosis (enteric fever), caused by *Salmonella enterica* serovars typhi (typhoid fever), and S. paratyphi A, B, and C (paratyphoid fever), which are limited to human hosts, are the most common types of *Salmonella* infections. The second is non-typhoidal *Salmonella*e, which are illnesses linked to other *Salmonella enterica* serovars such as *S. typhimurium*, *S. enteritidis*, and *S. choleraesuis* (NTS). In general, *Salmonella* infections have a substantial global socioeconomic impact and cause significant morbidity and mortality.

Quinolones are the most often prescribed antibiotic classes in the world used to treat a range of bacterial diseases in humans. Since the 1990s, the quantity of quinolone-resistant bacterial strains has been continuously increasing as a result of the widespread usage (and misuse) of these medications. The clinical usefulness of this significant medication class is threatened by the

rise of quinolone resistance, as is the situation with other antibacterial medicines. Gyrase and topoisomerase IV, the targets of quinolones, are transformed into poisonous enzymes that damage the bacterial chromosome (Ashley *et al*., 2017). High Quinolone-resistant strains of numerous *Salmonella* serotypes that are prevalent in both people and the environment are of concern (Gong *et al*., 2016). *Salmonella*'s quinolone-class antibiotic resistance mechanisms have attracted research from all over the world due to their complexity. Studies on *Salmonella* resistance to the quinolone class of antibiotics are not widely reported in Nigeria, and data on this organism's behavior, particularly in the Northern portions of Nigeria, is lacking in the literature. Hence, the reason why this short review is important

2.0 OVERVIEW OF *SALMONELLA*

2.1 Historical Background

Salmonella was initially identified by Theobald Smith in 1884. The second *Salmonella* specie (choleraesuis) was found and isolated a year later from the intestines of pigs with classical swine fever (hog cholera). The organism's original name was Bacillus choleraesuis, but Lignieres renamed it to *Salmonella* choleraesuis in 1900. (Bintsis, 2017).

Salmonella was classified based on the interactions between antibodies and the surface bacterial antigens in the 1920s and 1940s. Each *Salmonella* serotype is classified by the presence of a specific lipopolysaccharide (LPS) or O antigen and a flagellar or H antigen, and there are over 2500 serotypes (Kemal, 2014; Jejere, 2019).

2.2 Taxonomy

Salmonella strains have historically been named after their original isolation sites, such as *Salmonella indiana* and *Salmonella londona*. *Salmonella* is a member of the Enterobacteriaceae family, the Protobacteria phylum, and the Class Gamma Protobacteria class. It belongs to the Order Enterobacteriales, which is part of the Family Enterobacteriaceae. *Salmonella enterica* and *Salmonella bongori* were the two species that made up the genus *Salmonella*. *S. enterica subsp. enterica, S. enterica subsp. salamae, S. enterica subsp. arizonae, S. enterica subsp. diarizonae, S. enterica subsp. houtenae,* and *S. enterica subsp. Indica* are the six subspecies of *Salmonella enterica*. The remaining subspecies and *S. bongori* are primarily isolated from cold-blooded animals and account for less than 1% of clinical isolates. Whereas *Salmonella enterica subspecies* I is isolated from warm-blooded animals and accounts for more than 99 percent of clinical isolates (Parry, 2006; Grimont, 2007). The host preference is the basis for the epidemiological classification of *Salmonella*, which includes host-restricted serotypes like S. typhi that only infect humans. The other group also includes host-adapted serotypes, which are linked to one host species but can infect other hosts with disease, like *S. Pullorum* in birds. The most common serotypes of *Salmonella* recovered from humans each year are *Salmonella enteritidis*, *Salmonella typhimurium*, and *Salmonella heidelberg* (Card *et al*., 2016).

2.3 Biochemical Characteristics

Salmonella ferments glucose to create acid, converts nitrates to nitrite, and lacks cytochrome oxidase. Additionally, *S. typhi* produces gas (H2S) when sugar is fermented. With the exception of *S. typhi, S. paratyphi C*, and some strains of *S. dublin*, *Salmonella* are not capsulated (Getenet, 2008).

2.4 Pathogenesis

The serotype involved and the state of the human host both affect how severe a *Salmonella* infection is in people. Immunosuppressed patients, elderly persons, and young children are more vulnerable to *Salmonella* infection than healthy people. Almost all *Salmonella* strains are harmful because they can enter, multiply, and survive in human host cells, where they can cause potentially fatal disease. *Salmonella* has an amazing trait when it invades human host cells that are not phagocytic (Hansen-Wester *et al*., 2002). *Salmonella* actually stimulates phagocytosis in order to enter the host cell. *Salmonella* pathogenicity islands (SPIs), gene clusters positioned at the vast chromosomal DNA region and encoding for the structures required in the invasion process, contain the remarkable genetics underlying this clever tactic (Grassl and Finlay, 2008). The epithelial cells of the intestinal wall are susceptible to invasion by bacteria when they enter the digestive tract through polluted water or food. *Salmonella* can inject its effectors over the membrane of the intestinal epithelial cell and into

the cytoplasm using type III secretion systems, multi-channel proteins that are encoded by SPIs. The host cell's actin cytoskeleton is rebuilt once the bacterial effectors activate the signal transduction pathway, which causes the epithelial cell membrane to extend or ruffle outward to engulf the bacteria. The membrane's morphology resembles the phagocytosis process (Takaya *et al*., 2003). *Salmonella* strains must be able to survive inside of the host cell in order to cause disease; otherwise, they are not pathogenic (Bakowski *et al*., 2008). *Salmonella* is wrapped in a membrane compartment known as a vacuole, which is made of the membrane of the host cell, after being absorbed by the host cell. In a typical situation, the presence of the bacterial foreign body would trigger the immunological response of the host cell, leading to the fusion of the lysosomes and the secretion of digestive enzymes to destroy the intracellular bacteria. However, *Salmonella* modifies the compartment organization by introducing additional effector proteins into the vacuole via the type III secretion system. The modified vacuole prevents lysosome fusion, enabling intracellular survival and bacterial reproduction within the host cells. The bacteria can be transported in the reticuloendothelial system (RES) because they can thrive inside of macrophages (Monack *et al*., 2004).

3.0 QUINOLONES

About 50 years ago, during the chemical production of a batch of the antimalarial drug chloroquine, an impurity that was later identified as the first antibacterial quinolone was found. However, although having anti-Gram-negative antibacterial activity, its potency and antimicrobial range were insufficient for therapeutic usage. Later, nalidixic acid was commercialized, building on this lead. In addition to having a slight cytotoxic effect on the digestive tract and the central nervous system, this substance has no significant impact on Gram-positive bacteria. However, due to how nalidixic acid affects Gram-negative bacteria, it belongs to the first generation of quinolones (Tretter *et al*., 2012). A group of antibiotics known as quinolones have a bicyclic core structure similar to the chemical 4-quinolone. Since their early 1960s discovery, they have grown in significance as essential medicines for the treatment of both severe hospital-acquired infections and illnesses acquired in the community. Nalidixic acid, one of the group of 1-alkyl-1,8-naphthyridines created at the Sterling-Winthrop Research Institute in 1962, is generally regarded as the first quinolone antibiotic. The discovery of chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid in the late 1950s by (Geoge Lesher, 1962) was described as a byproduct of the synthesis of chloroquine. This modest antibacterial activity prompted further research on analogues, including nalidixic acid, in a 2015 perspective that looked more closely at the history of quinolone antibiotics. Imperial Chemical Industries (ICI) released patent applications containing antibacterial quinolones, including a 6-fluoroquinolone, at about the same time. A narrow-spectrum antibiotic against enteric bacteria called nalidixic acid is used to treat simple urinary tract infections (UTIs). The groundbreaking creation of fluoroquinolones, which exhibit a substantially wider spectrum of activity and superior phamacokinetics compared to the first-generation quinolone, significantly increased the coverage of the quinolone class during the 1970s and 1980s. These fluoroquinolones, including ciprofloxacin and ofloxacin are effective against both Gram-negative and Gram-positive infections; more significantly, they are also effective against Mycobacterium tuberculosis, the causative agent of tuberculosis. Due to their strong potency, wide range of activity, excellent absorption, practical formulations, high serum concentrations, and comparatively low frequency of side effects, quinolones have been favored as antibiotics for more than five decades. Quinolones are frequently given for a variety of human infections; however, they have some modest adverse effects as well as gastrointestinal and CNS responses, genotoxicity, and phototoxicity (Douros *et al*., 2015).

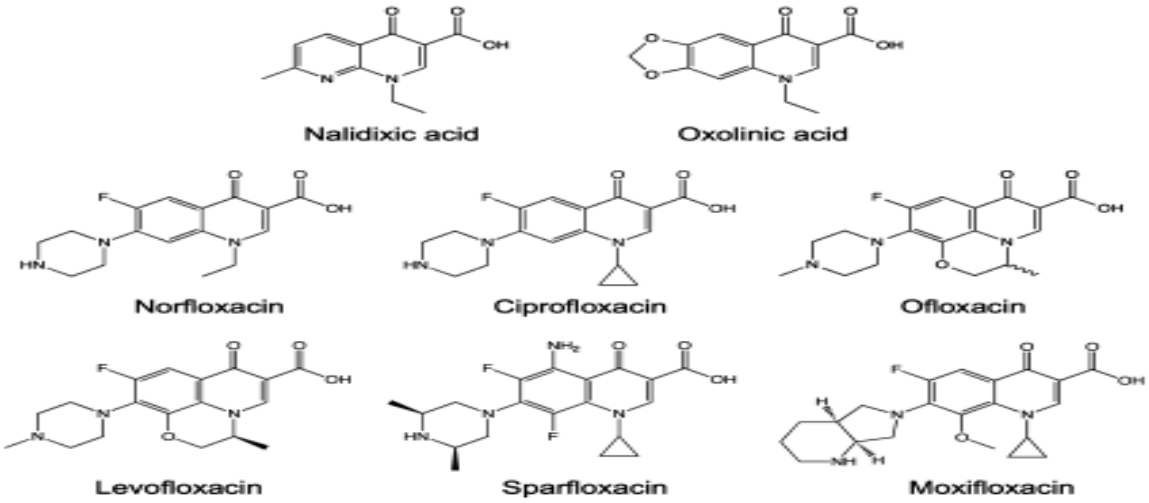

Fig.1: Structures of different classes of quinolones

3.1 Mechanism of Action

The suppression of bacterial topoisomerases II and IV is the basis for the quinolones' mode of action. Enzymes called topoisomerases are in charge of preserving the tertiary structure of DNA across a variety of biological activities, including DNA synthesis, replication, condensation, and decondensation, among others (Ashley *et al*., 2017). Topoisomerase II, also known as DNA gyrase, is a negative supercoiling enzyme, which implies that it splits the two strands of DNA and induces a twist to the left that is the opposite of the double helix's direction. This enzyme aids in the DNA synthesis and replication processes, as well as other processes that involve the winding and relaxing of DNA. The heterotetramer of the DNA gyrase is made up of two GyrA subunits and two GyrB subunits. The double helix incisions are made by the GyrA subunits, which take part in the union with the DNA. The GyrB subunits are active ATPases (Correia *et al*., 2017). Topoisomerase IV participates in the separation of daughter chromatids during DNA replication and is in charge of preventing the chromatids from becoming linked. Topoisomerase IV is composed of a tetramer, just as DNA gyrase. It consists of two ParC and two ParE subunits. These subunits, correspondingly, exhibit GyrA and GyrB homologous activity (Hooper and Jacoby, 2016). Due to genotoxic damage, topoisomerase II and IV are inhibited by quinolone interactions, which causes DNA damage and cell death.

3.2 Resistance Mechanisms

To counteract the effect of quinolones, bacteria have developed various resistance mechanisms to these antibiotics. Bacterial resistance to quinolones is mainly based on three points.

1. Chromosomal mutations in coding genes (mutations that alter the objectives of the drug).
2. Mutations associated with the reduction of the intracytoplasmic concentration of quinolones.
3. PMQR genes (plasmids that protect cells from the lethal effects of quinolones).

3.2.1 Chromosomal mutations in coding genes (mutations that alter the objectives of the drug)

Due to mistakes in the replication of the genes encoding the GyrA subunits of DNA gyrase and ParC of topoisomerase IV, the quinolone resistance linked to chromosomal alterations occurs (Hooper and Jacoby, 2016). Specific areas that interact with the DNA can be found in the amino acid sequences of the GyrA and ParC subunits. There are conserved domains in these regions known as the quinolone resistance determination region (QRDR). Such mutations arise specifically in the regions that encode each of the QRDR domains of

the GyrA and ParC subunit genes (Laponogov *et al*., 2013). Quinolone resistance has also been linked to mutations in the genes that produce the GyrB and ParE subunits, but these changes are less common and don't seem to have much of a clinical impact. There is proof that DNA gyrase is more vulnerable to inhibition than topoisomerase IV in Gram-negative bacteria. On the other hand, topoisomerase IV is more vulnerable to inhibition than gyrase in Gram positive bacteria, which results in the reverse outcome. The exception to the norm is that some germs have the opposite effect. Therefore, it can be stated that the majority of Gram-negative bacteria experience the phenomenon of resistance primarily in GyrA. Whereas, the majority of Gram-positive bacteria experience ParC inhibition as the most significant effect. In conclusion, changes in the sequences that code for the QRDR domains in GyrA-ParC and GyrB-ParE promote a reduction in the binding affinity of quinolones with the DNA-DNA gyrase and DNA-topoisomerase IV complex.

3.2.2 Mutations associated with the reduction of the intracytoplasmic concentration of quinolones

It has been deduced that majority of Gram-negative bacteria exhibit the phenomenon of resistance primarily in GyrA, whereas the majority of Gram-positive bacteria primarily inhibit ParC. Therefore, mutations in the sequences encoding the QRDR domains in GyrA-ParC and GyrB-ParE both favor a reduction in the binding affinity of quinolones with the DNA-DNA gyrase and DNA-topoisomerase IV complex.

This phenomenon is achieved through three mechanisms:

i. Efflux pumps that promote the active transport of quinolones to the outside of the bacterial cell.
ii. Decreased membrane permeability toward the antibiotic.
iii. A combination of both mechanisms.

Since there is no proof that a decrease in cytoplasmic membrane permeability works in Gram-positive bacteria, it has been suggested that the only mechanisms that diminish the intracytoplasmic concentration of quinolones are efflux pumps (Rahman *et al*., 2017). However, Gram-negative bacteria do possess both processes and work in concert with one another, with the cytoplasmic membrane's reduced permeability serving as these bacteria's primary mechanism (Ghai and Ghai, 2018). These two mechanisms are not brought on by the medications themselves and are responsible for the decrease in the intracytoplasmic concentration of quinolones. There is proof that these two methods result from mutations in the genes encoding regulatory proteins that regulate the outflow pump's transcription or the genes responsible for porin synthesis (Hooper and Jacoby, 2016).

3.2.3 Plasmid-mediated quinolone resistance genes (plasmids that protect cells from the lethal effects of quinolones)

When Klebsiella pneumoniae was isolated from a urine sample in 1998 a plasmid called pMG252 was located. This plasmid caused bacterial resistance to nalidixic acid and fluoroquinolones. Numerous bacteria with a deficiency in outer-membrane porins may develop this resistance phenomena. Additionally, the plasmid encouraged the rapid development and spread of resistance. The gene that caused this resistance was originally known as qnr and then changed to qnrA. (Jacoby, 2003). Working with the qnr plasmid in 2002, Tran and Jacoby, discovered an integron-like environment upstream of qacE1 and sulI. QnrA, a 218-aa protein, was the end product of this gene. The pentapeptide repeat family protein shared sequence homology with the immune system protein McbG. It was found that McbG shields DNA gyrase against the effects of several genotoxic substances. Due to the similarity between QnrA and McbG and the mechanism of action of quinolones (inhibition of topoisomerases I and IV), The ability of QnrA to cause resistance against quinolones by topoisomerase protection was determined by Tran and Jacoby. In 2005, two separate teams were able to identify that two other proteins known as QnrB and QnrS had the same activity as QnrA. (Hata *et al*., 2005). Another mechanism of action of resistance to quinolones was reported in 2006, which was mediated by the enzymatic action of aminoglycoside acetyltransferase, AAC(6′)-Ib-cr. Subsequent tests of the qnrA plasmid indicated that this plasmid was able to produce more resistance than expected. Moreover, the activity of

ciprofloxacin was decreased by N-acetylation at the amino nitrogen on its piperazinyl substituent, which was the method by which quinolone resistance was discovered. Three different research teams independently demonstrated another plasmid-encoded resistance mechanism in 2007. In another study quinolone efflux pumps controlled by the plasmids QepA and OqxAB was revealed (Périchon *et al*., 2007).

In summary, there are three mechanisms for PMQR:

i. The plasmid genes qnrA, qnrB, qnrC, qnrD, qnrS, and qnrVC encode proteins from the pentapeptide repeat family that shield DNA gyrase and topoisomerase IV from quinolone inhibition. The qnr genes are frequently integrated into sul1-type integrons and are typically connected to mobilizing or transposable elements in plasmids.
ii. The second pathway mediated by plasmids includes the acetylation of quinolones with a suitable amino nitrogen target by a version of the typical aminoglycoside acetyltransferase AAC(6′)-Ib-cr.
iii. Improved outflow produced by plasmid genes for QepAB and OqxAB pumps.

4.0 *SALMONELLA* RESISTANCE TO QUINOLONES IN NIGERIA

The development of quinolone resistance has been proven to be a widespread issue, and the QRDR has been shown to play a significant role in this development. Studies on *Salmonella* resistance to the quinolone class of antibiotics have received little attention in Nigeria. However, the efforts so far reported by different scholars are discussed.

Akinyemi *et al*. (2003). First isolated and reported *Salmonella* resistance case in Lagos, Nigeria. According to the study, *Salmonella* was less susceptible to ciprofloxacin and ofloxacin at MIC50 and MIC90 values of 0.015 and 0.03 g/mL, respectively. While, antimicrobial resistance patterns among typhoidal *Salmonella*e isolated in 2000 and 2005 did not differ significantly ($p>0.01$) based on their findings.

Akinyemi *et al*. (2004) also look at the Multidrug resistance in *Salmonella* enterica serovar typhi isolated from patients with typhoid fever *sequelae*, in Lagos state. The research confirmed the presence of MDR on S. typhi in Lagos. They ascertain that, although ciprofloxacin and ofloxacin are effective drugs for typhoid fever treatments however, resistance is expected to arise given the prevalent drug usage patterns in Nigeria at the time. Their findings offer an early warning indicator for the cautious of application of fluoroquinolone to maintain their efficacy.

In another research conducted by (Agbaje *et al*., 2019)Two meat-type turkey farms and three commercial layer poultry farms in Ogun State reported a high mortality rates in 2008. When the investigation was conducted for the possible reasons of the high mortality rate, they discovered that the presence of ciprofloxacin resistance in each of the five isolates was highly significant. Since fluoroquinolone resistance affects both veterinary and human medicine therefore, misuse of these drugs in poultry could lead to the establishment of resistant zoonotic pathogens.

While examining the prevalence and susceptibility pattern of S. typhi and S. paratyphi isolates in Zaria, Kaduna State, Adeshina *et al*. (2009) reported the resistance of numerous drugs previously used to treat typhoid fever. They suggested that in order to prevent the spread of resistant strains, it is necessary to regularly check the effectiveness of antibiotics before prescribing them. This is due to the emergence of *Salmonella* species isolates that are resistant to chloramphenicol, co-trimoxazole, amoxicillin, and ofloxacin.

Ogbolu *et al*. (2012). Investigated the effects of gyrA and parC mutations on quinolones-resistant clinical gram-negative bacteria from Southern Nigeria. They found that these changes led to significant levels of multidrug resistance in gram-negative bacilli bacteria to fluoroquinolones.

Similarly, on the quinolone-resistant determining regions (QRDRs) of *S. enterica serovars Typhi*, Onyenwe *et al*. (2013) found the resistance pattern and the presence of the genes responsible for floroquinolone resistance. They concluded that, the MDRST was caused by chromosomally encoded ESBLs and mutations. For the treatment *of S. enterica serovar typhi*, ceftriazone and

levofloxacine were discovered to be useful options. Also, in Southeastern Nigeria, *S. enterica serovar. Typhi* was initially discovered through their research to have mutations in the gyrA and parC genes.

The diversity of S. enterica serovars, antibiotic resistance, and the presence of PMQR genes in pigs in Ibadan, Nigeria were all investigated (Hendriksen and Fashae, 2013).They have concluded that antimicrobial resistance differed among serovars, with older medicines having a higher prevalence of resistance. The MDR serovars, especially *Salmonella Kentucky* that is ciprofloxacin-resistant, indicated strong antimicrobial selective pressure in some farms. Antimicrobials should be regulated and targeted control measures against the prevalent serovars should be implemented.

Ogunleye and Carlson (2017). Identified one strain of *Salmonella Give* isolated from a cloaca swab of an Agama agama lizard that was taken from a commercial poultry pen in Nigeria. By reporting the isolation and characterization of *Salmonella Give* from the lizard, they highlighted the public health risk that lizards pose for the spread of salmonellosis to humans and poultry in the study area. Additionally, the *Salmonella* serotype's multidrug resistance pattern suggests that a drug-resistant disease may spread from lizards to animals used as food as well as humans.

Ojo *et al*. (2012). Isolated bacteria from chicken carcasses in Abeokuta between 2009 and 2011 and found that there was decreased in quinolone resistance. They demonstrated how quinolone resistance in bacteria that cause bacterial infections in birds and resistant to treatment may increase economic loss. And they have suggested health advisory notes on the relevance of their potential to human transmission.

Antibacterial drug administration and antimicrobial resistance of *Salmonella* isolates Originating from the Broiler Production Value Chain in Nigeria were studied (Olosho *et al*., 2019). It was found that the three antibiotics with the highest antimicrobial resistance were perfloxacin (95%), penicillin (100%) and (89%). It was noted the high levels of use of a newer generation of antibiotics suspected of conferring high resistance on older generations of the same class without laboratory investigation.

Analysis of the antimicrobial resistance profiles of *Salmonella* serovars isolated from dressed chicken meat at slaughter house in Kaduna suggested that plasmid-mediated quinolone resistance genes may have been horizontally transferred, which may compromise the clinical use of fluoroquinolones (Agbaje *et al.,* 2019). And they suggested that better hygiene standards and the provision of adequate facilities at meat processing facilities could help reduce meat contamination and the spread of multi resistant strain through food.

Studies on the Antibiotic Resistance, and Virulence Factors of *Salmonella* Serovars isolated from intestinal Content of Slaughtered Chickens and Ready-to-Eat Chicken Gizzards in Ilorin Metropolis, Kwara State revealed the virulence genes in *Salmonella enterica subsp. enterica serovar and S. Haifa*, which suggested that were potentially virulent for humans in the area (Raji *et al.,* 2021).

In Delta State, Ehwarieme *et al*. (2021) investigated the prevalence of plasmid-mediated fluoroquinolone resistance genes in enteric bacteria isolated from human and animal sources. The investigation discovered that isolates from animal sources had higher levels of plasmid-mediated FQ resistance than isolates from human sources. And also, the cases of plasmid-mediated resistance were more common in chicken litter isolates than in fish pond water isolates. They further reported that the quinolone resistance determinants qnrA, qnrB, and qnrS were more strongly associated with the plasmid-mediated FQ resistance and were found on plasmids. (Ehwarieme *et al*., 2021).

The genomic characterisation of the *Salmonella Nigeria serovar* from pigs and poultry in Ilorin was first reported using Whole Genome Sequencing (WGS technology) (Rauf *et al.,* 2021). The study demonstrated that the majority of commonly antimicrobials used for clinical chemotherapy in human and veterinary practices have low levels of resistance, which calls for ongoing monitoring and education of the public about the risks associated

with the misuse of antimicrobials when they are not prescribed.

5.0 CONCLUSION

Quinolone resistance has been considered a global issue. The study of quinolone resistance in *Salmonella enterica* is clinically significant because ciprofloxacin is the drug of choice in Nigeria for treating invasive human salmonellosis. This review has highlighted the studies on Salmonella resistance to the quinolone class of antibiotics in Nigeria. The majority of the researches reported were carried out from the southern part of the country, and have shown that there is an increased widespread cases of quinolones resistance to *salmonella* species. Notably, there are limited number of studies conducted in Northern parts of Nigeria on this regard. Uncontrolled rate of antibiotic drug prescription in Nigeria may hasten the development of resistance, particularly among enteropathogenic organisms.

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