Chapter 6

Factors Contributing to the Emergence and Spread of Antibiotics Resistance in *Salmonella* Species

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Additional information is available at the end of the chapter

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Abstract

Salmonella, a genus of the family *Enterobacteriaceae* with over 2450 species, has been responsible for diseases ranging from non-typhoidal salmonellosis to typhoidal salmonellosis. Several groups of antibiotics such as β-lactams, aminoglycosides, tetracyclines, quinolones, cephalosporins and sulfonamides are used against *Salmonella* species. Many *Salmonella* species had developed resistance to several antibiotics over the years. Two major groups of mechanism of resistance demonstrated by this pathogen are (1) Biochemical Mechanisms; such as enzymatic inactivation, prevention of access to the target site by antibiotics and active efflux pumps. (2) Genetic mechanisms; such as mutation, horizontal gene transfer and vertical gene transfer. Some factors identified to contribute to the emergence and dissemination of antibiotic resistant-*Salmonella* include; miss-used of antibiotics, used of antibiotics in agriculture, unregulated sales of antibiotics, inappropriate prescription and dispensing practices, and poor hygiene practices (external or behavioural factors), the presence of mobile genetic elements in the organisms; plasmid DNA, transposons, integrons etc. The clinical and public health consequences, and the strategies to stem the growing tides associated with drugs resistance in Salmonella species are herein discussed. A more radical approach and commitment from the policy makers in health sector to solving problems emanating from increasing spread of resistant *Salmonella* is advocated.

Keywords: *Salmonella*, resistance, antibiotics, factors, chromosomes, plasmid

1. Introduction

Salmonella are Gram-negative, facultative anaerobes, rod-shaped bacteria and are trivially known as 'enteric bacteria' [1], with over 2587 serotypes. *Salmonella* are grouped into two basic species namely, *Salmonella enterica* and *Salmonella bongori* [2, 3]. *Salmonella* generally cause a disease

termed salmonellosis, which are both typhoidal and non-typhoidal in nature. Moreover, investigation of the molecular mechanisms of *Salmonella* virulence factors have shown that pathogenic *Salmonella* species are distinguished from non-pathogenic relatives by the presence of specific pathogenicity genes, often called pathogenicity island (PIs), which contributes to both natural and acquired resistance in *Salmonella* species [4, 5]. However, the ability of *Salmonella* to cause invasive infection varies with serovars, the age of the patient and environmental factors [6].

Drug resistance among *Salmonella* serotypes has been a public health concerns at global level [7]. This could be intrinsic (natural resistance) as seen in *S. enterica* serotype typhimurium definitive phage type (DT) 104 that contains the chromosomal *Salmonella*, genomic island type 1 (SGI-1), which harbours resistance genes that confer *ACSST* phenotype (resistance to ampicillin, chloramphenicol, streptomycin, sulphonamide and tetracycline) [8, 9]. Also, the intrinsic resistance could be as a result of impermeability of bacterial cell wall to antibiotic of interest [9]. Several factors have been identified to contribute to the acquired resistance in *Salmonella*, which include: inappropriate use of antibiotic (either through over-prescription, incomplete course of treatment or inadequate dosing, etc.), use of antimicrobial agents in agriculture (either as growth promoter or for prophylaxis purposes), hospital, mutation and transferable genetic materials (plasmid, transposons and integron) [1, 9, 10]. These factors are responsible for the acquisition (emergence) and dissemination (spread) of resistance in *Salmonella* species. Various mechanisms of antimicrobial inactivation exist in *Salmonella* spp., which lead to the emergence of multi-drug resistance (MDR) strains [11, 12]. Some of these mechanisms are as follows:

(i) Enzymatic inactivation of the drug (e.g. β-lactamase)

(ii) Prevention of access to the target agent

(iii) Change or mutation in the target site

(iv) Novel penicillin binding protein (PBPs)

(v) Altered membrane permeability

(vi) Active efflux pumps

(vii) Ribosome alteration

(viii) Creation of biofilm barriers, etc.

Mobile genetic elements such as plasmids, transposons and integrons play an important role in the evolution (emergence) and dissemination (spread) of multi-drug resistance by either horizontal or vertical gene transfer [13]. The role of integrons in the acquisition and dissemination of resistance in *Salmonella* species is crucial. Integrons are DNA elements that contain collection of genes (gene cassette). Integrons are frequently associated with plasmid, transposon and are therefore easily transferable among *Salmonella* and/or between different bacteria [14].

The presence of virulence encoded plasmid DNA *spv*A, *spv*B and *spv*C in several *Salmonella* serovars had been documented and the outer membrane proteins (OMPs) of *Salmonella* typhimurium have a role in the virulence of the organism and are potent candidate for vaccine development since it is immunogenic, capable of evoking both humoral and cell-mediated immune response. These OMPs indirectly play part in intrinsic resistance and can be

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disseminated between or among *Salmonella* species [15, 16]. Thus, resistance acquisition or dissemination in *Salmonella* species usually involves several factors [1, 13].

2. *Salmonella* virulence and mechanisms of resistance

2.1. *Salmonella* and its virulence factors

The ability of *Salmonella* to attach itself to the host, invade and penetrate intestinal epithelial cell is determined by its virulence factor [17]. Adherence of *Salmonella* is often mediated by fimbriae and/or non-fimbrial adhesion (lipopolysaccharide) [11]. Invasion process is not merely a passive consequence of bacterial contact with epithelial cells, but instead requires the active production and transport of secreted effector proteins by a Type III secretion system (T3SS) 1 & 2 and Type 1 secretion systems, which are encoded in *Salmonella* pathogenicity island I & 2 (SPI-I & 2), respectively [17]. In addition, invasion is also induced by flagella/flagellin since *Salmonella* is a flagellated facultative anaerobe. Many invasion regulators have been described, for examples, *Hil*A [18], *Hil*C [19], InvF [20], PhoP/PhoQ, *Hil*E [21], H-NS [19] and *Inv*A genes, PhoP/PhoQ pair is also essential for the expression of genes in *Salmonella* pathogenicity island 2 (SP1-2), which encodes a second Type III secretory system. SP1-2 is required for intra-macrophage survival, which is a cell-type encountered by *Salmonella* immediately after the invasion of epithelium. PhoP/PhoQ also serves to repress SP1-1 genes, a function mediated by H*il*A [22]. PhoP/PhoQ may thus act as a genetic switch, activating traits required for macrophages survival while repressing those not needed for invasion [17].

Other factors that are involved in *Salmonella* virulence are the MgtC in *Salmonella* typhimurium. This is required for growth at low—Mg^{2+} concentrations and intra-macrophage survival. Iron acquisition (for iron deprivation survival) this is achieved by the production of two siderophores, which are enterobactin and salmochelin in response to iron deprivation. Superoxide dismutase is used to counteract the reactive oxygen produced through the activity of the phagosome NADPH oxidase (NOX_2) that are required for the killing of intracellular pathogens and enterotoxin (responsible for food-intoxication) [23]. The genes coding for the above-mentioned factors and others are conserved in *Salmonella* pathogenicity island 3 (SP1-3), and is also present in the chromosomes of other *Salmonella enterica* serovars [23]. It has been reported by several researchers [15, 24, 25], that *stn* genes coding for *Salmonella* enterotoxin) *sef* genes for *Salmonella* Enteritidis fimbriae, and *pef* genes for plasmid encoded fimbriae are widely distributed in resistant *Salmonella* strains and are responsible for *Salmonella*-associated diseases in animal and human populations globally.

2.2. Resistance mechanisms exhibited by *Salmonella* species to some antibiotics

Various mechanisms of anti-microbials inactivation have been reported by [11, 26], which invariably lead to the emergence of multidrug resistance in *Salmonella* species. These mechanisms are summarized into two broad groups, namely:

- Biochemical mechanisms and
- Genetics mechanisms.

2.2.1. Biochemical mechanisms of antibiotic resistance by Salmonella species

Enzymatic inactivation: This may result into either destruction of antimicrobial agents, such as occurs with the β-lactamases, or lead to a major modification of the antibiotic so that it does not bind to its target as it's seen with the aminoglycoside and chloramphenicol [1]. The major mechanisms of resistance to beta-lactam antibiotics among *Enterobacteriaceae* involve production of β-lactamase or extended spectrum β-lactamase (ESBLs) [1]. ESBLs have traditionally been defined as transmissible β-lactamases that can be inhibited by clavulanic acid, tazobactam or sulbactam. They are group of enzymes that break down antibiotics belonging to the penicillin and cephalosporin groups and render them ineffective [1]. ESBLs are generally encoded by mobile genes that can be exchanged between bacteria [27]. It has been noted that when ESBL strains occur, they often have co-resistance with the aminoglycosides (gentamicin), tetracycline and trimethoprim/sulphamethoxazole [27]. CTX–M ESBLs arise by plasmid acquisition of pre-existing chromosomal ESBL genes; this proved that ESBL can be plasmid mediated and thus capable of spreading to other microorganisms of either related species or genera [28].

Prevention of access to the target site: This may be by substitutions, amplifications or modification of the drug target, thereby reducing the affinity of the drug to the target. For example, in *Salmonella*, the outer membrane proteins may be altered such that antibiotics are unable to cross its cell wall [26]. Gram-negative bacteria can regulate membrane permeability by altering expression of outer membrane porin (omp) proteins that form channels for passive diffusion. Loss or reduced levels of ompF has been implicated in anti-microbial resistance in *Salmonella* over the years [29].

Active efflux pumps: This involves the expellant of multiple kinds of antibiotics out of the cytoplasm of the microorganism to the external environment [11]. Increased expression of non-specific, energy-dependent efflux systems allow bacteria to prevent the accumulation of effective concentrations of quinolones inside the cell by actively pumping out the drug. In *Escherichia coli*, the AcrAB-TolC efflux pump plays a major role in quinolone efflux and studies suggest that this may be the primary mechanism of fluoroquinolone resistance in *Salmonella* [30]. It is thoughtful that these efflux systems cause low-level resistance to quinolones that can become clinically relevant when combined with mutations in the target enzymes [31].

Reduced permeability of the antimicrobial agent: This is a common mechanism of anti-microbial resistance usually exhibited my *S. enterica*. It involves the alteration in membrane permeability, which occurs when new genetic information, change the nature of proteins in the membrane. This alteration changes a membrane transport system pores in the membrane for an anti-microbial agent not to be able to cross the membrane. This form of resistance mechanism has been discovered in *Salmonella* typhi to tetracycline, quinolones and some aminoglycosides and sulphonamide antibiotics [32, 33].

2.2.2. Genetics mechanisms of antibiotics resistance in Salmonella species

The genes coding for antibiotics resistance and virulence at times share common features of being located in the bacterial chromosome, as well as on plasmid (**Tables 1** and **2**). They are

associated in gene clusters to form resistance or pathogenicity island, which are transferred by mobile genetic elements such as integrons, transposons or phage [34].

The major genetics mechanisms are as follows:

- Mutation
- Horizontal resistant gene transfer and
- Vertical resistant gene transfer.

Resistance in enteric bacteria: *Salmonella, E. coli, Shigella*, spp. etc., can be a result of gene mutation (a permanent change in the DNA of an organisms), which had been detected through several research studies globally or transfer of resistance determinant (R-determinants) between the same species or different species (Horizontal gene transfer) or by transfer of resistance genes from parental microorganism to its progeny or offspring (Vertical gene transfer) [13, 35]. Clinically, chromosomal and plasmid-mediated resistance in *Salmonella* to gentamicin and Beta-lactam antibiotics had been reported in some host animal and humans [35–37].

The role of integrons in the acquisition and dissemination of resistance in enteric bacteria such as *Salmonella* is very crucial. Integrons are genetic elements that capture and incorporate gene cassettes by using a site-specific recommendation mechanism [38]. The class 1 and class 2 integrons are known to play specific role in anti-book resistance in *Salmonella* spp., which usually contain conserved segments. For example, integron class 1 has been reported to carry *aad*A_2, *bla* and *pse*1 cassette [39, 40]. Most of these integrons are located within transposons that contribute to vertical transmission, favouring their mobilization between plasmid and

Antibiotic group	Members	Effect	Mechanism of actions
β-Lactarns	Penicillin(s), Amoxicillin Imipenem Cephalosporin (1st, 2nd, 3rd generation)	Cidal	Inhibit transpeptidation enzymes involved in cross-linking the poly saccharide chains of the bacterial cell wall peptidoglycan and also by activation of cell wall lytic enzymes (cell wall synthesis inhibition)
Aminoglycoside	Neomycin, Kanamycin, Amikacin, Tobramycin, Gentamycin and Streptomycin	Cidal	Bind to small ribosomal sub-unit (30s) and interfere with protein synthesis by directly inhibiting synthesis and causing misreading of mRNA. Thereby inhibiting protein synthesis
Tetracycline	Oxytetracycline, Chlortetracycline, Doxycycline, etc.	Static	Same as aminoglycoside
Quinolones and fluoroquinoles	Ciprofloxacin, Norfloxacin, etc.	Cidal	Inhibit DNA gyrase and topoisomerase II, thereby blocking DNA replication
Sulfonamides	Silver-sulphadiazine, Sulphamethoxazole, Sulphanilamide, Sulphisoxazole, etc.	Static	Inhibits folic acid synthesis by competing with *p*-aminobenzoic acid (PABA)

Adapted from Refs. [1, 40].

Table 1. Properties of some common antibacterial drugs commonly used against *Salmonella* species.

	Resistance genes	Resistance genes location(s)	Resistance mechanisms	Region(s)	References
Aminoglycosides	*aacC(3), aacC(3')-IIa, aacC(6'), aacC2, aadA, aadA1, aadA2, aadA12, aadB, ant(3")-Ia, aphAI, aphAI IAB, aph(3)-Ii-iv, aph(3)-IIa, strA, strB*	CH, P	Enzymatic modification and inactivation of aminoglycoside	Across the Globe	[33, 42]
β-Lactams	*omp*C, *omp*F, *bla*CMY-2, *bla*PSE-1, *bla*TEM-1, *bla*SHV-1, *bla*OXA-1, *bla*NDM-1	CH, P	β-Lactamases, ESBL, Modification of porin (*ompF),* Efflux of β-lactam(*ompC*)	Across the Globe	[33, 42, 44]
Quinolones and floro-quinolones	*GryA, GyrB, parC, parE,*	CH, P	Mutation in the Quinolones Resistance Determining Region (QRDR) *GryA, GyrB, parC, pare*	Across the Globe	[30]
Tetracycline	*tet(A), tet(B), tet(C), tet(D), tet(G),* and *tet(H)*	P	Efflux pumps, Modification of rRNA target, Inactivation of compound	Across the Globe	[33, 42, 45]
Sulphanamides	*Sul1, sul2 sul*3, *dfr*	CH, P	Dihydropteroate synthase	Across the Globe	[42–44]
Phenicol eg Chloramphenicol	*floR, cmlA, cat1*	CH, P	Efflux pumps (*floR, cmlA*) and chloramphenicol acetyltransferase	Across the Globe	[42, 45]

Table 2. Antibiotic resistance genes and resistance mechanisms found in *Salmonella* species.

the bacterial chromosome by transposition events [14]. They have the ability to integrate stably into regions of other DNA, where they deliver, in a single exchange multiple new genes, particularly for drug resistance [41]. Many of the gene cassettes in resistance integrons, probably originated from super-integron (larger integron structures with hundreds of accessory genes), which encode for resistance against newer antibiotics such as cephalosporin and carbapenems [22].

2.3. Antibiotics commonly used for the treatment of salmonellosis and their mechanisms of actions

Some groups of antibiotics used in the treatment of salmonellosis globally for public health purposes as shown in **Table 1** include:

Aminoglycosides: Salmonella resistance to aminoglycosides is usually by enzymatic modification and binding to the 30S ribosomal subunit, resulting in the inhibition of protein synthesis

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in the organism aminoglycoside phosphotransferase confirms resistance to Kanamycin and Neomycin. Major, resistance genes include *str*A, *str*B, *aac, aad*, etc. [42, 43].

Tetracycline: Tetracycline targets the 30S ribosomal subunit of the bacteria ribosome just as aminoglycosides. Resistance mechanisms include efflux, modification of rRNA and inactivation of the compound [43]. In *Salmonella*, active efflux systems are most commonly observed and it includes *tet*A, B, C, D, G and H [43].

β-lactams: β-lactams prevent synthesis and maintenance of the peptidoglycan component of the bacteria cell wall by mimicking one of the building blocks used by enzymes to construct peptidoglycan. Most resistance to β-lactams is confirmed by β-lactamase that enzymatically cleaves the β-lactams ring and prevents it from bonding to and inactivating cell wall enzymes. Furthermore, extended spectrum β-lactamase is an important group of β-lactamases newly discovered not more than one decade ago [44]. However, other resistance mechanisms reported in major regions across the globe include efflux of the β-lactams and modification of porin (e.g. *omp*F and *omp*C) [42, 45].

Phenicols: Phenicols, e.g. chloramphenicol and related compound such as florphenicol, inhibit protein synthesis by binding to the 50S ribosome subunit. Resistance to chloramphenicol is highly prevalence in developing countries based on its cheapness and easy accessibility in the counter e.g. Nigeria [10, 44], despite its ban in developed countries, e.g. USA, based on it toxicity [43]. Most resistance mechanisms exhibited by *Enterobacteriaceae* including *Salmonella* are efflux pumps such as *flo*R and *cml*A as well as inactivating enzymes such as chloramphenicol acetyltransferase *cat*1 [46].

Sulphonamides: They are also called *folate pathway inhibitors*. These are compounds that compete for substrate of the essential folic acid pathway in bacteria at two different steps, and the sulphanilamide inhibits DHPS (dihydrofolate reductase). Sulphonamides are bacteriostatic when used alone or bactericidal when combined with trimethoprim-sulphamethoxazole [47]. Resistance to both of these antimicrobials occurs by acquisition of gene-encoding enzymes that do not bind these compounds [43], these include, the *sul* genes eg *sul*1, *sul*2 and *sul*3, which encode for insensitive DHPs enzymes, and are found in *Salmonella* globally [46].

2.4. Phenotypic and genotypic detection of resistance in *Salmonella*

Drug or antibiotic resistance is the decreased sensitivity of microbes to drug or antibiotics that are capable of causing cell death or inhibition of growth [48]. This is determined through antimicrobial sensitivity testing of *Salmonella* species (isolates) in order to determine its susceptibility or resistance to the antibiotics [49]. Resistance in *Salmonella* is encoded by genes that are present on either chromosome or extra-chromosomal DNA (plasmid) or transferable genetic materials (transposons, integrons), which is determined by genetic or molecular method [50]. The most common method is the Kirby-Bauer method [49]. Although resistance may occur due to mutation in key genetic loci in the bacterial genome, but most resistance to antimicrobial agents mediated by genes are acquired via mobile genetic elements such as plasmid and transposons [50]. The identification of resistance genotype is accomplished through detection of novel genetic materials and characterization of mutations in specific genes through polymerase chain reaction

(PCR). Several genetic methods including DNA probes, PCR and other amplification techniques are now used in varieties of clinical laboratories for identification and quantification of pathogenic organisms [51, 52].

2.5. Some identified factors for the emergence and spread of resistance in *Salmonella* species

The emergence of resistance is the natural response of microbes to the presence of antimicrobial agents [53, 54]. Several factors contribute to the increase in multi-drug resistance by *Salmonella* species, which can be grouped into two, namely:

- *Behavioural factors* (external factors): which include misuse of antibiotics, use of antibiotics in agriculture, unregulated sales of antibiotics, inappropriate prescription and dispensing practices and poor hygiene practices.
- *Genetics factors*: the mobile genetic elements, which include plasmids, transposons, integrons, etc.

2.5.1. Behavioural factors

These involve attitudinal conduct of the prescribers (Doctors), dispensers (Pharmacist), patients, agriculturists and/or government to prescription, sales, usage and regulation of antibiotics. These are elucidated as follows:

Inappropriate prescribing and dispensing: Lack of access to update information makes prescribers to prescribe less rationally [55]. Economic incentive and enticement from pharmaceutical companies further pressure the prescriber to prescribe unnecessarily or inappropriately [56]. Moreover, it is a common practice in many developing countries for antibiotics to be dispensed without a prescription. Also, over the counter sales of antibiotics is common. These practices had been attributed to weak enforcement of laws in such countries with resultant increase in acquisition of drug resistance in *Salmonella* species and high morbidity and mortality of *Salmonella*-associated diseases [10, 56].

Patients: Patient attitude contributes to the emergences of resistance through poor compliance to the prescribed course of treatment [1], especially if their symptoms are mild and resolved quickly [57]. The attitudes of self-medication in most patients has seriously contributed to the emergence of MDR in *S*. typhi to most first line drugs such as chloramphenicol, cephalosporin, streptomycin, tetracycline, ampicillin, etc. [10]. More also, poor hygiene practices of handling raw animal product and food in general with inadequate heat treatment has greatly contributed to the spread of antibiotic resistant strains from animal products and food to human [58, 59]. Furthermore, improper cooking methods; re-heating of food by food handlers in restaurants and canteens have been identified as also a major factor responsible for the spread of multidrug resistant *Salmonella* species since most of developing countries (e.g. Nigeria) population live below the average level of $1 per day meal, hence they resort to patronizing restaurants and canteens of questionable cooking standards [60, 61].

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Hospitals and laboratories (*medical centres*): Majority of antimicrobials usages occur in the community, of which most intense usage occurs in hospital [64]. The strong selective pressure together with the multitude of opportunities for resistant strains of *Salmonella* to spread from patient to patient is of high increase, this then means that hospital-acquired infections (Nosocomial infection) are mainly caused by multi-drug resistant strains, as seen in *S*. typhi in the case of typhoid fever [10]. Early discharges from hospitals either through changes in practice (e.g. cost reduction in developed countries) or lack of patient's ability to pay (particularly in developing countries) contribute to the emergence and dissemination of multi-drug resistance strains of *Salmonella* species [56]. However, hospitals work based on laboratory diagnosis must of the time not relying on clinical diagnosis alone since the former is the most reliable means of diagnosing a patient. But it is in the other way in developing countries based on exclusive reliance on Widal test as a means of diagnosing typhoid fever, which can be misleading as individuals with pyrexia are assumed and erroneously diagnosed as having typhoid fever based on single Widal agglutination test [62].

Government: contributes to the emergence of resistance in *Salmonella* species and other disease causing organisms that are of public health concern in the following perspective:

(1) Weakness in legislation or its enforcement contributes to resistance by allowing the circulation in the market of substandard or counterfeit antimicrobials.

(2) Poor regulation of advertisement and promotion of drug undoubtedly increases sales, and encourages unnecessary use of antimicrobials.

(3) Lack of adequate training and certification of prescribers and dispensers may be due to poor provision or regulation by government.

(4) Poor availability of potable water.

(5) Poor diagnostic facilities of salmonellosis (typhoidal and non-typhoidal) in terms of isolation of the causative agent for quality treatment.

(6) Poor sewage disposal and waste treatment channels.

It should also be noted, that lack of information about prevalence of resistance problems or poor supply chain management or long-term facilities (poor diagnostic facilities) contribute to poor diagnosis and effective treatment of disease that are of public health concern, which result in emergence of multi-drug resistance strains that eventually result to high cost of treatment of these diseases [1, 10, 63]. Furthermore, non-availability of *S*. typhi vaccines in developing countries like Nigeria is also one of the contributing factors to the spread of resistance in *Salmonella* species [64].

Contribution of non-human uses of antimicrobials: The worldwide increase in the use of antibiotics in poultry, fishery and livestock production industries to treat and prevent infections, or as growth promoter, has greatly contributed to the increased antibiotics resistance in potential food-borne pathogens (*Salmonella, Shigella, Campylobacter*, etc.) in the past years [58, 64]. The increased use of antibiotics in agriculture has played a significant role in the emergence and spread of antibiotic resistant food-borne pathogens in human as a result of the consumption

of poultry and dairy products [59]. The summary of the behavioural factors and their contribution to antibiotic resistance is shown in **Figure 1**.

2.5.2. The genetic factors

The major mechanism in the spread (dissemination of resistance genes between or among bacteria of the same species or different species is through genetic mechanism. Since resistance genes for instance in *Salmonella* have often been located within plasmid, integrons sometimes

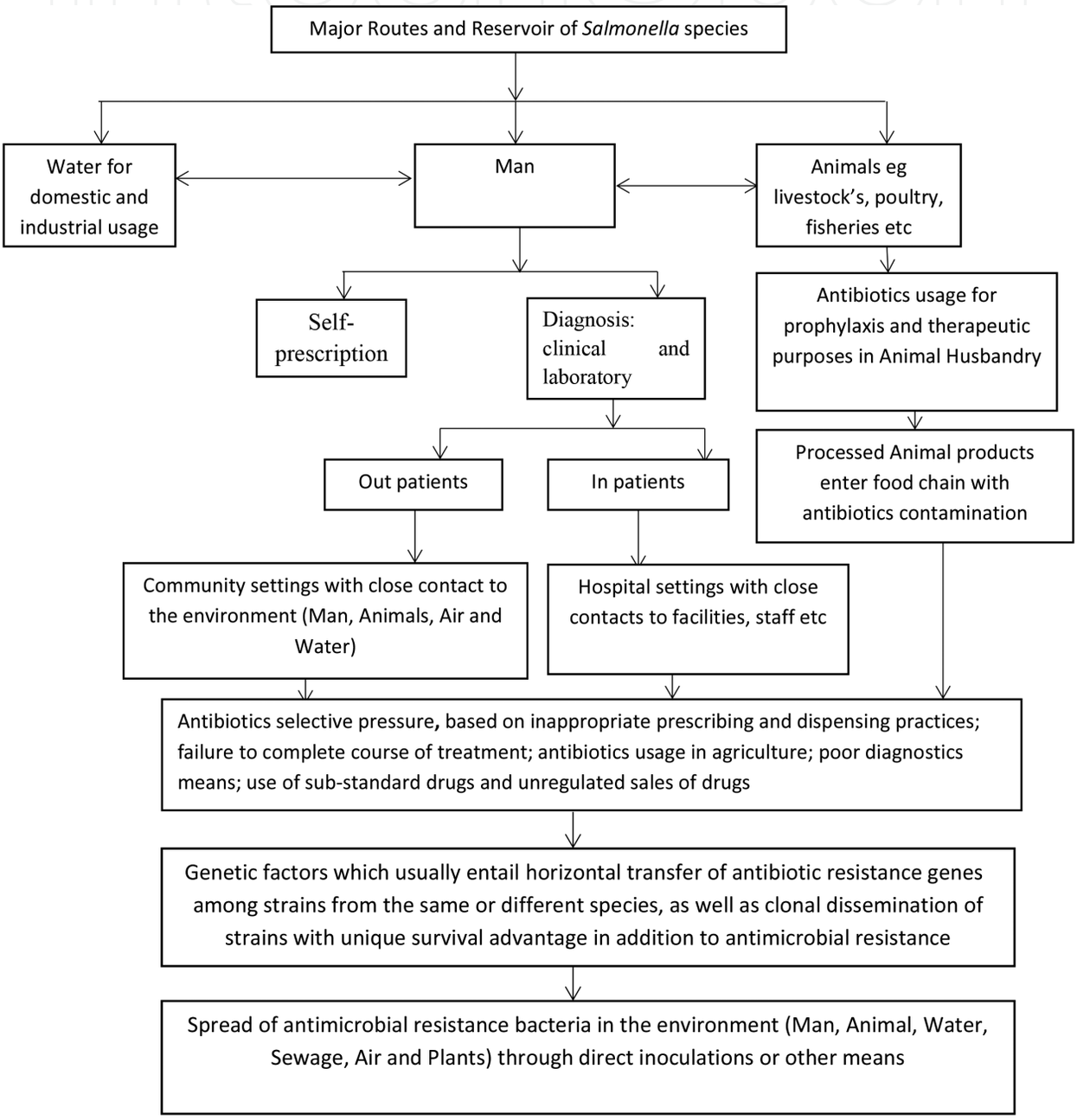

Figure 1. A flow chart showing the spread of antibiotic resistance in *Salmonella* species in both man and animal populations.

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associated with transposons and also insertion sequence [1, 56, 65]. The major factors involved in the genetic mechanism of spread are the integrons, transposomes and plasmids [13].

Integrons are mobile genetic elements of specific structure that consist of two conserved segment capable of flanking through a central region in which resistance gene cassettes are inserted [36]. Also, on the 5[1]-conserved segment is an *int* gene that encodes a site-specific recombinase, capable of capturing DNA, including resistance genes [66].

Transposons: These are mobile genetic elements that contain insertion sequence (0.2–6.0kb), which can move (transpose) from one site to the other site within the same or different chromosome or plasmid and thus replicate along with it [56].

Plasmid (4–400kb) are self-replicating, extra chromosomal DNA that contain genes either for resistance, virulence and other functions and are dispensable under certain conditions. Incompatibility group of plasmid DNA (Inc) HI1 are important vectors of antibiotic resistance in *S*. typhi. It was first detected from a large outbreak in 1972 in Mexico [64]. However, some larger plasmids are conjugative (R-plasmid) and are transferable between organisms, spreading along resistance genes in *S*. typhi [38]. It is should be noted that, as resistance genes move to other plasmids or chromosomes, they sometimes link with other resistance genes in resistance clusters, whose transfer can then result in spontaneous acquisition of resistance to several unrelated drugs, which eventually result to multi-drug resistance by recombination process [56].

2.6. Consequences of resistance in *Salmonella* species to public health

There are several clinical and public health consequences associated with antimicrobial drugs resistance in *Salmonella* species. These include:

(1) Failure in therapy, thereby resulting to limitation in the choice of treatment after the establishment of microbial diagnosis [67].

(2) Increased burden of illness and outbreaks in settings where patients are treated with antimicrobial drugs [67].

(3) Increased virulence of *Salmonella* species as a result of 'drug-bug combination' that poses selective pressure on the microorganism [25].

(4) Increased mortality and morbidity, thereby posing threats to public health [10, 67].

(5) Increased cost of treatments [1].

(6) Longer stay in hospital, which increases the risk of acquisition of nosocomial infections.

(7) Increased transmission of resistant *Salmonella* strains [67].

2.7. Strategies to combat resistance problems posed by *Salmonella* species

Several efforts have been adopted by several organizations, government and researchers to combat antimicrobial resistance imposed by some pathogenic organism that are of public

health significant (*Salmonella* spp.) [68]. The 2006 IFT report led to the publication of the World Health Organization (WHO) list of critically important antimicrobials for human medicine and veterinary importance. This propelled the U.S Food and Drug Administration (FDA) to categorize various classes of anti-microbials as important, highly important and critically important and has since issued rules that prohibit most extra labelled use of some critically important antimicrobials such as fluoroquinolones and cephalosporin in food animal species [69].

Other efforts to address threats posed by antimicrobial resistance include: monitoring programmes for antimicrobial resistance microbes that integrates human, animals and food sampling scheme. Examples include: National Antimicrobial Resistance Monitoring System (NARMS) in the United States and the Danish Integrated Antimicrobial Resistance Monitoring Programme (DANMAP) in Denmark. These programmes in collaboration with CDC, WHO and FDA had really helped to trace the incidence of resistance particularly in foodborne pathogens (*Salmonella* and *Campylobacter*) globally, thereby embarking several strategies such as giving updated information, rules/laws, social and financial help, etc. to combat resistance threats.

Also, effort to combat resistance posed by *Salmonella* is the modification of drugs that led to the production of third – and fourth generation cephalosporins, and the use of medicinal plants also known as herbal medicine had been proven to have bactericidal effect on *S*. typhi; the causative agent of typhoid fever, also with the use of combined therapy, that is, the use of two or more different classes of antibiotics for the treatments of a particular disease e.g. Salmonellosis [1, 57].

Furthermore, the following are also needed to be done to track-down the current rise in the spread of resistant *S. enterica*: Intensive surveillance of vended foods in developing countries to reduce microbial risk associated with their consumption [60]. Public enlightenment to discourage the patronage of vended foods should be intensified as vended foods especially in Lagos is a potential vector responsible for the spread of resistant *Salmonella* species, or high level of hygiene practice should be maintained by food vendors under strict supervision and monitoring by food regulatory authorities if at all vended foods will be patronized [60].

3. Conclusion

Several factors such as misuse of antibiotics, use of antibiotics in agriculture, poor hygiene practices by hospitals and individuals, unregulated sales of antibiotics and genetic factors, such as plasmids, integron, transposons, etc., contribute to selective pressure on antibiotics and resistance gene transfer, respectively, in *Salmonella* species. This has led to the emergence and spread of resistance in this microorganism and resultant therapeutic failures. Several strategies have been adopted by governmental organizations and pharmaceutical companies in the areas of resistance monitoring, restriction in the use of antibiotics in agriculture, production of modified drugs, the use of combined therapy, future plans on the use of bioactive compounds from medicinal plants against MDR bacterial strains. There is a need to enforce regulatory laws governing procurement and sales of antibiotics in developing countries.

Also, good sanitation and hygiene practices as well as sensitization of people about the danger associated with indiscriminate purchase and use of antibiotics are essential to steam the growing trends of antibiotic resistance in bacterial pathogens especially *Salmonella* species.

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