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Review Article

Drug Resistance in Nontyphoidal *Salmonella*- Challenges for the Future

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Abstract

Nontyphoidal *Salmonella* is an important pathogen implicated in causing food-borne illness worldwide. Antibiotic treatment in nontyphoidal salmonellosis is usually reserved only in severe and invasive illness and in extremes of age and immunosuppressed. Emergence of multidrug resistant *Salmonella* strains due to illicit and un wanted usage of antibiotics in humans and veterinary medicine is of global concern. Resistance to older drugs like chloramphenicol, Ampicillin, sulphonamides and trimethoprim is declining and emergence of resistance to fluoroquinolones and extended spectrum cephalosporins that are traditionally used for treatment in severe cases is of particular concern. Hence it is necessary to have periodic accurate antimicrobial resistance monitoring systems in the developing countries to monitor the trends in antimicrobial resistance in Nontyphoidal *Salmonella* serovars.

ABBREVIATIONS

NTS: Nontyphoidal *Salmonella*; ESBL: Extended Spectrum Beta Lactamases

INTRODUCTION

Traditionally based on the infections caused in humans, *Salmonella* are divided into Typhoidal and Nontyphoidal *Salmonella* (NTS). Nontyphoidal salmonellosis refers to the infections caused by all the serotypes of *Salmonella* except *S.*Typhi, Paratyphi A, Paratyphi B, Paratyphi C and Sendai. They are mainly of zoonotic origin and are found as asymptomatic colonizers in major live stock species- cattles, pigs and poultry. Whereas typhoidal *Salmonella* that causes typhoid fever are seen exclusively in humans [1]. Nontyphoidal Salmonellosis is a leading cause of food borne illness worldwide. They are important food-borne pathogens that cause self-limiting gastroenteritis to rarely bacteraemia and extra intestinal focal infections.

Microbiology and nomenclature- what needs to be known?

Salmonella is a motile Gram negative rod shaped bacillus belonging to the Enterobacteriaceae family. Organism is named after the veterinary surgeon Daniel Elmor Salmon even though his research assistant Theobald Smith first isolated *Bacillus suipestifer* (renamed as *Salmonella cholerasuis*) from intestine of pigs diagnosed with hog cholera in 1885 [2]. The nomenclature of this particular organism is never stable and has evolved from initial one serotype-one species concept, put forward by Kauffman, in which each serotype was considered separate species [3]. According to the current nomenclature accepted by World Health Organization and American society of microbiology based on the DNA-DNA hybridization studies, there are just two species in the genus *Salmonella*- *S.*Enterica which contains six subspecies designated by roman numerals I-VI (*enterica*, *salamae*, *arizonae*, *diarizonae*, *houtenae*, and *indica*), and *S.*Bongori which contain one subspecies [4]. Members of these seven subspecies can be divided into one of the more than 2,500 identified serotypes or serovars based on the reaction to specific antibodies. According to the Kauffman-White classification scheme, *Salmonella* is classified into different O groups and serovars based on the expression of somatic lipopolysaccharide O antigen and flagellar H antigen. Majority of the 2500 known serovars that causes disease in warm blooded animals is found in *Salmonella* Enterica subspecies *enterica* and these various serovars are characterized by their host specificity [5]. Nontyphoidal *Salmonella* serotypes are usually zoonotic pathogens having wide range of animal reservoirs. Most cases of human salmonellosis are associated with consumption of contaminated water and food sources like poultry, eggs, meat and meat products. Other modes of transmission are direct contact with the infected pet animals and person to person transmission especially in hospitals [6,7].

Antimicrobial drug resistance

Most of the infections caused by these NTS are self-limiting gastrointestinal disease with symptoms of diarrhoea, fever and abdominal cramps. Bacteremia and other extra intestinal focal manifestations usually do not result from mild forms of the disease. Antimicrobial treatment is reserved only in invasive infections, in immunosuppressed and in extremes of ages as antimicrobials can prolong the illness and excretion in Nontyphoidal Salmonellosis [1,6-11]. Commonly used drugs

for the treatment are fluoroquinolones and extended spectrum cephalosporins. However there are reports of antimicrobial resistance among these *Salmonella* strains to different classes of antibiotics and that has left us with only few options for treatment. Multidrug resistant Nontyphoidal Salmonellosis has become a global concern now. Community and healthcare associated outbreaks have been reported all over the world due to these resistant strains. Development of antimicrobial resistance is a naturally occurring phenomenon and it is often enhanced by use of antimicrobial agents for the treatment and prevention of infections in humans and animals as well as addition of these antibiotics as growth promoters or for feed efficiency in the food of animals which has favoured the selection and transference of drug resistant strains of *Salmonella*. These uses typically involve administration of antibiotics at sub therapeutic levels in food or water of an entire herd or flock to promote faster growth with less feed [12]. There are several studies confirming the use of antibiotics in the food of animals as the source for multidrug resistant *Salmonella* serovars. Multidrug resistance is often associated with mobile genetic elements like plasmids and transposons that encode multiple resistance genes. With globalization and increasing global travel, worldwide spread of these multidrug resistant strains is of particular concern.

Mechanisms of drug resistance

Different classes of antibiotics are used for the treatment of Nontyphoidal Salmonellosis. There has been increasing number of reports of drug resistance in *Salmonella* and it is quite worrisome because *Salmonella* is one of the most common causes for food-borne gastroenteritis worldwide. Because the resistance in *Salmonella* is serotype dependent and varies from place to place, it's not easy to speak about the overall resistance pattern of *Salmonella*. A much higher rate of resistance is found in *S.enterica* serovar Typhimurium and Newport when compared to other serovars and is associated with severe disease outcome. Literature search revealed that not much data is available on the antimicrobial resistance rates in Nontyphoidal *Salmonella* from developing countries. Present review aims to provide an insight on the current situation of antimicrobial drug resistance in Nontyphoidal *Salmonella*, mechanisms of drug resistance and its clinical implications.

Chloramphenicol

This broad spectrum antibiotic active against both Gram positive and Gram negative organisms has been used for treatment of Salmonellosis in both humans and veterinary medicine for a long time. The usage of this antibiotic was curtailed due to the emergence of resistance.

There are two mechanisms by which *Salmonella* has conferred resistance to Chloramphenicol- 1) presence of by non-enzymatic chloramphenicol resistance gene *cmlA* and *flo* gene against synthetic fluorinated analogue of chloramphenicol, florfenicol both of which codes for efflux pumps thereby preventing the antibiotic from reaching its target site. 2) By plasmid located enzymes called chloramphenicol acetyltransferases (CAT). There are two subcategories of Cat enzymes- *Cat A* and *Cat B* of which *Cat B* is located on integrons and has been found in *Salmonella* serovar Typhimurium, Derby, Enteritidis and Haardy. The genes encoding for the efflux pumps –*flo* gene and *cmlA* gene has been found in various bacterial species and different serotypes of *Salmonella* like Typhimurium, Albany, Newport, Paratyphi B and Agona [17,21,23].

Aminoglycosides

There are three main mechanisms by which an organism can become resistant to aminoglycosides antibiotics- decreased permeability and reduced uptake of the antibiotic, alteration of target site and finally enzymatic modification. Bacterial resistance to aminoglycoside antibiotics in *Salmonella* are often conferred by the plasmids which O-phosphorylate, o-adenylylate or N-actetylate the antibiotic using aminoglycoside modifying enzymes. These enzymes are mainly of three types- acetyl transferases, nucleotidyl transferases and phosphotransferases. As a result of these enzymatic modifications antibiotic is unable to enter the cell and bind to their target site ribosome [13,14].

Acetyl transferases are the enzymes that catalyse the Co-A dependent acetylation. One of the common enzymes present and widely distributed in many Gram negative bacilli is 3-*N*aminoglycoside acetyltransferase (AAC-3). There are distinct types of AAC-3, each with their own substrate specificities. Apramycin is a veterinary aminoglycoside antibiotic used extensively all over the world since 1980 for the treatment of enteric infections in live stock animals. It is an aminocyclitol antibiotic with bicyclic sugar moiety and a monosubstituted deoxystreptamine. Because of its unique structure when compared to other aminoglycoside antibiotics, when it was introduced into use in animals it was thought that development of resistance to this antibiotic is impossible [12]. However, resistance to this antibiotic also emerged and resistance was shown to be transferable and plasmids responsible for this resistance specified the enzyme 3-*N*aminoglycoside acetyltransferase type IV (AAC (3) IV) which also conferred resistance to related antibiotics including gentamicin and tobramycin [14-16]. Gentamicin resistance was first reported in *S*. Typhimurium in 1982. Resistance to gentamicin and related aminoglycosides in Typhimurium has primarily been identified in phage type 204C (DT204c). Aminoglycoside phosphotransferases can confer resistance to neomycin and kanamycin and are usually named *aph.* Aminoglycoside nucleotidyl transferases can confer resistance to gentamicin, tobramycin or streptomycin.

Fluoroquinolones

Quinolones and its derivatives are synthetic broad spectrum antibiotics that act mainly by preventing the bacterial DNA from unwinding and duplicating. They have been used in the human and veterinary medicine for treatment of serious infections owing to their low toxicity and broad spectrum of action and development of resistance to these novel antibiotics pose a real threat. A number of fluoroquinolones like enrofloxacin, difloxacin, marbofloxacin, and sarafloxacin has been used in the food animals for treatment and prophylaxis of various infections [17].

The main mechanisms of resistance to quinolones that has been recognized are

1. Mutations in the quinolone-resistance determining regions (QRDRs) of target genes (*gyr A* and *gyr B* coding for DNA gyrase and *par A* and *par C* genes coding for Toposiomerase IV),

2. Over expression of efflux pumps AcrABTolC efflux pump and its regulatory genes-*mar*ROB and *sox*RS leading to decreased accumulation of drug inside the cell and

3. Presence of plasmids like qnr, qepA, oqxAB and aac (6′)-Ib-cr a that protect the cells from lethal effects of quinolones [18]. Most frequently observed point mutations in *gyrA* of fluoroquinolones resistant *Salmonella* are the changes of the amino acids at codon 83 from serine to phenylalanine, tyrosine, or alanine and at codon 87 from aspartic acid to glycine, asparagine, or tyrosine and in *gyrB* is substitution of tyrosine for serine at codon 463. These mutations are associated with Nalidixic acid resistance and reduced susceptibility to fluoroquinolones like ciprofloxacin. Qnr comprises a group of pentapeptide repeat proteins first reported in 1998 that protect bacteria against quinolones by binding to the DNA gyrase holoenzyme and its subunits [19]. QepA is a plasmid-encoded major facilitator superfamily (MFS) efflux pump that significantly affects susceptibility to ciprofloxacin, enrolfloxacin and norfloxacin due to its ability to extrude hydrophilic fluoroquinolones. oqxAB, another multidrug efflux pump originally isolated from a conjugative plasmid in *Escherichia coli* is also seen in *Salmonella* which also confers resistance to chloramphenicol. Aac(6′)-Ib-cr is a modified aminoglycoside N-acetyltransferase that acetylates some fluoroquinolones, including ciprofloxacin and is responsible for the low level ciprofloxacin resistance. These mechanisms provide low-level resistance to quinolone in vitro to facilitate the emergence of higher level of resistance in the presence of quinolones at therapeutic levels. It has been found that no single mutations result in high level resistance to quinolones and it is the accumulation of mutations and the interplay between various resistance mechanisms that often results in high level resistance [17,20,21]. Interactions between plasmid mediated quinolone resistance (PMQR) genes and mutations in QRDS can result in high fluoroquinolones Minimum Inhibitory Concentrations (MIC).

Tetracycline

This broad spectrum antibiotic has been used extensively for the treatment and prophylaxis of infections in humans as well as in animals and also as growth promoters in animal feeds at sub therapeutic levels. It has been used in food animals to combat vector borne diseases like borreliosis, erlichiosis, and tularaemia and also for the treatment of infections including listeriosis and brucellosis. However, development of resistance to this antibiotic was first identified in *Shigella dysenteriae* as early as 1953 and has limited its use [22]. Resistance to tetracycline in *Salmonella* is either due to the presence of newly acquired genes which codes for energy dependent efflux of tetracycline or proteins that offer protection of its target site, ribosome from the action of tetracycline. At least 35 different tetracycline resistant genes (*tet*) has been characterized and these genes codes for membrane bound efflux proteins belonging to the MFS super family. These efflux proteins exchange a proton for tetracycline cation complex.

In *Salmonella*, the most common *tet* genes belong to the classes A, B, C, D, G and H and these genes are found in the *Salmonella* genomic island. These genes are often located on mobile genetic elements like plasmids, transposons and integrons and co-associated with genes coding for resistance to other antibiotics [23-25].

Sulphonamides and trimethoprim

Sulphonamides are the oldest synthetic drugs introduced more than 80 yrs ago into clinical use. These antibiotics act selectively on the bacteria and thus could be used for treatment of systemic infections. Trimethoprim is a synthetic antifolate truly new antibiotic introduced into the clinical practice. Both sulphonamides and trimethoprim act on the folic acid pathway of the bacteria interfering with the production of dihydrofolic acid. Being synthetic antibiotics, naturally occurring enzymes degrading or modifying the drug is unlikely. Sulphonamide resistance in *Salmonella* is primarily mediated by *sul*1, *sul*2 and *sul*3 genes encoding for drug insensitive dihydropterase synthetase (DHS) enzyme. *Sul*1 gene is normally found in class 1 integrons linked with other resistance genes whereas *sul*2 is found in small nonconjugative plasmids or large transmissible multidrug resistant plasmids. *sul*3 has only been recently discovered and is found to be associated with plasmids and class 1 integrons in *Salmonella* [23,26-28]. Sometimes, sul3 gene occurs in *Salmonella* carrying class 1 integrons with *aadA* and *dfrA* gene cassettes, which allows isolates to survive exposure to co-trimoxazole, a combination frequently used in therapeutics. Resistance to trimethoprim is due to DHFR encoding genes-either *dhfr* or *dfr* or both.

Beta lactam drugs

Beta lactam antibiotics are the most commonly used class of antibiotics owing to their broad spectrum of activity, ease of delivery and minimal side effects. They act by inhibiting the bacterial cell wall synthesis. This group of antibiotics include penicillins, cephalosporins, carbapenems and the non classical beta lactam antibiotics monobactams. Extended spectrum cephalosporins especially third generation cephalosporins are mainly used for the treatment of invasive Nontyphoidal Salmonellosis especially in children. Of particular concern is the development of resistance to ceftriaxone or other third generation cephalosporins used for the treatment of complicated NTS especially in children. Widespread and irrational use of this versatile group of antibiotics has led to the development of resistance. A closely related cephalosporin antibiotic ceftiofur is licensed for use in food animal production which can induce cross resistance. It's mainly seen in the serovars Newport, Heidelberg, Dublin and Typhimurium from human strains.

Beta lactamase production in the form of Extended Spectrum Beta lactamases (ESBLs) and Amp C is the major mechanism of resistance to beta lactam drugs seen in *Salmonella* similar to other Gram negative bacilli. The principle mechanism of resistance to extended spectrum cephalosporins (cefotaxime, ceftriaxone, ceftazidime, ceftizoxime, cefoperazone) in *Salmonella* strains is by the production of class A beta lactamases or ESBLs. These beta lactamases confer resistance to most of the beta lactam antibiotics including oxyimino-cephalosporins and aztreonam, but are not active against cephamycins and can be inhibited by beta lactam- beta lactamase inhibitor combinations. Although reports of ESBL production in *Salmonella* is rare when compared to other Gram negative bacilli, *Salmonella* are found to possess large number of ESBLs like TEM, SHV, PER, CTX-M families with TEM and CTX-M being the most common [29]. Common TEM group of ESBLs found in NTS are TEM-3, TEM-27 and TEM-52 [30-34].

Salmonella species showing resistance to extended spectrum cephalosporins have been known since 1988 and has been isolated from different countries like India, South Korea, North and South America, Europe and Africa. These strains were isolated mainly from the hospitalised patients and carried

plasmid mediated ESBLs like TEM, SHV, PER, OXA and CTX-M families and often carried resistance to other antibiotics like aminoglycosides, tetracyclins and co-trimoxazole [35].

CTX-M (cefotaximases) is a novel family of Ambler class A beta lactamases that possess higher levels of hydrolytic activity against cefotaxime than ceftazidime, aminopenicillins (e.g ampicillin or amoxicillin), carboxypenicillins (e.g. ticarcillin), ureidopenicillin (e.g. piperacillin) and are inhibited by beta lactamase inhibitors and is primarily carried by plasmids and transposons [36]. This is one of the most common types of ESBLs encountered in *Salmonella*. CTX-M-2 beta lactamase was first identified in *S.enterica* serovar Typhimurium in Argentina in 1990. Since then a number of serovars like Virchow, Enteritidis, Stanley, Anatum are found to process large number of CTX-M beta lactamases [37,38].

Second most important mechanism of resistance to extended spectrum cephalosporins in *Salmonella* is by AmpC beta lactamase production. These beta lactamases confer resistance to all beta lactam antibiotics except cefepime, cefpirome and carbapenems and are not inhibited by beta lactam- beta lactamase inhibitor combination [39]. Globally, majority of the AmpC beta lactamase genes reported in *Salmonella* belong to *bla* CMY-2 which are usually less active against cefpirome and cefepime than ESBLs [29,40,41]. This gene was first identified in a multidrug resistant *S.enterica* serovar Senftenberg strain in 1994 in Paris [42]. Since then it has been reported to be carried by several ceftriaxone resistant *Salmonella* species. Other Amp C beta lactamase genes found in *Salmonella* are DHA, ACC, BIL, LAT etc [43,44].

Carbapenems are the last resort antibiotics used for the treatment of multidrug resistant pathogens. Carbapenem resistance due to carbapenemase production in nontyphoidal *salmonella* is rarely reported. Imipenem resistance due to KPC production in *Salmonella* was first reported in a clinical isolate of S.*enterica* serotype Cubana from stool specimen of a 4 year old boy suffering from gastroenteritis in a hospital in Maryland in 1998 [45]. Other carbapenemase producing genes found in NTS are VIM-1 and OXA-48 [46,47]. In 2010, a carbapenem resistant strain of *Salmonella enterica* serovar Typhimurium was isolate from a 77 yrs old woman with nephritic syndrome and chronic renal insufficiency from urine, stool and wound cultures. This particular strain carried *bla* CMY-2 containing TM6092 in a conjugative plasmid and had Omp D deficiency (2). The strain further developed OmpC deficiency while on ertapenem therapy and became resistant to carbapenems. Another strain of particular concern is S.*enterica* serotype Kentucky ST 198 clone displaying high level resistance to ciprofloxacin first reported in 2011 in patients from Europe. Since then the strain has been isolated with resistance to third generation cephalosporins and carbapenems from different parts of the world [49,50]. Since the discovery of NDM in enteric pathogens, there has been a continuous threat of its transfer to *Salmonella*. Few cases of NDM producing *S.enterica* serovar Senftenberg, Stanley, Westhampton and Agona has been reported from U.S, China and Pakistan [46,51,52]. Carbapenem resistance due to combination of beta lactamase production and porin loss is rarely seen in *Salmonella* when compared to other members of Enterobacteriaceae family. Till now there has been only one report of imipenem resistance in *Salmonella enterica* serovar Wein due to CMY-4 beta lactamase production and porin loss [53].

S.Typhimurium monophasic variant 4,5,12:i:-

S.enterica subspecies enteric serotype 4,5,12:i:- is a serotype that is genetically and antigenically closely related to *S.Typhimurium* except that it lacks the second flagellar protein. This particular serovar has been classified among the top ten serovars responsible for cases of food borne salmonellosis in several countries and it has been recognized recently as an emerging cause of food borne infection worldwide. The incidence of human salmonellosis caused by *.enterica* serotype 4,5,12:i:- has been increasing in Europe, North and South America and Asia since the mid-1990s. Multidrug resistant patterns seen in this particular serovar are ASSuT tetra resistant pattern and ACKGSuTm (resistant to Ampicillin, chloramphenicol, kanamycin, gentamicin, streptomycin and tetracycline).

Fluoroquinolones and extended spectrum cephalosporin co-resistance

Traditionally, resistance to nalidixic acid is used as surrogate marker for decreased susceptibility to ciprofloxacin in *Salmonella* serotypes Typhi, Virchow and Senftenberg. Decreased susceptibility to fluorquinolones has also been noted in nontyphoidal *salmonella* serovars even in nalidixic acid susceptible strains. Resistance to extended spectrum cephalosporins is mainly due to Class C beta lactamase production. The common serotypes in which the co-resistance is seen are Newport and Typhimurium. Decreased susceptibility to both drug classes was identified in Thailand in 1993 (ser. Anatum, Derby, Enteritidis, Typhimurium, Weltevreden, and I 4,5,12:i:-), the United Kingdom in 1998 (ser. Senftenberg, Typhimurium, and Virchow), Belgium as early as 2001 (ser. Virchow), the United States in 2002 (ser. Mbandaka), France in 2003, and Taiwan in 2004 (ser. Choleraesuis, Cairo, and Kaduna). Even though co-resistance to both fluoroquinolones and extended spectrum cephalosporins is rare, it would limit the therapeutic options available for complicated NTS[54].

MULTIDRUG RESISTANCE

During 1990s there was an upsurgence in beta lactam drug resistance in *Salmonella* with the emergence of multidrug resistant epidemic strain of *S.enterica* serotype Typhimurium of phage type (Definitive type) DT104 with genes encoding resistance to five agents- ampicillin, chloramphenicol, tetracycline, sulphonamides and streptomycin. Antibiotic resistant genes are clustered in *Salmonella* genomic island 1(SGI 1) [55-57].According to National Antimicrobial Resistance Monitoring System (NARMS) 2014 surveillance report on enteric pathogens, for NTS multidrug resistance phenotype implies resistance to at least ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline (ACSSuT). In the recent years, an important phenotype that has emerged is ASSuT phenotype without chloramphenicol resistance. Another important phenotype includes ACSSuT phenotype plus resistance to amoxicillin-clavulanic acid and ceftriaxone (ACSSuTAuCx). The most common serovars showing multidrug resistant phenotype is Typhimurium, Dublin, Heidelberg and Newport serovars.

SPREAD OF DRUG RESISTANCE

Resistance may be disseminated through clonal expansion of multidrug resistant strains or through horizontal transfer of genetic elements coding for these resistance determinants. Dissemination and spread of multidrug resistant *S.enterica* serovar Typhimurium of phage type (Definitive type) DT104 is an excellent example for clonal expansion and global dissemination of these multidrug resistant strains across multiple countries and continents. Another important method by which antimicrobial drug resistance is disseminated is through the horizontal transfer of resistance determinants through mobile genetic elements like plasmids, transposons and integrons [58].

CONCLUSION

To conclude, the resistance to drugs that are therapeutically used now for complicated Nontyphoidal Salmonellosis like fluorquinolones and third generation cephalosporins are on rise thus challenging the treatment of these infections. The most concerning part about this antimicrobial resistance is development of multidrug resistant phenotype that will leave us with very few therapeutic options. Hence there is an urgent need to contain the illicit and unwanted use of antibiotics both in humans as well as in veterinary medicine and improve measures to prevent further spread of these multidrug resistant strains.

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