Review Article: A trends of Salmonella and antibiotic resistance


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Abstract
Salmonellosis has become a major problem in developed and developing countries. It also represents an important public health concern worldwide. As such, due to intense interest Salmonella research has gained great concern from scientific communities as well as the general public. The purpose of this review is to discuss the historical perspective, classification and nomenclature, antibiotic and antimicrobial definition, mechanism of antibiotic resistance, integrons and antibiotic resistance Salmonella.

1. Introduction
Nontyphoidal salmonellosis is caused by numerous Salmonella species other than serovars Typhi and Paratyphi. The genus Salmonella are facultative anaerobes, non-sporing, rod shape bacillus and Gram negative motile belonging to the family Enterobacteracae (Ellermeier and Slauch, 2006). Morphologically Salmonella is rod shaped bacteria with diameter ranging from 0.7-1.5 μm and 2-5 μm in size with optimal growth condition of 37°C (Ellermeier and Slauch, 2006).

Salmonellosis represents a serious threat to public health resulting in considerable economic consequences in many parts of the world. The emergence of antimicrobial-resistant Salmonella and other enteric pathogens has become a major concern. The use of antimicrobials in therapeutic, prevention of disease and growth promotion in domestic livestock, can potentially lead to widespread dissemination of antimicrobial-resistant bacteria (Tollefson, 1997; Gomez-Lus, 1998; Witte, 1998).

2. Historical perspective of Salmonella
As early as the 18th century, scientist developed interest on Salmonella as a potential etiological agent of typhoid fever (Cunha, 2004). In 1873, William Budd diagnosed Typhoid fever in clinical patients, and this was the first time Salmonella was determined as a source of the infection for the disease (Ellermeier and Slauch, 2006). Later on, Karl Eberth (1833-1926), discovered a rod-shaped organism in spleens and lymph nodes of a Typhoid fever patient. Similarly, in the 18th century, George Gaffky (1850-1918) was credited for his successful cultivation of Salmonella serovars Typhi from a patient in Germany (Ellermeier and Slauch, 2006). At the same time Salmonella Choleraesuis was isolated from porcine intestines in 1885; Theobald Smith (1859-1934) and Damon Elder Salmon (1850-1914) described the bacterium of swine Plague in 1886 which was published in the Second Annual Report of Bureau of Animal Industry (Enersen, 2007). Finally, in 1990 a French bacteriologist, Joseph Léon Marcel Ligniéres suggested the adoption of the name “Salmonella” in honour of D.E. Salmon to encompass the entire genus (Enersen, 2007).

3. Salmonella Classification and Nomenclature
Over the years, various methods for the nomenclature and classification of the Salmonella species, subspecies, subgenera and serotypes have been proposed. Almost a century ago Kauffmann-White scheme classified Salmonella into three categories on the bases of serological identification of flagellar (H) antigens, somatic (O) antigens and virulence (Vi) capsular K antigens. In the mid-1930s, the scheme was adopted by the International Association of Microbiologist (Scherer and Miller, 2001). The antibodies agglutination specific for the various O antigens is employed to group Salmonellae into the 6 serogroups: A, B, C1, C2, D and E. For instance, S. Paratyphi A, B, C and S. Typhi express O antigens of serogroups A, B, C1 and D, respectively. Under the system currently used by the Center for Disease Control and Prevention (CDC), The World Health Organization (WHO) Collaborating Centre, and some other Salmonella reference laboratories. The genus consists of two main species based on sequence analysis differences, Salmonella enterica and Salmonella bongori (Lan et al., 2009). Salmonella enterica was further divided into six subspecies, designated by roman numerals I-VI and consist of more than 2,500 serovars or serotypes. Among all the serovars, only about 80 are frequently associated with human and animal Salmonellosis (Freitas Neto et al., 2010). Most of the strain under subspecies I are sources
from warm-blooded animals and humans while the remaining subdivisions and S. bongori usually originate from the environment.

4. Antimicrobial Definition
Antimicrobial agents can be defined as chemicals, drugs or substances that can reduce or eliminate the growth of a micro-organism (CDC, 2008a). Antibiotic resistance is defined as the ability of bacteria to stop the inhibitory (bacteriostatic) or killing (bacteriocidal) effects of antibiotics to which it is previously sensitive and effective (Lee et al., 2009). An organism can be resistant intrinsically to an antibiotic agent due to changes in the genetic constituent and it can also be susceptible naturally (Forbes et al., 2002). The antimicrobials are characterized by their specificity of targeting entities or organisms; an example is antiviral agent, antibacterial drugs and antifungal (CDC, 2008a).

In the early 20th century, penicillin was isolated from the fungus Penicillium notatum. A decade later, the mass pharmaceutical production of antibiotics started that saved many lives and transformed the beginning for modern medicine. Penicillin was widely available commercially in 1943, and the demand grew drastically. It was perceived as a miracle drug and people developed generalized expectations for a quick and rapid cure. Unfortunately, the rampaged used of the antibiotics led to the development of resistance (Levy, 2002). Over the years, there was increasing concern about the prevalence of resistance that was reported in many pathogens, spreading rapidly in different geographical regions of the world (Byarugaba, 2005). This has been as a result of selective pressures of antimicrobial use, changes in microbial characteristics, and technological changes that enhanced the modern development and transmission of drug-resistant microbes. At the same time, antimicrobial resistance is a natural occurring phenomenon, and it is often enhanced as a result of infectious etiological agents’ adaptation and exposure to antimicrobials used in humans and veterinary medicine or widespread use in agricultural farm and disinfectants at household levels (Walsh, 2000).

However, the most concerning aspect of antimicrobial resistance is the multidrug resistance of pathogens, which makes the choice of antimicrobials more difficult in the therapy of the clinical disease.

5. Mechanism of antibiotic resistance in Salmonella
The mechanisms for antibiotic resistance can be categorised as (i) modification or destruction of the antimicrobial agent, (ii) pumping the antimicrobial agent out from the cell by efflux pumps, (iii) modification or replacement of the antibiotic target, and (iv) decrease in cell membrane permeability. Thus, microorganisms are developing resistance mechanisms by developing modifications in the gene locations of target proteins or acquiring mobile genetic elements carrying resistance genes such as plasmid, integrons and transposons (Walsh, 2003). There are many classes of antimicrobial drugs, but the most common antimicrobials that Salmonella has developed resistance at the present were reviewed. They are namely; aminoglycosides, β- lactams, chloramphenicol, quinolones, tetracyclines, sulfonamides and trimethoprim.

5.1 Aminoglycosides
The aminoglycosides is active and effective against gram negative bacteria. It can also be used in combination with other antibiotics drugs to have broad-spectrum of activity (Gonzalez and Spencer, 1998). This combination may serve the sequence within 16S rRNA subunit of the 30S ribosomal (Mascaretti, 2003), where by leading to misreading codon and translation inhibition when form the binding. Majority of aminoglycosides are bactericidal by killing the bacteria, while others like spectinomycin inhibit the bacterial growth known as bacteriostatic by mode of action (Mascaretti, 2003).

There are three mechanisms by which bacteria become resistant to aminoglycosides: reduction in antibiotic uptake or decreased permeability, alteration of ribosomal binding sites and antibiotic modifications. In other enterobacteria such as E.coli, the resistance to aminoglycoside is by efflux pumps which takes out antibiotic within the cell (Aires and Nikaido, 2005; Rosenberg and Nikado, 2000). This mechanism does not play any a significant role in Salmonella aminoglycoside resistance, but facilitates its defiance against other antibiotics. Ribosomal modification has not been reported as a cause of resistance to Salmonella aminoglycosides. The Salmonella uses mechanisms such as expression of plasmid-mediated aminoglycoside modifying enzymes against aminoglycoside (Gebreyes and Altier, 2002; Guerra, 2002). According to Shaw et al., (1993), in his short review of aminoglycosides, these enzymes are categorised into three groups and are named based on reactions they perform; this includes acetyltransferases, phosphotransferases, and nucleotidyltransferases.
Aminoglycoside acetyltransferases (AAC), catalyze acetyl CoA-dependent acetylation of an amino group (Mascaretti et al., 2003; Shaw et al., 1993). There are four groups of this enzyme based on the areas that they alter: AAC (1), AAC (2'), AAC (3), and AAC (6') (Mascaretti, 2003). Also, genes encoding these enzymes are typically designated aac (Vanhoof et al., 1993). Many of this genes have been found in varieties of Salmonella subtypes, including Agona, Typhimurium, Newport, Typhimurium var. Copenhagen, Kentucky and 4,5,12:i:- (Mulvey et al., 2004; Chen et al., 2004; Doublet et al., 2004; Levings et al., 2005). The aac genes have been found as part of Salmonella genomic islands (Doublet et al., 2004), integrons (Levings et al., 2005; Pai et al., 2003), and plasmids (Guerra et al., 2001). Aminoglycoside acetyltransferases provide resistance to tobramycin, gentamicin, and kanamycin (Mascaretti, 2003).

These enzymes such as aminoglycoside phosphotransferases, catalyze ATP-dependent phosphorylation of a hydroxyl group (Mascaretti, 2003; Shaw et al., 1993). This too is classification into groups depending on the specific sites of phosphorylation. Groups APH (3') and APH (6), provide resistance to streptomycin (Mascaretti, 2003) and have been found encoded on plasmids harbored by Salmonella (Gebreyes and Altier, 2002). Most genes having these encoding enzymes are designated as aph (Vanhoof et al., 1998) and these genes, aph (3')-Ib and aph (6)-Id, are commonly known as strA and strB, respectively (Madsen et al., 2000 and Shaw et al., 1993). Salmonella serotypes Blockely, Bredeney, Agona, Anatum, Derby, Give, London, Saintpaul, Hadar, Heidelberg, and Typhimurium have been found to possess genes from both families (Madsen et al., 2000 and Pezzalla et al., 2004). Genes encoding enzymes of the APH (3') subgroup provide resistance to kanamycin and neomycin (Mascaretti, 2003), and have been found in several Salmonella subtypes such as Enteritidis, Haardt, Derby (Chen et al., 2004), Typhimurium (Gebreyes and Altier, 2002), and Typhimurium var. Copenhagen (Frech et al., 2003).

The nucleotidyl transferase is the final group of enzymes providing aminoglycoside resistance (Mascaretti, 2003, Shaw et al., 1993). These enzymes are divided into several groups based on the site of modification and also target the hydroxyl groups. Genes encoding these enzymes are usually designated aad (Vanhoof et al., 1998), some are also designated as ant. The gene aadA, is referred to as ant (3') (Shaw et al., 1993), found in Salmonella providing resistance for streptomycin (Mascaretti, 2003). Also many of these variants genes have been found in serotypes Bredeney, Derby, Agona, Anatum, Enteritidis, Give, Heidelberg, Saint Paul, and Typhimurium (Chen et al., 2004; Madsen et al., 2000; Pezzella et al., 2004). The aadB gene, also known as ant (2')-Ia (Shaw et al., 1993), confers resistance to tobramycin and gentamicin (Mascaretti, 2003). It has been found in serotypes Typhimurium and Typhimurium var Copenhagen (Carattoli et al., 2001; Antunes et al., 2005; Frech et al., 2003). Both aadA and aadB have been found in integron-borne gene cassettes (Pezzalla et al., 2004; Winokur et al., 2001).

5.2 Beta-lactams

These family groups comprised of penicillins derivatives, cephalosporins, carbapenems and monobactams (Petri, 2006; Queenan and Bush, 2007). Their mechanism of action is by interfering penicillin-binding proteins (PBPs) with a group of seven proteins. These proteins facilitate the synthesis of peptidoglycan, an important component of the bacterial cell wall. Beta lactams are generally considered bactericidal; also the activity varies among betalactams, organisms, and target PBP. Furthermore for enteric bacteria such as Salmonella and E. coli, it appears that inhibition of the essential PBPs, 1 through 3, leads to bactericidal activity. Many organisms are now becoming resistant to ampicillin and methicillin due to their wide clinical use (Angulo et al., 2000). Also, as a consequent of this, cephalosporins were developed as second class of beta lactams. There is close structural similarity between Cephalosporins and penicillins, but there have a 6, rather than a 5 member beta-lactam ring (Hornish and Kotarski, 2000). These structural differences provide cephalosporins with a wide range of efficacy and stability in the present beta-lactamases. Cephalosporins are grouped into four generations according to their spectrum of activity and the time of the agent’s introduction (Hornish and Kotarski, 2000). The increased use of the drugs for treatment has made more resistant. Carbapenems is the latest beta-lactam groups to be discovered. They are paired with beta-lactamase inhibitors sometimes, and are cross between the 5-member beta-lactam ring of penicillins and with cephalosporins extra functional group (Mascaretti, 2003). The carbapenems are more effective against gram positive and gram negative bacteria than other beta-lactam family, and are very stable against beta-lactamases, because they diffuse easily in bacteria are considered as broad spectrum β-lactam antibiotic. For this reason, their clinical used are reserved for a multidrug resistance bacteria. There is an indication of resistance to carbapenems such as imipenem by Salmonella species (Arman-Lefevre et al., 2003; Mariagou et al., 2003). At the time the beta-lactams transverse the bacterial cell wall to reach their targets PBP by using two porins OmpC and OmpF with facilitate the passage (Jaffe et al., 1982). Studies have
shown that decreases in either OmpF or OmpC porin levels have generated an increase in resistance (Bellido et al., 1989; Medeiros et al., 1987). In other report, decrease in porin content found that the reduction in OmpF and OmpD porin expression actually lead to decreased resistance to most beta-lactams other than mecillinam and imipenem in Salmonella envB mutants, this is due to the other effect of envB mutation on the organisms (Oppezzo et al., 1991).

To date, there is growing concern about more than 340 beta lactamases resistance genes, such as blaTEM, blaOXA, blaPER, blaPSE, blaSHV, blaCTX-M, and blaCMY, while some are more prevalent in Salmonella globally (Armand-Lefevre et al., 2003). In Salmonella, the secretion of a beta-lactamase is the common mechanism of resistance to beta-lactamases. These enzyme acts by hydrolyzing the structural rings of the B-lactam, by producing beta amino acids with no antimicrobial activity. In Salmonella encoding genes are found or carried on the plasmid (Mascaretti, 2003).

Ambler classification of beta lactamases is the most widely used. It divides blactamases into four classes (A, B, C and D) based upon their sequences of amino acid (Mascaretti, 2003). Moreover, in Salmonella the class A beta-lactamases are the most commonly found class of beta-lactamases. They provide a range of resistance against penicillins, cephalosporins, and carbapenems and are plasmid encoded. There are many more different gene families encoding for enzymes in this class, with TEM being the most common among Salmonella. The genes blaTEM-1 and blaTEM-52 have been found in many Salmonella serotypes including Enteritidis, Dublin, Haadrt, Muenchen, Panama and Typhimurium (Chen et al., 2004, Gebreyes and Thakur, 2005). The blaKPC-2 is a class A beta-lactamase, which is more active resistant to imipenem, was recently discovered in a Salmonella serotype Cuban isolate (Miriagou et al., 2003). The emergence of another class A beta-lactamases, known as cefotaximases (CTX-M), which confer resistance to ampicillin and cephalosporins, is of clinical importance to watch (Batchelor et al., 2005). Also in Salmonella serotypes Anatum, Enteritidis, Stanley, Typhimurium, and Virchow, BlaCTX-M variants have been identified in isolates from other European countries (Batchelor et al., 2005, Weill et al., 2004).

The class C beta-lactamases is the second most common class of beta-lactamases that provides resistance against cephalosporins such as cefoxitin and ceftriaxof that are encoded by chromosomal ampC genes. These genes are harbored in plasmids carried by Salmonella instead Salmonella carries no chromosomal ampC gene, (Morosini et al., 2000). However, more research is primarily focused on blaCMY-2 which is presence and has been associated with resistance to ceftriaf (Alcaine et al., 2005). Ceftriaxof is a group of third generation cephalosporin and are closely related to ceftriaxone. The resistant to this drugs and the spread of the gene is a public health problem worldwide as ceftriaxone is a drug choice for treating Salmonella infection in infant. Likewise many Salmonella serotype such as Typhimurium, Agona, and Newport (Alcaine et al., 2005, Doublet et al., 2004), have been found to carry this resistance genes (Alcaine et al., 2005, Winokur et al., 2000).

The Class B beta-lactamases like Metallo-beta-lactamases, this enzyme provides resistance to all beta-lactam antibiotics, including carbapenems (imipenem) and are usually encoded chromosomally, though plasmid mediated class B beta-lactamases, such as IMP-1 and VIM-1, do exist (Mascaretti, 2003). These Class B beta-lactamases are not commonly found in Salmonella. At last Class D beta-lactamases are uncommon among Salmonella. This class of enzymes provides resistance to lactams closely related to oxacillin, such as cloxacillin and methicillin. The gene blaOXA-1 was found in a Salmonella serotype Paratyphi (Cabrera et al., 2004) and blaOXA-30 has been found in serotypes Muenchen and Typhimurium (Antunes et al., 2004; Hanson et al., 2002).

5.3 Chloramphenicol

Chloramphenicol is specific and potent inhibitor of protein by binding to the peptidytransferase center of the 50s ribosomal unit, thus preventing formation of peptide bonds (Mascaretti, 2003). As a result of the binding to enzymes, the drugs will prevent elongation of the peptides.

Chloramphenicol is a broad-spectrum antibiotic against both the gram negative and gram positive bacteria and it is effectiveness and ability to cross the blood-brain barrier makes it the drugs of choice for systematic infections therapy. The most serious adverse effect of the drugs can cause damage in bone marrow and aplastic anemia. Chloramphenicol is being use in human and veterinary medicine for the treatment of Salmonellosis for a long
time and has now given rise to resistance strains. There are two mechanisms in which *Salmonella* resistance to chloramphenicol is conferred: (i) by the plasmid-located enzymes called chloramphenicol acetyltransferases (CAT) or nonenzymatic chloramphenicol resistance gene cmlA and (ii) Efflux pump in which the antibiotic is removed. *Salmonella* Typhi isolates have been found to encoding genes for CAT and are plasmid-borne (Guerra et al., 2000; Shanahan et al., 2000). However, CAT genes, such as *cat1* and *cat2*, have also been found in *Salmonella* serotypes such as Derby, Haardy, Enteritidis and Typhimurium (Chen et al., 2004). The *cmlA* (Cabrera et al., 2004) and *floR* (White et al., 2001) are closely related genes encoded in Chloramphenicol eflux pumps in *Salmonella* that have been reported. Also *floR* genes appear to be very widespread in *Salmonella*, whereas *cmlA* is less widely distributed. There are various *Salmonella* serotypes such as Agona, Kiambo, Albany, Newport, Typhimurium, Typhimurium var Copenhagen that have been found to carry *floR* (Alcaine et al., 2005; Cabrera et al., 2004; Doublet et al., 2004; Meunier et al., 2003). This genes has been found in *Salmonella* genomic islands (Weill, et al., 2005); as well as in many different plasmids due to a highly mobility (Meunier et al., 2003), and closely associated with multi-drug resistance (Alcaine et al., 2005; Doublet et al., 2004) most likely due to its presence on plasmids carrying multiple resistance genes.

5.4 Quinolones

There are many generations of quinolones, which are more effective against bacterial infection. However, their mode of action varies, the early and late generation of quinolones target DNA gyrase and DNA topoisomerase IV (Mascaretti, 2003).

Quinolone’s mechanism of action is quite complex and not well comprehended (Mascaretti, 2003). Many studies have indicated that quinolones target topoisomerases. The antibiotic does not actually bind to the topoisomerase, but to the double stranded DNA in the topoisomerase complex (Shen and Pernet, 1985). While there are reports of *Salmonella* with low-level resistance to other Quinolones and resistance to nalidixic acid (Breuil et al., 2000; Molbak et al., 1999), a high-level resistance to quinolones is still rare (Olsen et al., 2001).

*Salmonella* resistance to quinolone has been classified into to two mechanisms. The first is the two *gyrA* and *gyrB*, genes which encode for the subunits of DNA gyrase, will be targeting mutations in the quinolone resistance-determining region (QRDR), and in the *parC* subunit of topoisomerase IV (Baucheron et al., 2004; Casin et al., 2003; Levy et al., 2004). Also the second mode of action involves changes in the AcrAB-ToIC efflux system expression, as a result of mutations in the regulator genes of this system, that due to over expression of this efflux system (Koutsoliotouou et al., 2001; Levy et al., 2004; Olliver et al., 2005), which make quinolone sensitivity decreased. However, it is an accumulation of all these mutations that provides resistance, because no one mutation confers high-level resistance to quinolones (Heisig, 1993). At the present time, acquiring multiple of unlinked mutations by *Salmonella* are necessary, and that some of those mutations reduce fitness, particularly those involved in the regulation of the efflux pump (Giraud et al., 2003). While in some bacterial organism, such as *E. coli* and *Klebsiella pneumonia* (Wang et al., 2004), the expression of a plasmid mediated gene called *qnr* has also been linked to quinolone resistance (Li et al., 2005). The gene expresses a protein that appears to bind to DNA-gyrase and protect it from quinolone inhibition (Li et al., 2005). The study conducted on plasmids harboring *qnr* showed that it could be transferred via conjugation from other bacterial species to *Salmonella* (Martinnez et al., 2005). While a recent study indicated that the spread of such plasmids to *Salmonella* has occurred and plasmid-mediated quinolone resistances in *Salmonella* are rare (Cheung et al., 2005). The occurrence of plasmid-mediated quinolone resistance in *Salmonella* appears to be a very important emerging public health concern globally. Other resistance genes have been found harboring plasmids *qnr* in *Salmonella* (Martinnez-Martinnez et al., 1998).

5.5 Tetracycline

Tetracycline is clinically known as broad spectrum antibiotic and is effective against many gram positive and negative bacteria such as chlamydias, mycoplasms, and even some protozoa (Chopra and Roberts, 2001; Mascaretti, 2003). Tetracyclines mostly act by stopping the binding of tRNA to the A site of the 30S ribosomal subunit by inhibiting protein synthesis (Mascaretti, 2003). However, the rise of antibiotic resistant bacteria has severely limited the use of tetracycline. Many finding indicated that tetracycline resistance in *Salmonella* can be attributed to the production of an energy dependent efflux pump to remove the antibiotic from within the cell. The modification of the ribosomal target, enzymatic inactivation of tetracycline, and other mechanism of resistance, have been documented in other bacterial species but has yet to be reported in *Salmonella* (Chopra and Roberts, 2001; Mascaretti, 2003).
In *Salmonella* several different tetracycline (*tet*) genes have been discovered as conferring resistance to tetracyclines in *Salmonella* serotypes. The most common types of *tet* genes belong to classes A, B, C, D, and G (Chopra and Roberts 2001). Also the *tet* (G) gene was found in *salmonella* genomic island 1, located within the *S. enterica* serotype Typhimurium DT104 chromosome (Boyd et al., 2001; Cloeckaert and Schwarz, 2001). The *tet* (A) gene was found on plasmids as well as on the chromosome, whereas the genes *tet*(B), *tet*(C), and *tet*(D) were identified on the chromosomes of many *Salmonella enterica* serotypes, including Typhimurium, Saintpaul, Enteritidis, Hadar and Choleraesuis (Freh and Schwarz, 2000). It has been found in serotypes Agona, Anatum, Blockley, Bredeney, Colorado, Derby, Give, Haardt, Heidelberg, Infantis, Orion, Settenberg, (Chen et al., 2004; Pezzella et al., 2004). The *tet*(B) gene is very common. It has been found in serotypes Agona, Dublin, Choleraesuis, Heidelberg, Typhimurium (Chen et al., 2004; Freh and Schwarz, 2000; Guerra et al., 2002). Like *tet*(A), *tet*(B) genes has also been located on transferable plasmids (Guerra et al., 2002). These genes are easily transferred and are wide spread among *Salmonella*. Also, most are tend to be found in isolates that having multi-drug resistance (Carattoli et al., 2002; Chen et al., 2004; Pezzella et al., 2004), making them an important identification marker in identifying potentially serious of the *Salmonella* infections.

### 5.7 Sulfonamide and trimethoprim

These classes of antibiotics are bacteriostatic and it mode of action is by competitively inhibiting enzymes involved in the synthesis of tetrahydrofolic acid. Sulfonamides inhibit dihydopteroate synthetase (DHPS), while trimethoprim inhibits dihydrofolate reductase (DHF) (Mascaretti, 2003). The resistance of *Salmonella* to sulfonamide has been attributed to the presence of an extra *sul* gene which expresses an insensitive form of DHPS (Antunes et al., 2005; Mascaretti, 2003). The *sul1*, *sul2*, and *sul3* are the three main genes have been indentified; The gene *sul1* has been harbored by a wide range of *Salmonella* serotypes such as Enteritidis, Hadar, Heidelberg, Orion, Rissen, Agona, Albany, Derby, Djugu, and Typhimurium (Antunes et al., 2005; Chen et al., 2004; Doublet et al., 2004). The class I integrons that contain other resistance gene, have often been associated with this genes (Guerra et al., 2002; Sandvang et al., 1998). At time these integron gene cassettes have been located on transferal plasmids (Guerra et al., 2002) and as part of *Salmonella* genomic island variants (Boyd et al., 2002; Doublet et al., 2004). While sometimes discovered in isolates also harboring *sul1* (Antunes et al., 2005; Chen et al., 2004), *sul2* appears to relate with plasmids, but not class I integrons (Antunes et al., 2005). Many *Salmonella* serotypes Enteritidis, Agona, and Typhimurium isolates have been found harbouring *sul2* (Chen et al., 2004).

Also *sul3* has only been recently known to be associated with plasmids and class I integrons in *Salmonella* (Guerra et al., 2002; Antunes et al., 2005). *sul3* has already been found in many serotypes 4,5,12:i:-, Anatum, Bradenburg, Heidelberg, Rissen, Agonaad Typhimurium (Antunes et al., 2005, Guerra et al., 2002). Trimethoprim resistance is attributed to the activity of DHFR (Mascaretti, 2003). Serotypes known to have trimethoprim resistance genes are 4,5,12:i:-; Agona, Djugu, Hadar, Neport, Rissen Albany, Derby, and Typhimurium (Antunes et al., 2006; Doublet et al., 2004; Doublet et al., 2003; Martinez et al., 2005). Likewise, these genes have been found as part of integron-borne gene cassettes also associated with *sul1* and *sul3* (Antunes et al., 2005), on transferable plasmids carrying other resistance genes (Villa and Carattoli, 2005), and *Salmonella* genomic islands (Doublet et al., 2004).

### 6. Integrons

These are two component gene capture and dissemination system, initially discovered in relation to antibiotic resistance and are found in plasmids, chromosomes and transposons. The elements are divided in to three (3) classes based on the general gene arrangement that they encode and IntI integrase. Before 2001, there were only four classes of integrons which had been known, mainly from clinical isolates. These are integrons class-1, class-2, class-3 and class-4 (Mazel and Davies, 1998; Stokes and Hall 1989; Collis et al., 2002). The most prevalent integrons among clinical strains are Class-1 integrons (Fluit and Schmitz, 1999). They are unique and characterized by the presence of two conserved sequences, known as the 5’CS and 3’CS, which flank a variable region (Bennett, 1999). The essential component of class I integrome are integrase gene (IntI1) and a gene cassette attachment site (attI) are contained in the 5’-conserved region. The 3’-conserved region is identified by the presence of a sulphonamides resistance gene (sul1), a quaternary ammonium compound resistance gene (qacEΔ1), and open reading frames orf5 and orf6, with unknown functions. The class-1 integrons can code for one or more gene cassettes in the variable region (Hall and Stokes, 1993).
The presence of class 1 integron have been reported in several *Salmonella* serotypes, such as *Salmonella* serotypes Typhimurium, Enteritidis, Ohio, Panama, Virchow, Hadar, and Muenhen (Guerra et al., 2000). The development of multidrug resistance depends on the capacity of integrons to cluster the gene cassettes and to express antimicrobial resistance genes. Mostly integrons are not mobile by themselves, but may be integrated into transposable elements, such as Tn1696 or located on plasmids, and then can be spread with these elements (Schwarz et al., 2006). Antunes et al. (2006) have reported the presence of class 1 and 2 integrons in *Salmonella* serotypes Typhimurium, Enteritidis, Muenhen, Rissen, Derby, Saintpaul, Heidelberg, Bredeney, Brandenburg, Brikama and IIIb: 65:1v:enxz15 isolated from humans, food products and environment.

7. Antibiotic resistance *Salmonella*

The misuse of antimicrobial agents as chemotherapy in human and veterinary medicine or as growth promoter in food animals can potentially lead to widespread dissemination of antimicrobial resistance *Salmonella* and other pathogens via mobile genetic elements (Bouchrif et al., 2009). Recent findings showed the consequences of antibiotic resistant on human health. These consequences can be divided into two categories: first, the infections that may not have occurred and secondly, the high incidence of treatment failures and increase in the severity of disease (WHO, 2009). Moreover, resistance can spread from non-human sources to human by various routes such as animal, water and contaminated foods. However, contact with *Salmonella* carrier animal is the most important pathway in transmission of resistance to humans. Resistance to combinations of many classes of antimicrobial agents in *Salmonella* has led to the re-emergence of multidrug resistance *Salmonella* (MDR) strains that may pose a risk to humans (White et al., 2001; O’Brien, 2002). Many research indicate that in the last two decades the occurrence of MDR strains in different *Salmonella* serovars. Also, MDR *Salmonella* strains have been found to be of many serotypes such as Agona, Anatum, Pullorum, Schwarzengrund, Choleraesuis, Derby, Dublin, Heidelberg, Kentucky, Newport, Senftenberg, Typhimurium, and Uganda (Chen et al., 2004; Gebreyes and Thakur, 2005; Zhao et al., 2008). Nowadays, interest in antimicrobial resistance *Salmonella* has increased. The emergence and persistence of antibiotic resistance in *Salmonella* spp. continue to pose serious risks to human health (Joseph et al., 2008). The most common *Salmonella* serotype having multidrug resistance is *S. Typhimurium* definitive phage type DT104 found to display a phenotype of resistance to ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline (ACSSuT), these are the most common drug classes used in veterinary medicine (Mulvey et al., 2006). Later follow by other serotypes such as *S. Typhi*, *S. Paratyphi*, *S. Infantis*, *S. Uganda*, *S. Agona*, and *S. Newport*, *S. Hadar*, *S. Heidelberg* are exhibited multidrug resistance in addition to *S. Typhimurium* (Holt et al., 2007; Nógrády et al., 2007; Zhao et al., 2007).

8. Conclusions

Regular epidemiological studies may help in monitoring the occurrence of salmonellosis and in developing firm strategies for its prevention. The knowledge and understanding about factors that contribute to the occurrence, distribution and establishment of the *Salmonella* disease may be helpful in eliminating its survival in the environment, thereby protecting and promoting public health. Other important preventive measures include improvements in sanitation, availability of clean drinking water, promotion of safe food handling practices, and public health education. In view of the re-emergence of sensitivity to first-line drugs, large-scale systematic studies are required to determine whether these drugs can again be used for the treatment of Salmonellosis in developing countries. The occurrence of antibiotic resistances in the *Salmonella* is worrisome as it could pose a risk to animal and human health.

References


