Chapter 35

Mechanisms of antimicrobial resistance in *Salmonella*

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ABSTRACT
Salmonella enterica subsp. *enterica* is considered one of the most common causes of foodborne illness (FOBD) and animal products are responsible for a significant number of human cases of salmonellosis. In addition to the risk posed by *Salmonella* as a foodborne pathogen, there is worldwide concern about the emergence of strains resistant to multiple antimicrobial agents. Over the years, several studies have identified genes and mutations conferring antimicrobial resistance in *Salmonella* isolates, which will be discussed in this chapter.

Keywords: cephalosporins, fluoroquinolones, tetracyclines, resistance genes, plasmids, integrons.

1 INTRODUCTION

Treatment of *Salmonella* infections in both animals and humans has been hampered due to the emergence of strains resistant to multiple antimicrobial agents. Fluoroquinolones, such as ciprofloxacin, and third-generation cephalosporins, such as ceftriaxone, are commonly used to treat severe infections caused by *Salmonella. According to* the annual report of the United States National Resistance Monitoring Program, 13.8 % (65/471) of isolates of *S*. Enteritidis, a major serovar involved in Foodborne Diseases (FOD), have reduced susceptibility to ciprofloxacin (NARMS, 2015). Resistance to ceftriaxone is observed in 2.7 % of non-typhoidal *Salmonella* isolates, and is most common in serovars Dublin (66.7 %), Childs (6.9 %) and 4,[5],12:i:- (6.0 %) (NARMS, 2015). As fluoroquinolones and cephalosporins are the antimicrobials of choice for the treatment of salmonellosis, the emergence of resistance to these two classes are of great public health importance.

In recent years, an increase in the prevalence of multi-resistant *Salmonella* strains has been a global problem. In the US, the percentage of non-typhoidal *Salmonella* isolates exhibiting resistance to three or more classes of antimicrobials amounts to 12.5% (NARMS, 2015). The Typhimurium serovar belonging to phage type DT104 was identified in the 1990s as a multi-resistant clone associated with antimicrobial

use in animals (THRELFALL, 2000). This phage exhibits resistance to five antimicrobials: ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracyclines (ACSSuT phenotype). The genes responsible for the resistance phenotype are bla_{PSE}, *floR*, *aadA2*, *sul1* and *tet*(G), respectively. Multi-resistance is associated with the presence of the chromosomal multi-resistance island called *Salmonella Genomic Island* 1 (SGI1) (MULVEY et al., 2006). According to the NARMS annual report, the prevalence of the ACSSuT resistance profile among *S.* Typhimurium isolates is 10.8 % in the USA (NARMS, 2015).

Another public health concern is the emergence of *S. enterica* serovar 4,[5],12:i:- showing resistance to four antimicrobials: ampicillin, streptomycin, sulfonamides, and tetracyclines (ASSuT). *Salmonella* 4,[5],12:i:- is considered the monophasic variant of *S.* Typhimurium (4,[5],12:i:-1,2) due to the great antigenic and genotypic similarity (ECHEITA et al., 2001; ZAMPERINI et al., 2007). The monophasic variant has been involved in several outbreaks, with reports of severe infections and deaths in humans (MOSSONG et al., 2007). In the USA, the emergence of the ASSuT profile among isolates of the monophasic variant 4,[5],12:i:- has seen a considerable increase in recent years, from 1 % in 2006 to 59.1 % in 2015 (NARMS, 2015). The monophasic variant of *S.* Typhimurium is considered pandemic in Europe and pigs are recognized as the main reservoir (HOPKINS et al., 2010). In Denmark, the proportion of isolates from pork showing the ASSuT profile increased from 17 % to 56 % (DANMAP, 2012).

The use of antimicrobials in production animals plays an important role in the development of antimicrobial resistance in zoonotic bacteria such as *Salmonella*. Outbreaks of human salmonellosis by multi-resistant strains have been caused by consumption of contaminated food or direct contact with infected animals. Isolates of *S.* Typhimurium DT104 obtained during an outbreak in Denmark were resistant to six classes of antimicrobials. These isolates were associated with the consumption of *carpaccio* (thin slices of raw beef) served in a restaurant (ETHELBERG et al., 2007). An outbreak of *S.* Typhimurium DT104 related to the consumption of cured meat affected 16 people in London and the isolates showed the characteristic penta-resistance profile (MINDLIN et al., 2013). In France, an outbreak involving the monophasic variant 4,[5],12:i:- resistant to ampicillin, streptomycin, sulfonamides and tetracyclines was associated with the consumption of pork sausage (GOSSNER et al., 2012). Thus, *Salmonella* strains presenting multi-resistance profiles represent a public health risk.

To monitor and control the spread of multi-resistant strains of *Salmonella,* it is essential to understand the mechanisms responsible for the development of resistance and how transmission occurs between these strains. The development of resistance to antimicrobial agents is attributed to several mechanisms such as: changes in the permeability of the bacterial cell wall, which restrict the access of the antimicrobial agent to the target; active efflux of the antimicrobial agent from within the bacterial cell; enzymatic modification of the antimicrobial agent; degradation of the antimicrobial agent; acquisition of an alternative metabolic pathway to the one inhibited by the antimicrobial agent; modification in the target of the antimicrobial agent; and overproduction of the target enzyme. Since resistance is considered a process

of bacterial evolution, other as yet unknown resistance mechanisms may be involved in resistance in *Salmonella*.

2 RESISTANCE OF *SALMONELLA* TO DIFFERENT CLASSES OF ANTIMICROBIALS

2.1 RESISTANCE TO Β-LACTAMS

Agents of the β-lactam class are widely used to treat a variety of infections caused by Gram-positive and Gram-negative microorganisms in both human and veterinary medicine. There are numerous classes of β-lactams including penicillins, cephalosporins, carbapenems, and monobactams (WORTHINGTON & MELANDER, 2013). In the European Union, penicillins, aminopenicillins and first to fourth generation cephalosporins are subgroups authorized for use in animals, and penicillins are often used in combination with β-lactamase inhibitors such as clavulanic acid (EFSA, 2011). In Brazil, there are no restrictions on the therapeutic use of β-lactams in animals, only the monitoring of residues in tissues of pigs, poultry, cattle and horses. However, the Brazilian legislation prohibits their use as zootechnical performance-enhancing additives or as preservatives in animal feed (BRASIL, 2009).

The β-lactams act by inhibiting bacterial cell wall synthesis through binding to the so-called *penicillin-binding proteins* (PBPs), which are responsible for cross-linking the cell wall peptideoglycan. Four mechanisms of resistance to β-lactam agents have been described: 1) alteration of penicillin-binding proteins (PBPs); 2) alteration of bacterial outer membrane permeability; 3) active efflux of the antimicrobial through the cell, and 4) production of β-lactamase enzymes (LLARRULL et al., 2010).

The production of β-lactamase enzymes is one of the most important mechanisms of resistance to β-lactams in Gram-negative bacteria (POOLE, 2004). Some β-lactamases are associated with certain bacterial species while others are spread among different bacterial species and genera. Some have a restricted spectrum of activity against a limited number of antimicrobial agents, while broad-spectrum or extended-spectrum β-lactamases are capable of degrading a wide range of antimicrobials (ARLET et al., 2006). There are several classification systems for β-lactamase enzymes, two of them being widely used: the Bush, Jacoby and Medeiros (BJM) classification based on functional and structural characteristics of the enzymes (BUSH et al., 1995); and the older classification, Ambler's, based on the molecular structure of β-lactamase enzymes according to the amino acid sequence (AMBLER, 1980).

Among the β-lactamase enzymes, the so-called *extended-spectrum beta-lactamases* (ESBL) are able to promote resistance to important subclasses of β-lactam agents such as penicillins (ampicillin, amoxicillin), cephalosporins (cefotaxime, ceftazidime and ceftriaxone) and monobactams (aztreonam), through the hydrolysis of the β-lactam ring. However, they are not able to hydrolyze cephamycins and carbapenems and are inhibited by β-lactamase inhibitors such as clavulanic acid (EFSA, 2011). ESBLs belong to group 2be according to the functional classification of Bush, Jacoby and Medeiros and to class A according to the molecular classification of Ambler (AMBLER, 1980; BUSH et al., 1995). The most

frequently encountered ESBLs belong to the TEM, SHV and CTX-M families and the genes are commonly located in plasmids. Since β-lactam agents play an important role in infection control in animals and humans, isolates producing ESBLs represent a public health risk and have been associated with economic losses in animal production (CANTÓN et al., 2012).

The first ESBLs found were derived from genes encoding broad-spectrum β-lactamases such as TEM-1 and SHV-1, which were discovered around 1960 (PATERSON & BONOMO, 2005). Due to mutation points in TEM and SHV, β-lactamases have expanded from only broad-spectrum penicillinases and cephalosporinases to extended-spectrum β-lactamases (BRADFORD, 2001). Among the TEM-type β-lactamases, those encoded by the genes *blaTEM-1* and *blaTEM-135* represent the broad-spectrum penicillinases and cephalosporinases and belong to class 2b. Other genes, such as *bla*$_{TEM-3}$, *bla*$_{TEM-4}$, *blaTEM-20, blaTEM-25, blaTEM-27, blaTEM-52, blaTEM-63, blaTEM-131*, *blaTEM-144*, *blaTEM-149* and *blaTEM-188* belong to class 2be and encode extended-spectrum β-lactamases. Among the SHV-type β-lactamases found in *Salmonella* are the *bla* genes$_{SHV-2}$, *blaSHV-2a*, *bla*$_{SHV-5}$, *blaSHV-9* and *blaSHV-12*.

TEM- and SHV-type ESBLs were the predominant variants during the 1980s and 1990s, found mainly in *Klebsiella pneumoniae*, *E. coli* causing nosocomial infections and other genera of the *Enterobacteriaceae* family (PATERSON & BONOMO, 2005). Since 2000, CTX-M type enzymes have become the most prevalent ESBLs (CANTÓN et al., 2012; ZHAO & HU, 2013). In contrast to TEM- and SHV-type ESBLs, CTX-M enzymes exhibit greater hydrolytic activity against cefotaxime than against cefotazidime. The family of CTX-M-type β-lactamases includes at least six groups: CTX-M1, CTX-M2, CTX-M8, CTX-M9, CTX-M25 and KLUC, which differ from each other in at least 10 % of amino acid residues (D'ANDREA et al., 2013). Currently, more than 150 variants of the CTX-M group have been described. The *blaCTX-M* genes found in clinical isolates of *Enterobacteriaceae* are usually located on large conjugative plasmids (ZHAO & HU, 2013), although in some strains they have been found on chromosomal DNA.

AmpC-type β-lactamases are cephalosporinases encoded by chromosomal or, more recently, plasmid genes in many Gram-negative bacteria. These enzymes determine resistance to penicillins and cephalosporins and can hydrolyze cephamycins (cefoxitin), oximinocephalosporins (ceftazidime, cefotaxime and ceftriaxone) and monobactams (aztreonam), with the exception of fourth generation cephalosporins and carbapenems (LIEBANA et al., 2013). In contrast to other ESBLs, β-lactamases of the AmpC type are not inhibited by clavulanic acid. Resistance to cephalosporins occurs due to mutations in the *bla* gene$_{AmpC}$, resulting in over-expression of the enzyme. Bacteria lacking the chromosomal *bla* gene$_{AmpC}$ *,* can acquire it through conjugative plasmids (JACOBY, 2009). Different families of AmpC-type β-lactamases have been described: CMY, ACC, ACT, DHA, FOX, MIR and MOX. Among the acquired AmpCs, CMY-2 is the most frequently reported (LIEBANA et al., 2013). Many of these enzymes have already been found in isolates of the *Enterobacteriaceae* family from farm animals and food .

2.2 TETRACYCLINE RESISTANCE

Since the discovery of chlortetracycline produced by *Streptomyces aureofaciens* in 1948, several tetracyclines have been identified occurring naturally mainly in *Streptomyces* species (oxytetracyclines and tetracyclines) or as semi-synthetic products (doxycycline and minocyclines) (CHOPRA & ROBERTS, 2001). Tetracyclines have become popular due to their minimal adverse effects and broad spectrum of action. They exhibit activity against Gram-negative and Gram-positive bacteria, both aerobic and anaerobic. They have a bacteriostatic effect by preventing the binding of tRNA to the 30S subunit of the bacterial ribosome, resulting in the inhibition of protein synthesis (PAVELQUESI et al., 2021). Although tetracyclines play an important role in human and veterinary medicine, the emergence of resistance has limited their effectiveness. In Brazil, the use of tetracycline is prohibited as a zootechnical performance-enhancing additive or as a preservative for animal feed (BRASIL, 2009).

Tetracycline resistance in most bacteria is due to the acquisition of mobile genetic elements, mutations in the ribosome binding region, and chromosomal mutations allowing for increased expression of intrinsic resistance mechanisms. The three main mechanisms of tetracycline resistance include efflux pumps, production of ribosomal protection proteins (RPPs), and enzymatic inactivation of the drug (ROBERTS & SCHWARZ, 2016; PAVELQUESI et al., 2021). Initially, tetracycline resistance genes were given the name *tet* followed by letters of the Roman alphabet, such as *tet*(A) or *tet*(B). However, the number of *tet genes* employed all letters of the alphabet and to accommodate new genes, a nomenclature employing numbers was introduced. A *tet* gene is identified as novel when it exhibits < 79 % identity in amino acid sequence with all previously described genes (CHOPRA & ROBERTS, 2001).

More than 60 *tet* genes conferring resistance to tetracyclines and three *ort genes* conferring resistance to oxytetracyclines, termed *ort*(A), *ort*(B) and *ort*(C), have been described to date (http://faculty.washington.edu/marilynr/tetweb4.pdf). Among these determinants, 35 *tet* genes, two *ort genes* and one *tcr3 gene* encode efflux pumps, while 11 *tet genes* and one *ort gene* encode ribosomal protection proteins and 14 *tet* genes are responsible for the enzyme inactivation mechanism (http://faculty.washington.edu/marilynr/tetweb1.pdf). The genes encoding efflux pumps and ribosomal protection proteins are found in Gram-negative, Gram-positive, aerobic and anaerobic bacteria. The enzyme inactivation mechanism has been observed only in Gram-negative microorganisms (ROBERTS & SCHWARZ, 2016).

In *Salmonella*, the active efflux system is the most commonly observed resistance mechanism. According to the review by Pavelquesi et al. (2021), the most investigated tetracycline resistance genes are *tet*(A) with 21 studies (94.5%), *tet*(B) with 19 studies (86.4%), *tet*(C) with 11 studies (50%) and *tet*(G) with 10 studies (45.5%), while the least researched are *tet*(D) with 3 studies (13.6%) and *tet*(E) with 2 studies (9.1%). Among multi-resistant *Salmonella* serovars obtained from animals, food and humans in the United States and Canada, the tetracycline resistance genes found were *tet*(A), *tet*(B), *tet*(C) and *tet*(D), with *tet*(A)

being detected in 80% of isolates (GLENN et al., 2013). Zhang et al. (2019) reported that among 105 tetracycline-resistant *Salmonella* isolates, the *tet*(A) gene was the most frequently detected (80.9%) and only 4.8% of isolates carried the *tet*(B) gene.

Many tetracycline resistance genes are located in mobile genetic elements. In Gram-negative bacteria, *tet* genes are often located on large conjugative plasmids, which may explain the wide spread of these genes among bacteria (SHEYKHSARAN et al., 2019 ~~HENTSCHKE et al., 2010~~). Transposons, such as Tn10 carrying the *tet*(B) gene and Tn1721 carrying the *tet*(A) gene, have also been described in members of the *Enterobacteriaceae* family, including *Salmonella* (PASQUALI et al., 2005). The *tet*(G) gene has been detected as a component of the *Salmonella* Genomic Island (SGI-1) associated with the multi-resistance *cluster* that was first described in *S*. Typhimurium DT104 (MULVEY et al., 2006). *Tet* genes have also been identified in integrative and mobilizable elements such as ICEPmu1 from *Pasteurella multocida* and ICEMh1 from *Mannheimia haemolytica* (MICHAEL et al., 2012; EIDAM et al., 2015).

The regulation of *tet* gene expression is often associated with a repressor protein of the TetR family. In the absence of tetracycline, the repressor protein binds directly to the *tet* gene, blocking transcription of both the efflux protein and the repressor protein. When tetracycline is present, the tetracycline-Mg complex^{2+} enters the cell and binds to the TetR protein, allowing tetR-associated gene expression to occur (CHOPRA & ROBERTS, 2001).

2.3 AMINOGLYCOSIDE RESISTANCE

Aminoglycosides are antimicrobials that bind to the 30S fraction of ribosomes preventing the correct reading of messenger RNA and the corresponding protein synthesis (VAKULENKO & MOBASHERY, 2003). They have a broad spectrum of action and present synergism with other antimicrobial agents. In the mid-1940s, the first aminoglycoside, streptomycin, obtained from *Streptomyces griseus,* was discovered and successfully used in the treatment of tuberculosis. After the initial discovery of streptomycin and its success in clinical practice, several aminoglycosides were characterized, such as neomycin (1949), kanamycin (1957), gentamicin (1963), and tobramycin (1967) (BECKER & COOPER, 2013).

Resistance to aminoglycosides is widespread among microorganisms and can be caused by i) active efflux, ii) decreased cell permeability, iii) alteration in ribosomes, and iv) inactivation of the drug by enzymes (VAN HOEK et al., 2011). Enzymatic modification is the most common mechanism of resistance to aminoglycosides. Depending on the type of modification, enzymes are classified into aminoglycoside-acetyltransferases (AAC), aminoglycoside-adenyltransferases (AAD) (also known as aminoglycoside-nucleotidyltransferases [ANT]) and aminoglycoside-phosphotransferases (APH) (BECKER & COOPER, 2013).

Different naming systems for aminoglycoside-modifying enzymes (AMEs) can be used. The first refers to the enzyme action and consists of three letters (AAC, ANT, APH), followed by a number in

parentheses identifying the site of modification and then a Roman numeral to designate the subclass or subtype, e.g. AAC(3)-IIa. The other naming system refers to the coding gene, using three lowercase italicized letters for each type of activity (*aac, aad, aph*), a capital letter to identify the site of modification, and a number for the subtype of the gene. The designation *aph(3")-Ib,* for example, refers to the type of modification (*aph* for aminoglycoside-phosphotransferase), the position where the modification is introduced (*3"*) and also lists the subtype of the gene (*Ib*). The *strA* designation, used for the same gene, is an alternative nomenclature that is based only on the corresponding resistance phenotype (*str* for streptomycin resistance) and the subtype of the gene (A) (MICHAEL et al., 2006).

There are four classes and numerous subclasses of the AACs enzymes: AAC(1), which has no subclasses; AAC(3)-I to X; AAC(2')-I and AAC(6')-I to IV (BECKER & COOPER, 2013). Among these four different classes of N-acetyltransferases, only those that induce acetylation at position 3' [AAC(3)] and 6' [AAC(6')] have been detected in *Salmonella* isolates (MICHAEL et al., 2006). The gentamicin resistance genes *aac(3)-IIa*, *aac(3)-III* and *aac(3)-IV* are examples of genes belonging to the AAC(3) family detected in *Salmonella* (LIM et al., 2013; BEUTLICH et al., 2013). The enzyme with the greatest clinical relevance within the AAC(6') class is encoded by the *aac(6')-Ib* gene. It is present in 70 % of Gram-negative isolates carrying *aac(6')-I-*, causing resistance to amikacin, sisomycin, tobramycin and netilmicin (BECKER & COOPER, 2013). In *Salmonella,* the *aac(6')-Ib gene* was identified in gene cassette inserted into class 1 integron (LAI et al., 2013).

The aminoglycoside-phosphotransferases (APH) enzymes, encoded by *aph* genes, are responsible for the phosphorylation of hydroxyl groups on aminoglycosides, resulting in a dramatic change in their ability to bind to ribosomes. Seven classes and some subclasses of these enzymes, APH(2")-I to IV, APH(3")-I to VII, APH(3")-I, APH(4)-I, APH(6)-I, APH(7")-I and APH(9)-I have been identified (VAKULENKO & MOBASHERY, 2003; BECKER & COOPER, 2013). Only those whose phosphorylation occurs at position 3', 3" and 6 have been identified in the genus *Salmonella*. The *aph(3')-IIa* gene*,* responsible for the kanamycin and neomycin resistance phenotype, was recently identified among *Salmonella* isolates in Austria, as was the *aph(3')-IIIa* gene, which confers additional resistance to amikacin (WOEGERBAUER et al., 2014). The aph*(3")-Ib* (also known as *strA*) and *aph(6)-Id* (also known as *strB*) genes are responsible for resistance to streptomycin only. The *aph(3")-Ib* was the most commonly found gene among isolates of clinical origin belonging to the *Enterobacteriaceae* family, with a prevalence of 65.4 % (MIRÓ et al., 2013). Often, these genes are found physically linked to each other and preceded or followed by the *sul2 gene*, responsible for promoting resistance to sulfonamides (YAU et al., 2010; ANANTHAM & HALL, 2012).

The aminoglycoside adenyltransferases (AAD) enzymes (also known as aminoglycoside-nucleotidyltransferases [ANTs]) are divided into five classes: ANT(2"), ANT(3"), ANT(4'), ANT(6), and ANT(9). There are no subclasses with the exception of ANT(4"), which includes subclasses I and II.

Although they are the smallest family of SMAs, they have great clinical importance because they confer resistance to tobramycin, amikacin and gentamicin (BECKER & COOPER, 2013). In *Salmonella*, those genes whose products act at positions 3' [*aadA*, *ant(3'')*] and 2'' [*aadB*, *ant(2'')*] are frequently identified. In the *aadA* group, which confers resistance to streptomycin and spectinomycin, at least 12 subtypes have been reported among *Salmonella* isolates and are available in the database: *aadA1*, *aadA2, aadA4*, *aadA5, aadA6, aadA7, aadA12, aadA21, aadA22, aadA23,* aadA24, *and aadA26* (www.ncbi.nlm.nih.gov/). Many of these genes are found in gene cassettes located in integrons. In *Salmonella* serovar 4,[5],12:i:2-, the *aadA1* and *aadA2* genes were found as gene cassettes located in class 1 integrons, which in turn were located in IncA/C-type plasmids (GARCÍA et al., 2011). Pérez-Moreno and colleagues (2013) reported the presence of the genes *aadA1, aadA2, aadA5, aadA7* and *aadA13* in gene cassettes of class 1 integrons in different *Salmonella* serovars.

2.4 RESISTANCE TO PHENICOLS

In 1947, chloramphenicol was purified from *Streptomyces venezuelae* by David Gottlieb and was shown to be a broad spectrum antibiotic. Chloramphenicol is a molecule with a simple structure and was therefore the first drug to be marketed as a product of chemical synthesis. Since 1950, chloramphenicol has been produced exclusively synthetically (SCHWARZ et al., 2004). Chloramphenicol is a very effective antimicrobial agent in the treatment of a considerable range of diseases. However, it is an extremely toxic drug, and can cause aplastic anemia due to profound depression of bone marrow activity leading to pancytopenia (decrease in all blood cells) (ROBERTS & SCHWARZ, 2016). In Brazil, the Ministry of Agriculture, Livestock and Supply banned the use of this antimicrobial in production animals (BRASIL, 2003), following the ban that had already occurred in most countries. While chloramphenicol is not licensed for use in production animals, florfenicol is indicated for the treatment of respiratory and digestive tract infections in pigs and cattle.

Antimicrobial agents from the phenicol group bind reversibly to the 50S subunit of the 70S portion of the bacterial ribosome and inhibit protein synthesis by preventing peptide chain elongation. Chloramphenicol and florfenicol act bacteriostatically against Gram-negative, Gram-positive, aerobic and anaerobic bacteria, as well as chlamydiae, rickettsiae, and mycoplasmas (SHAW, 1983; YAO & MOELLERING, 1999). The most common resistance mechanism in Gram-negative bacteria is enzymatic inactivation through chloramphenicol acetyltransferases (CATs), which inactivate chloramphenicol but not florfenicol (ROBERTS & SCHWARZ, 2016). CATs can be divided into two types with a trimeric structure consisting of three identical monomers and the respective *cat* gene codes for the monomer. The size of classical CATs ranges from 207 to 238 amino acids, while CATs of the second type range from 209 to 219 amino acids (SCHWARZ et al., 2016; WRIGHT, 2005). In *Salmonella*, the *catA1* gene is the most frequently found, having been detected in plasmids from *S.* Infantis (DIONISI et al., 2011), *S.* Typhimurium

(BEUTLICH et al., 2013) and *S*. Typhi (PARKHILL et al., 2001). Among the genes encoding B-type CATs, *catB3* was detected in gene cassettes located in integrons in *S*. Typhimurium and *S*. Indiana (LAI et al., 2013).

In addition to enzyme inactivation, there are other chloramphenicol resistance systems, such as inactivation by phosphotransferases, mutations in the drug target, changes in permeability, and active efflux systems. Among them, the active efflux mechanism via the *cmlA* and *floR* genes is the best known (SCHWARZ et al., 2016). The *cmlA* gene causes resistance to chloramphenicol, but not to florfenicol. Among *Salmonella* isolates, the *cmlA* exporter gene has been identified in gene cassette located in class 1 integrons in *S*. Indiana (MENG et al., 2011) and *S*. Stanley (KRAULAND et al., 2010). A variant of the gene, named *cmlA9*, was identified as part of a multi-resistance island SGI-2 in *S*. Emek (LEVINGS et al., 2008).

The *floR* gene, also referred to as *flo*, flo_{St} , *pp-flo* or *cmlA-like*, is a chloramphenicol and florfenicol exporter. Despite the variation in nomenclature, these genes are closely related and have 96-100% identity in their nucleotide sequences and 88-100% identity in their amino acid sequence (SCHWARZ et al., 2004). The *floR* gene was identified as part of the multi-resistance island SGI-1, located on the chromosome of *S*. Typhimurium DT104 (BRIGGS & FRATAMICO, 1999). Additionally, the *floR* gene has been identified in IncA/C multi-resistance plasmids of *S*. Typhimurium (WIESNER et al., 2011). The *floR gene* has also been identified in plasmid of *S*. Typhimurium associated with the gene encoding β-lactamases CMY-2 (TAMAMURA et al., 2013).

2.5 RESISTANCE TO SULFONAMIDES AND TRIMETHOPRIM

Since 1968, the combination of sulfonamides and trimethoprim has been widely used in the treatment of bacterial infections, mainly due to its low cost. These compounds are bacteriostatic antimicrobial agents that act competitively by inhibiting enzymes involved in folic acid synthesis. Consequently, these drugs are active against a broad spectrum of bacteria, being able to inhibit both Gram-positive and Gram-negative bacteria. Sulfonamides are analogues of p-aminobenzoic acid, inhibiting the enzyme dihydropteroate synthase (DHPS), while trimethoprim acts by inhibiting the enzyme dihydrofolate reductase (DHFR) (MAKA et al., 2019). The combination of these agents is commonly used to treat urinary tract or respiratory tract infections in animals, but is also used in human medicine. The use of sulfonamides as additives or as preservatives in animal feed is prohibited in Brazil (BRASIL, 2009).

Sulfonamide resistance in *Salmonella* isolates has been attributed to the presence of the *sul* gene, which encodes a resistant variant of the target enzyme dihydropteroate synthetase (DHPS). Four main *sul genes* have been identified: *sul1*, *sul2, sul3* and *sul4* (MAKA et al., 2019). The *sul1* and *sul2* gene have been identified in the *Enterobacteriaceae* family, particularly in *Escherichia coli* and *Salmonella* (XU et al., 2019). The *sul1* gene is found in different *Salmonella* serovars and often reported as part of the

conserved region of class 1 integrons (PÉREZ-MORENO et al., 2013). The *sul2* gene can appear physically linked to the *strA-strB* streptomycin resistance *cluster,* commonly found in plasmids, but not related to integrons (YAU et al., 2010). Different *Salmonella* serovars*,* such as Typhimurium and 4,[5],12:i:-, have revealed the presence of the *sul2* gene (BEUTLICH et al., 2013; MULVEY et al., 2013). In 2003, the *sul3* gene was detected in *Escherichia coli* from pigs in Switzerland (PERRETEN & BOERLIN, 2003). Later, the link between the *sul3* gene and class 1 integron was evidenced in *S.* Choleraesuis and *S.* Typhimurium (CHIU et al., 2005; ANTUNES et al., 2007). In 2017, the *sul4* gene was detected conferring clinical resistance in isolates of the *Enterobacteriaceae* family (RAZAVI et al., 2017).

Resistance to trimethoprim is attributed to the expression of the resistant variant of the DHFR enzyme. According to structure, these enzymes are subdivided into two families, which are encoded by the *dfrA* and *dfrB* genes (VAN HOEK et al., 2011). Members of the *dfrA* group have at least 474 nucleotides (157 amino acids) and are often found inserted in gene cassettes. The gene cassette containing *dfrA1* is commonly reported and has been found, for example, in *S.* Braendenburg (MARTÍNEZ et al., 2007) and *S.* Bredeney (MICHAEL et al., 2008). Members of the second *dfrB* group have 237 nucleotides (78 amino acids) and are identified less frequently than members of the *dfrA* group (VAN HOEK et al., 2011). The first description of the *dfrB* gene in *Salmonella* occurred in 2006, when a gene cassette containing *dfrB6* was found in class 1 integron from *S*. Infantis (LEVINGS et al., 2006).

2.6 RESISTANCE TO QUINOLONES AND FLUOROQUINOLONES

Quinolones represent a class of synthetic antimicrobials effective in the treatment of various infections, especially those of bacterial origin. The first quinolone, nalidixic acid, was introduced into medical practice in 1962 (ALCAINE et al., 2007; VAN HOEK et al., 2011). This antimicrobial was used to treat urinary tract infections caused by Gram-negative bacteria. In Brazil, the use of quinolones as feed additives or preservatives is prohibited (BRASIL, 2009), but they are molecules widely used in the treatment of various infections that affect pigs (BARCELLOS et al., 2012).

The addition of a fluorine atom at position 6 and the replacement of the main ring at position 7 of the quinolone molecule led to the creation of a new generation of compounds, the fluoroquinolones. During the 1980s, several fluoroquinolones were developed, such as ciprofloxacin, norfloxacin, and ofloxacin. These compounds show greater activity against Gram-negative bacteria, are active against some Gram-positive species and achieve a thousand-fold higher antibacterial activity than nalidixic acid (HOOPER, 2000; KING et al., 2000). Later, further changes resulted in the development of the third generation fluoroquinolones, such as levofloxacin and sparfloxacin, achieving potent activity against Gram-negative and Gram-positive bacteria (HOOPER, 2000; KING et al., 2000).

Quinolones and fluoroquinolones inhibit the action of the enzymes DNA gyrase and topoisomerase IV, which are essential for DNA replication in the bacterial cell. DNA gyrase is composed of two subunits,

GyrA and GyrB. The topoisomerase IV has a similar structure, also composed of two subunits called ParC and ParE (HOOPER, 2000). *Salmonella* resistance to quinolones and fluoroquinolones is related to chromosomal mutations in genes encoding target proteins, such as the enzymes DNA gyrase and topoisomerase IV; or due to mutations causing decreased drug accumulation by increased expression of efflux pumps (AcrAB-TolC system); or due to the presence of resistance plasmids (*Plasmid-mediated quinolone resistances-PMQR*) (AZARGUN et al., 2020 ALCAINE et al., 2007).

The most important mutation point in *Salmonella* is in the *gyrA* gene, which encodes the A subunit of the enzyme DNA gyrase. Mutations in *gyrA* occur in a region between amino acids 67 and 106, called the quinolone *resistance-determining region* (*QRDR*). Substitutions at amino acid Ser-83 (for Phe, Tyr, or Ala) or amino acid Asp-87 (for Gly, Asn, or Tyr) are frequently observed in nalidixic acid-resistant strains (BALLESTÉ-DELPIERRE et al., 2013; VELHNER et al., 2013). Double mutations at residues 83 and 87 have already been identified in clinical isolates of *S*. Typhimurium DT204 with high resistance to fluoroquinolones (HEISIG et al., 1995). In the *parC* gene, mutations can occur in a region between amino acids 63 and 102. In *Enterobacteriaceae*, the high level of quinolone resistance is related to a series of sequential mutations: mutation in the *gyrA* gene, mutation in Ser-80 or Glu-84 in the *parC gene*, another mutation in *gyrA,* and then finally another mutation in *parC*. During these events, the minimum inhibitory concentration (MIC) for ciprofloxacin increases from 0.125-0.25 to 128 mg/L (AZARGUN et al., 2020).

A spontaneous double mutation is considered a rare genetic event, occurring at a frequency of 10^{-14} to 10^{-16} for fluoroquinolones. For this reason, a mutational phenomenon does not provide a satisfactory explanation for the frequency with which resistance has emerged. In 1998, the first plasmid mediating quinolone resistance (*Plasmid-mediated quinolone resistances-PMQR*) was discovered, due to the presence of the *qnrA* gene (MARTÍNEZ-MARTÍNEZ et al., 1998). The qnr protein protects the DNA gyrase complex, the target of quinolones and fluoroquinolones, promoting quinolone resistance and reduced susceptibility to fluoroquinolones. More *qnr* genes, such as *qnrB, qnrC*, *qnrD* and *qnrS* have been described subsequently (VAN HOEK et al., 2011).

In *Salmonella*, the *qnrA3* gene was detected in *S*. Enteritidis isolated from humans in Hong Kong (CHEUNG et al., 2005). Among the QnrB family of proteins, the *qnrB19* gene was identified in an *S*. Typhimurium isolate obtained in 2004 from a case of human gastroenteritis in Italy (DIONISI et al., 2009). In addition, the *qnrB19* gene has been detected in *S*. Typhimurium isolates from humans in the Netherlands (GARCÍA-FERNÁNDEZ et al., 2009), in *Salmonella isolates from* reptiles in Germany (GUERRA et al., 2010), as well as in *Salmonella* isolates from humans in Korea (JEONG et al., 2011). There are also reports of the *qnrD1* gene in isolates of *S*. Kentucky and *S*. Bovismorbificans in China (CAVACO et al., 2009). The *qnrS1* gene was also found among *Salmonella* isolates in the United Kingdom and the Netherlands (HOPKINS et al., 2007; GARCÍA-FERNÁNDEZ et al., 2009).

In addition to the *qnr* genes, a second quinolone resistance gene located on plasmids, the *aac(6')-Ib-cr* gene, has been identified. This gene encodes the enzyme aminoglycoside acetyltransferase, which confers resistance to kanamycin and reduced susceptibility to ciprofloxacin and norfloxacin (ROBICSEK et al., 2006). The *aac(6')-Ib-cr* gene has been observed in *S*. Enteritidis concomitantly with the *qnrA* and *qnrB genes* (AL-GALLAS et al., 2013). A new variant of the *aac(6')-Ib-cr* gene, designated *aac(6')-Ib-cr4,* was found in plasmid from *S*. Typhimurium (DE TORO et al., 2013). Additionally, the plasmid gene *qepA* was responsible for promoting quinolone resistance. The *qepA* gene has two variants *qepA1* and *qepA2* (CATTOIR et al., 2008), which encode an efflux pump capable of expelling hydrophilic fluoroquinolones, such as ciprofloxacin and enrofloxacin (YAMANE et al., 2007). A gene with 100 % identity with *qepA* was found in *S*. Typhimurium, although it was not associated with the phenotype of reduced susceptibility to quinolones (LUNN et al., 2010).

3 HORIZONTAL TRANSFER OF RESISTANCE GENES

Horizontal gene transfer corresponds to the transfer of genetic material between bacteria of the same generation. Acquired resistance genes are often located in mobile genetic elements, which have the ability to translocate from one part of the genome to another or between genomes (VAN HOEK et al., 2011). Mobile genetic elements can spread horizontally between bacteria of the same species, but also between different species or different bacterial genera (THOMAS et al., 2005). Many resistance genes present in *Salmonella* strains are also present in other bacterial genera. One example is the resistance gene *aadA* which confers combined resistance to streptomycin and spectinomycin and can be found in both Gram-negative and Gram-positive bacteria (KEHRENBERG et al., 2005).

The spread of resistance genes between members of different bacterial species and genera under natural conditions requires horizontal transmission by conjugation, transduction or, less often, transformation. Natural transformation has been described for bacteria such as *Haemophilus*, *Campylobacter* or *Pseudomonas*, among others (THOMAS et al., 2005). Bacteriophages also play an important role in the dissemination of DNA between bacteria, acting as a vehicle for resistance genes. Under natural conditions, conjugation is the most common mechanism for transfer of plasmids and transposons. Conjugation is a process in which contact between cells is established and a pore is formed in the bacterial wall, so that the passage of DNA from the donor cell to the recipient cell occurs (VAN HOEK et al., 2011). The horizontal transfer of mobile genetic elements contributes to the acquisition, maintenance and spread of antimicrobial resistance genes (DOMINGUES et al., 2012). Some elements including plasmids, transposons, integrons and gene cassettes, as well as genomic islands can be present in antimicrobial resistant strains.

3.1 PLASMIDS

Plasmids are circular double-stranded DNA molecules that can replicate independently of the host cell's chromosomal DNA. The plasmids can be present in almost all bacterial species varying in size and number of copies per cell (WATERS, 1999). They can harbor genes essential for the initiation and control of replication and accessory genes that may be useful to the host cell, such as resistance or virulence genes (SCHWARZ et al., 2006). Plasmids that have genes for conjugation are called conjugative and have a transfer origin (*oriT*). The genes required for plasmid conjugation are clustered in the *tra* operon of size >15 kb (SMILLIE et. al., 2010). Therefore, conjugative plasmids must be larger than 20 kb. Small plasmids can be mobilized together with large plasmids during the conjugation process (VAN HOEK et al., 2011).

Some types of plasmids cannot coexist in the bacterial cell and this fact has given rise to the division into incompatibility groups (COUTURIER et al., 1988). Plasmids with the same replication control system are called "incompatible", while plasmids with different replication control system are known as "compatible". Thus, two plasmids belonging to the same Inc group cannot propagate in the same cell lineage (COUTURIER et al., 1988). Inc group identification has often been used for the classification of plasmids. In 2005, Carattoli and co-workers developed a method for the identification of the major plasmid groups circulating among *Enterobacteriaceae*, called PCR based replicon typing (PBRT). In this method, 18 pairs of primer oligonucleotides were designed to perform five multiplex PCR assays and three simplex PCR assays, recognizing the groups FIA, FIB, FIC, HI1, HI2, I1-Iγ, L/M, N P, W, T, A/C, K, B/O, X, Y, F, and FIIA.

Plasmid groups do not occur as frequently among members of the family *Enterobacteriaceae*, with some being more prevalent and diffuse than others. In 2008, García-Fernández and colleagues developed a plasmid *multi-locus sequence typing (*pMLST) scheme to identify related clonal lineages, similar to the MLST conducted for bacterial genomes. This method is available for the most prevalent plasmid families in *Enterobacteriaceae*, such as IncI1, IncF, IncHI2 and IncN (http://pubmlst.org/plasmid/) (CARATTOLI, 2013).

3.2 TRANSPOSONS

The simplest mobile genetic elements are insertion sequences (ISs). ISs are small segments of DNA (< 2.5 kb), which encode only functions necessary for transposition within and between genomes and the genes of the proteins (transposases) that promote it (SIGUIER et al., 2006; SCHWARZ et al., 2006). When an IS has accessory genes, not involved in its translocation, it is called a transposon. A simple transposon contains only one accessory gene (usually resistance gene) in addition to the transposase gene (ROBERTS et al., 2008). Transposons are double-stranded DNA elements of variable size (2 - 20 kb), which unlike plasmids, do not have an autonomous replication system. These elements need to be integrated into chromosomal DNA or plasmids for their replication to occur (WOZNIAK et al., 2010).

Based on their structure, transposons can be differentiated into compound or complex transposons. The basic structure of compound transposons can be schematized by: a) a central region with genes not related to transposition (generally antimicrobial resistance genes) and b) two modules that delimit this central region and that are insertion sequences, which encode the transposition activities. Examples of compound transposons are *Tn5* (REZNIKOFF, 2002) conferring resistance to aminoglycosides and *Tn7* (CRAIG, 2002), which confers resistance to trimethoprim and aminoglycosides. Complex transposons usually have short inverted repeats at the ends ranging from 15 to 40 bp and an internal repeat region, which separates the part responsible for transposition functions from the part responsible for resistance functions. Tn1721 harboring the tetracycline resistance gene *tet*(A) is an example of a complex transposon (HENTSCHKE et al., 2010).

The movement of transposons plays an important role in the acquisition of antimicrobial resistance genes in *Salmonella*. Transposons harboring tetracycline resistance genes have already been described in several bacteria, including members of the family *Enterobacteriaceae*. The tetracycline resistance gene *tet*(A), which encodes an efflux protein, is associated with the transposon Tn1721 in several *Salmonella* serovars (GARCÍA et al., 2011). The *bla* gene$_{TEM-1}$, which confers ampicillin resistance, has been detected in the Tn3 transposon located in conjugative and non-conjugative plasmids, or in the chromosomal DNA of *Salmonella* (PASQUALI et al., 2005; MARTÍNEZ et al., 2010). In addition to these transposons, Tn10 harboring the *tet*(B) gene, which confers tetracycline resistance, has already been described in *Salmonella* (CAIN & HALL, 2012a). The *catA1* gene, responsible for chloramphenicol resistance, has also been described as part of a Tn9 in *Salmonella* multi-resistance plasmids (MARTÍNEZ et al., 2007). The study by Cain & Hall (2012b) demonstrated the presence of a plasmid, harboring 10 antimicrobial resistance genes, in a transposon derived from Tn2670 in *S*. Typhimurium.

3.3 GENOMIC ISLANDS

The *Salmonella* genomic island 1 (SGI1) is 43 kb in size and contains a multi-resistance region conferring resistance to ampicillin, chloramphenicol/florfenicol, streptomycin/spectinomycin, sulfonamide and tetracycline, encoded by the *bla*$_{PSE-1}$, *floR, aadA2*, *sul1* and *tet*(G) genes. The resistance genes are located within integrons, named In104, which belong to the In4 family (MULVEY et al., 2006). SGI1 is horizontally transferred and has been identified as a mobilizable integron element (DOUBLET et al., 2005). The island was first identified in a multidrug-resistant strain of *S*. Typhimurium phageotype DT104. Subsequently, SGI1 was also identified in other *Salmonella* serovars and in *Proteus mirabilis* (AHMED et al., 2007; DOUBLET et al., 2004a, DOUBLET et al., 2004b).

Since the discovery of SGI-1, numerous variants have been described among *Salmonella* serovars. Most of them demonstrate a gain, loss or exchange of resistance genes. Beutlich and colleagues (2011) identified seven different SGI1 variants associated with multi-resistance. The authors reported the presence

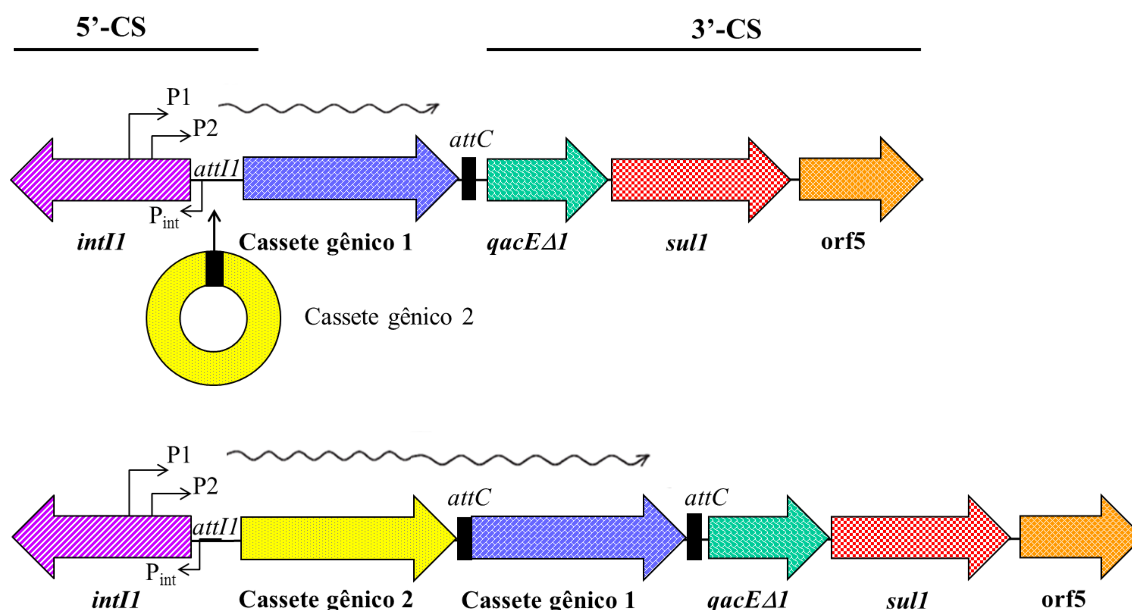
of SGI1-A and SGI1-C in the Derby serovar, SGI1-F in Albany, SGI1-L in Newport, SGI1-K in Kentucky, and SGI1-M in Typhimurium. A new variant similar to SGI1-C with additional resistance to gentamicin, encoded by the *aadB* gene, was also found. A retrospective study of *S*. kentucky strains isolated from human patients between 1969 and 1999 revealed the presence of a new variant, termed SGI1-J6, containing the *aadA2, floR2*, *tet*(R), *tet*(G) and *sul1* genes located in an integron complex. In addition, a novel insertion sequence named *ISSen5* was identified inserted into ORF S023 of SGI1 (LE HELLO et al., 2012). These studies demonstrate that a large phenotypic and genotypic diversity can be observed among SGI1 positive isolates.

3.4 INTEGRONS

The term integron describes a large family of genetic elements capable of capturing small elements, called gene cassettes (Figure 1) (HALL, 2012). The main component of a functional integron is the *intl* gene, which is responsible for producing the integrase enzyme. This enzyme catalyzes the excision and integration of gene cassettes. Cassette integration occurs at a specific site immediately adjacent to the *intl gene*, called the primary recombination site (*attI*). Integrons have a promoter region, which is responsible for the expression of gene cassettes. The expression of these genes occurs through the Pc promoter, which is incorporated into the *intl gene* or the *attI recombination* site (CAMBRAY et al., 2010). Integrons consist of two conserved segments (CS), 5'-CS and 3'-CS, which flank the variable region containing one or more gene cassettes. The 5'-CS part contains the integrase gene, the recombination site and the promoter. The 3'-CS part houses the *qacE* gene*Δ 1*, a semi-functional gene derived from the *qacE gene* that confers resistance to quaternary ammonium compounds, the sulfonamide resistance gene *sul1* and an open reading stage of unknown function called ORF5 (SCHWARZ et al., 2006).

Gene cassettes are among the simplest mobile genetic elements, but they are not mobile by themselves; they require the action of Intl. The gene cassette usually consists of a single gene or an open reading *frame* and an *attC* recombination site, which allows it to be recognized by Intl and is therefore essential for the mobility of the cassette (HALL, 2012). The recombination site was originally called the *59-base* element, however, it can range in size from 57 bp to 140 bp. Due to the nature of site-specific recombination that promotes integration of a cassette into the free circular form, a small part of the *attC* is found at the beginning of the linearized cassette and another part at the end (RECCHIA & HALL, 1995).

FIGURE 1 - Schematic representation of a class 1 integron and a model for gene cassette acquisition.



Different classes of integrons have been defined according to the homology of integrase sequences, with classes 1, 2 and 3 being frequently involved in the dissemination of multi-resistance phenotypes and having a higher occurrence when compared to the other classes (CAMBRAY et al., 2010). Members of the same class possess the same integrase, but may contain different gene cassettes. Integrases of different classes are distinguished by differences in their amino acid sequences. Intl1 has 46 % identity with Intl2, while Intl1 has 60 % identity with Intl3 (HALL, 2012). Since 2009, a unique database for sequences of integrons, integrases and gene cassettes has been developed, called INTEGRALL (http://integrall.bio.ua.pt) (MOURA et al., 2009). Performing a search with the word "*Salmonella*" in the field "Organism", 629 records of integrons and gene cassettes are found (last access on 09/12/2022).

Class 1 integrons are the most widespread and clinically important, being detected in 22% to 59 % of Gram-negative bacterial isolates. They are usually associated with functional and non-functional transposons derived from Tn402, which may be housed in large transposons such as Tn21 (CAMBRAY et al., 2010). Class 1 integrons are the most frequent among isolates of the genus *Salmonella as* well. A diverse set of class 1 integrons, revealing eight different types of gene cassettes, was observed in a recent study (HSU et al., 2013). In that study, the *intl1* gene was present in 83.6 % of a collection of 499 *Salmonella* isolates obtained from humans and animals, belonging to different serovars. Among the strains positive for the *intl1 gene*, 86.3 % showed the class 1 integron harboring gene cassettes, which revealed sizes ranging from 1 to 2 kb, and 13.7 % showed the class 1 integron empty, without the presence of gene cassettes.

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