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REVIEW ARTICLE

# ANTIMICROBIAL RESISTANCE OF *SALMONELLA* SPP. ISOLATED FROM FOOD

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## ABSTRACT

This review summarizes current data on resistance among *Salmonella* spp. isolates of food origin from countries in different regions of the world. The mechanisms of resistance to different groups of antimicrobial compounds are also considered. Among strains resistant to quinolones and/or fluoroquinolones the most prevalent mechanism is amino acid substitutions in quinolone resistance-determining region (QRDR) of genes *gyrA*, *parC* but mechanism of growing importance is plasmid-mediated quinolone resistance (PMQR) associated with genes *qnrA, qnrB, qnrC, qnrD, qnrS* but frequency of their detection is different. Resistance to sulfonamides is mostly associated with genes *sul1* and *sul2*, while resistance to trimethoprim is associated with various variants of *dhfr* (*dfr*) genes. Taking into account *Salmonella* spp. strains isolated from food, resistance to β-lactams is commonly associated with β-lactamases encoding by $bla_{TEM}$ genes. However strains ESBL and AmpC – positive are also detected. Resistance to aminoglicosides is commonly result of enzymatic inactivation. Three types of aminoglycoside modifying enzyme are: acetyltransferases (AAC), adenyltransferases (ANT) and phosphotransferases (APH). Resistance to tetracyclines among *Salmonella* spp. isolated from food is most commonly associated with active efflux. Among numerous genetic determinants encoding efflux pumps *tetA*, *tetB*, *tetC*, *tetD*, *tetE* and *tetG* are reported predominatingly. One of the most common mechanisms of resistance against chloramphenicol is its inactivation by chloramphenicol acetyltrasferases (CATs), but resistance to this compound can be also mediated by chloramphenicol efflux pumps encoded by the genes *cmlA* and *floR*.

It is important to monitor resistance of *Salmonella* isolated from food, because the globalization of trade, leading to the long-distance movement of goods, animals and food products, encourages the spread of resistant pathogens around the world.

**Key words:** *foodborne pathogens, multiresistance of Salmonella spp., antimicrobial resistance, food safety, food*

## STRESZCZENIE

W artykule przedstawiono aktualne dane na temat mechaniznów lekooporności pałeczek *Salmonell*a spp. pochodzących z żywności. Wśród szczepów opornych na chinolony i/lub fluorochinolony najczęściej identyfikowanym mechanizmem są substytucje aminokwasów w obrębie regionów determinujących oporność na chinolony (QRDR-quinolone resistance-determining region) w genach *gyrA* i *parC*, jednak coraz częściej identyfikowane są geny qnr (*qnrA, qnrB, qnrC, qnrD, qnrS*) związane z plazmidami (PMQR - plasmid-mediated quinolone resistance). Oporność na sulfonamidy jest najczęściej związana z genami *sul1* i *sul2*, natomiast różne warianty genów *dhfr* (*dfr*) warunkują oporność na trimetoprim. Biorąc pod uwagę szczepy *Salmonella* spp. pochodzące z żywności, oporność na antybiotyki β-laktamowe związana jest zazwyczaj z produkcją β-laktamaz kodowanych przez geny $bla_{TEM}$. Jednakże coraz powszechniej identyfikowane są szczepy produkujące β-laktamazy o rozszerzonym spektrum substratowym (ESBL) oraz cefalosporynazy AmpC. Oporność na aminoglikozydy najczęściej wynika z wytwarzania enzymów modyfikujących cząsteczki leku: acetylotransferaz (AAC), adenylotransferaz (ANT) oraz fosfotransferaz (APH). Oporność wobec tetracyklin wśród pałeczek *Salmonella* spp. izolowanych z żywności najczęściej związana jest z mechanizmem aktywnego usuwania leku za pomocą pomp (efflux) kodowanych, najczęściej przez geny *tetA*, *tetB*, *tetC*, *tetD*, *tetE* i *tetG*. Jednym a najczęściej wykrywanych mechanizmów oporności na chloramfenikol jest jego inaktywacja w wyniku działania acetylotransferazy chloramfenikolowej (CAT). Oporność na chloramfenikol może być również związana ze zjawiskiem aktywnego wypompowywania leku. Pompy efflux są kodowane przez geny *floR* (warunkujące oporność także na florfenikol) lub *cml*.

Istotne znaczenie ma monitoring lekooporności wśród szczepów *Salmonella* spp. pochodzących z żywności, ponieważ transport środków spożywczych oraz zwierząt do i z krajów całego świata ułatwia rozprzestrzenianie się szczepów lekoopornych.

**Słowa kluczowe:** *patogeny żywności, wielolekooporność Salmonella spp., lekooporność, bezpieczeństwo żywności, żywność*

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## INTRODUCTION

Although new microbilogical hazards are detected in food [76], *Salmonella* spp. remain one of the most common foodborne pathogens worldwide. More than 2600 *Salmonella* serovars have been identified [24]. These bacteria are prevalent in the environment, and are found in both domestic and wild animals as pathogens or commensals. They can infect humans, mainly via the contaminated food: chicken, pork, dairy products, eggs, fruits, vegetables and others [92, 98].

The clinical symptoms of salmonellosis are usually fever, abdominal pain, diarrhoea and vomiting, although the same strain may sometimes cause different symptoms in separate hosts. The nature of the illness can depend on factors including the type of contaminated food, the infecting dose, the gut flora and the immunological condition of host. More severe salmonellosis occurs in immunocompromised people, the very young and the elderly.

*Salmonella* is a serious problem for food safety and public health, and is one of the most common human foodborne pathogens in the European Union (EU). In 2014, *Salmonella* spp. was most frequently detected in poultry meat and less often in pig or bovine meat. It is one of the major factor of reported foodborne outbreaks. A total of 88'715 confirmed human cases of salmonellosis were reported in the EU in 2014 and of these, 34.4% were hospitalized (hospitalization status was provided for 10.4% of all confirmed cases) [25].

*Scallan* et al. estimated that each year in the United States, non-typhoidal *Salmonella* spp. cause 1.0 million cases of foodborne illness (11% of all foodborne illnesses). Non-typhoidal *Salmonella* spp. are the leading cause of hospitalizations and mortality due to the consumption of contaminated food in the USA. Infections with non-typhoidal *Salmonella* spp. are also responsible for the majority of deaths among people in the USA who have eaten contaminated food. The costs resulting from salmonellosis in the USA amount to several billions of dollars [85].

In Australia, in 2010, more than one-third of the notified diseases or infections commonly transmitted by food were caused by *Salmonella*. Just over one-third (34%) of all foodborne and suspected outbreaks were due to *S.* Typhimurium [62].

Another serious problem and a major challenge for medicine is antimicrobial resistance among pathogens. Each year, about 25,000 patients die in the EU, Iceland and Norway from infections with antibiotic-resistant bacteria, two-thirds of them Gram-negative. Infections by resistant bacteria result in annual costs due to additional healthcare and lost productivity, of at least EUR 15 billion in the EU [22].

## ANTIMICROBIAL RESISTANCE AS A FOOD SAFETY PROBLEM

The growing importance of antimicrobial resistance as a problem for food safety has been recognized by various international organizations [91]. This problem is multifaceted and intersectoral, and cooperation and the exchange of information between the sectors of agriculture, veterinary, food production and public health appear to be essential. The globalization of trade, which depends on the movement of goods, animals and food products, means that resistant bacteria can become widely distributed and transferred to consumers around the world.

Another route of resistance transfer is from the environment contaminated by the disposal of high levels of antibiotics and antibiotic-resistant bacteria. One example is the application of manure from pig farms, where large amounts of antibiotics are used in preventive treatments [74]. The contamination of vegetables and fruits can occur through their contact with contaminated soil or water during growth, and then resistant bacteria are transferred via the fecal-oral route [40, 86].

Resistant bacteria are transferred from food animals to man via the food chain. After the ingestion of contaminated food, commensal and pathogenic bacteria in the gut can exchange mobile genetic elements mediating resistance. Recent epidemiological studies have revealed that human infections with resistant *Salmonella* spp. are associated with prolonged illness, an increased risk of invasive disease and hospitalization, and excess mortality [59].

The spread of resistance to some antibiotics is particularly worrying. Farm animals and meat products often contain resistance genes active against 3rd and 4th generation beta-lactams, which are crucial antibiotics in human medicine. Resistance against these drugs mediated by the AmpC and Extended Spectrum Beta-lactamase (ESBL) families is often found in *E. coli* and *Salmonella* spp. [98]. Genetic analyses of the bacterial strains and resistance genes in farm animals, food and humans have found strong similarities/common genetic features [45]. These studies provide indirect evidence that ESBL genes, mobile genetic elements and resistant strains are transmitted to people via the food chain.

Another widespread problem is the use of fluoroquinolones in the poultry industry. Quinolone-resistant bacteria (*E. coli*, *Salmonella* spp. and *Campylobacter* spp.) spread through the ingestion of contaminated food, have been shown to have an impact on the management of human infections [23, 26].

Table 1. Resistance of *Salmonella* spp. of food origin to various antimicrobial compounds

| Country | Year(s) | Source | Antimicrobials (percentage of resistance) | | | | | | | | | | | | | | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | AMP | AMC | CRO | CAZ | IPM | TE | CN | STR | NA | CIP | SUL | SXT | W | C | |
| Morocco | 2002-5 | food | 13 | 9 | nd | 0 | nd | 21 | 0 | 6.7 | 3.8 | 0 | nd | 2.8 | nd | 4 | [9] |
| UK | 2003-5 | Beef | 41.2 | nd | nd | nd | nd | 58.8 | 0 | 64.7 | 0 | 0 | 64.7 | nd | 5.9 | 29.4 | [48] |
| UK | 2003-5 | Lamb | 50 | nd | nd | nd | nd | 50 | 0 | 56.3 | 25 | 0 | 56.3 | nd | 6.3 | 37.5 | [48] |
| UK | 2003-5 | Pork | 42 | nd | nd | nd | nd | 76 | 0 | 44 | 6 | 4 | 54 | nd | 26 | 34 | [48] |
| Senegal | 2003 | beef | nd | 0 | nd | 0 | nd | 0.4 | 0 | 21.5 | 0.4 | 0 | 14.7 | nd | 0 | 0.8 | [73] |
| Ethiopia | 2003 | food | 20 | nd | 0 | nd | nd | 16 | nd | 26 | nd | nd | 14[a] | nd | nd | 0 | [97] |
| Austria | 2004* | ** | 17 | nd | nd | nd | nd | 33 | nd | 27 | 42 | 9.6 | nd | nd | nd | 17 | [50] |
| Brazil | 2004-6 | chicken carcasses | 38 | nd | 6 | nd | nd | 12 | 12 | 78 | 40 | 4 | 58 | 10 | 10 | 6 | [54] |
| Brazil | 2005 | fresh pork sausage | 30.9 | nd | nd | nd | nd | 71.6 | 2.5 | 28.4 | 24.7 | nd | 55.6 | 29.6 | nd | 30.9 | [60] |
| China | 2005 | pork | 16.7 | 0 | 0 | 8.3 | nd | 33.3 | 0 | 0 | 50 | 0 | 83.3 | 50 | nd | 16.7 | [92] |
| China | 2005 | chicken | 47.4 | 10.5 | 0 | 5.3 | nd | 47.4 | 31.6 | 36.8 | 73.7 | 42.1 | 89.5 | 57.9 | nd | 42.1 | [92] |
| China | 2005 | beef | 0 | 0 | 0 | 0 | nd | 0 | 0 | 0 | 6.7 | 0 | 86.7 | 33.3 | nd | 0 | [92] |
| China | 2005 | mutton | 0 | 0 | 0 | 0 | nd | 6.7 | 0 | 6.7 | 6.7 | 0 | 73.3 | 26.7 | nd | 0 | [92] |
| China | 2005 | seafood | 10 | 0 | 0 | 0 | nd | 10 | 5 | 5 | 15 | 0 | 95 | 65 | nd | 0 | [92] |
| Turkey | 2005-6 | chicken carcasses | 85.2 | nd | nd | nd | nd | 67.6 | 14.7 | 61.7 | nd | nd | nd | nd | nd | 10.2 | [96] |
| Spain | 2006 | chicken | 10.5 | 10.5 | nd | nd | nd | 21.1 | 0 | 36.8 | 100 | 0 | nd | 5.3 | nd | 5.3 | [5] |
| Iran | 2006-7 | chicken and beef | 4 | 3.2 | nd | 0 | 0 | 69 | 0 | 42 | 82 | 0 | nd | nd | 63 | 1.6 | [16] |
| India | 2006-7 | chicken eggs | 41.1 | nd | nd | nd | nd | 0 | 29.4 | 0 | nd | 0 | 70.6[b] | nd | | 23.5 | [70] |
| India | 2006-8 | fish and sprouts | 2.8 | nd | 2.8 | nd | nd | 62 | nd | 2.8 | 5.6 | 1.4 | 50.7[b] | nd | 2.8 | 2.8 | [43] |
| Tunisia | 2006-8 | raw meat | 16.2 | 5 | nd | 1.2 | nd | 1.2 | 0 | 6.2 | 1.2 | nd | 1.2 | 1.2 | nd | 0 | [2] |
| Malaysia | 2006-9 | retail meats | 19.7 | 1.5 | 0 | 0 | nd | 72.7 | 3 | 66.6 | 40.1 | 3 | 69.7 | 19.7 | nd | 10.6 | [79] |
| Malaysia | 2006-9 | street foods | 9 | 0 | 0 | 0 | nd | 77.3 | 0 | 31.8 | 54.5 | 0 | 45.5 | 18.2 | nd | 9 | [79] |
| Canada | 2007-8 | chicken | 31 | 21 | 21 | nd | nd | 49 | 0 | 40 | 0 | 0 | 7[a] | 0 | nd | 1 | [7] |
| Canada | 2007-8 | turkey | 29 | 25 | 25 | nd | nd | 54 | 4 | 29 | 0 | 0 | 8[a] | 4 | nd | 4 | [7] |
| Canada | 2007-8 | pork | 0 | 0 | 0 | nd | nd | 0 | 0 | 33 | 0 | 0 | 33[a] | 33 | nd | 0 | [7] |
| Algeria | 2007-8 | *** | 4.8 | nd | nd | nd | nd | 12.9 | nd | 16.1 | 16.1 | nd | 87.1 | 4.8 | 4.8 | 4.8 | [56] |
| Vietnam | 2007-9 | pork and chicken | 39.8 | 2.9 | nd | 0 | nd | 58.5 | 17.8 | 47.3 | 27.8 | 5 | 58.1 | nd | 34 | 37.3 | [78] |
| Poland | 2008-12 | meat and meat products | 28.3 | 16 | 0 | 0 | 0 | 32.1 | 6.6 | 28.3 | 52.8 | 0 | 26.4 | 3.8 | 3.8 | 7.5 | [51] |
| Poland | 2008-12 | products other than meat | 4.9 | 2.5 | 0 | 0 | 0 | 1.6 | 1.6 | 1.6 | 35.2 | 0 | 6.6 | 0 | 0 | 0.8 | [52] |

AMP – ampicillin; AMC – amoxycillin/clavulanic ac.; CRO – ceftriaxone; CAZ – ceftazidime; IPM – imipenem; TE – tetracycline; CN – gentamicin; STR – streptomycin; NA – nalidixic ac; CIP – ciprofloxacin; SUL – sulphonamides comp; SXT – trimethoprim/sulphametoxazole; W – trimethoprim; C – chloramphenicol.

Antibiotic resistance in *Salmonella* spp. has led to more frequent hospitalizations, more complicated and prolonged illnesses, treatment failures, a higher risk of invasive disease and a twofold increase in the risk of death in the two years following infection. The growing problem of antimicrobial resistance has resulted in a decrease in the efficacy of antimicrobials and a situation similar to the pre-antibiotic era in some cases [47, 91]. In richer countries, routine laboratory susceptibility testing assists in the selection of the appropriate antimicrobial treatment, but this is not possible in low-income communities, and blind therapy may lead to treatment failure, long-term disability and increased mortality rates. Inappropriate antibiotic therapy can result in *Salmonella* remaining in the host's cells (intracellular) and thus resulting in asymptomatic carriage, which is associated with further complications and the development of resistance [75].

The dissemination of antimicrobial resistance is often via mobile genetic elements such as plasmids, transposons and gene cassettes in integrons [64]. The most common integrons involved in antimicrobial resistance are class 1 integrons that are abundant in the genomes of many bacterial species [4].

Increasing resistance among foodborne pathogens is linked to the excessive use of antimicrobials in animals. *Mellon* et al. [55] estimated that annual non-therapeutic antibiotic use in animals has increased in the USA from 16.1 million pounds in the mid-1980s to 24.6 million pounds in the 2000s. The amounts would be even higher if antimicrobials used therapeutically for animals were included.

According to data collected in 10 European countries, the amounts of veterinary antibacterial agents relative to the sum of the biomass of food-producing animals varies from 18 to 188 mg/kg per country [33]. Overall, tetracyclines accounted for 48% of the sales of veterinary antibacterial agents, sulphonamides and trimethoprim (as sulphonamides or in combination) for 17%, and β-lactams for 16%.

## ANTIMICROBIAL RESISTANCE OF SALMONELLA ISOLATED FROM FOOD

Surveys of antimicrobial resistance in *Salmonella* strains isolated from food have been conducted in various countries around the world and have examined a broad spectrum of antimicrobial compounds. To facilitate a useful comparison between the results of these studies, we have chosen to focus on the antimicrobials that are most often used for *Salmonella* tesitng by authors of articles i.e. ampicillin, tetracycline, gentamicin, streptomycin, nalidixic acid, ciprofloxacin, sulfonamides, sulphametoxazole/trimethoprim and chloramphenicol (Table 1).

*Salmonella* spp. resistant to ampicillin have been frequently isolated from food products. Only among isolates from pork in Canada and those from beef and mutton in China was resistance to this antibiotic not found.

Similar results have been obtained for tetracycline, with reported frequencies of resistance to this antibiotic among *Salmonella* spp. isolates often ≥50.0%: 50.0 – 76.0% among strains isolated from various meats in the UK, 71.6% from pork sausage in Brazil, 67.6% from chicken carcasses in Turkey, 69.0% from chicken and beef in Iran, 62.0% from fish and sprouts in India, 72.7 – 77.3% from foods in Malaysia, 54.0% from turkey in Canada, and 58.5% from pork and chicken in Vietnam. However, it is noticeable that resistance to tetracycline has been less frequently detected among *Salmonella* spp. strains isolated from foods in African countries: only 0.4% among isolates from Senegal and up to 21.0% among those from Morocco.

Susceptibility to aminoglycosides was examined in all surveys and differences between the levels of resistance to gentamicin and streptomycin were found. Only isolates from beef in China and from chicken eggs in India were fully susceptible to streptomycin. The highest incidence of resistance to streptomycin was observed among *Salmonella* strains isolated from chicken carcasses in Brazil (78.0%), retail meats in Malaysia (66.6%), beef in the UK (64.7%) and chicken carcasses in Turkey (61.7%). The frequency of resistance to gentamicin was lower and amounted to no higher than 31.6% among isolates from chicken in China. Moreover, three fifths (15/25) of the results obtained for different origins, reported that 100.0% of *Salmonella* spp. isolates were susceptible to gentamicin.

Almost all of the surveys examined susceptibility to nalidixic acid and ciprofloxacin. Of these antimicrobials, ciprofloxacin is definitely more effective against *Salmonella* spp., and the majority of surveys reported no resistance to this compound. Only isolates from chicken samples collected in China displayed relatively frequent resistance (42.1%) to ciprofloxacin, while 73.7% of these strains were resistant to nalidixic acid. The highest rate of resistance to this quinolone was observed among *Salmonella* isolates from chicken products in Spain (100.0%).

The frequency of resistance to sulfonamides ranged between 1.2% (raw meat in Tunisia) and 95.0% (seafood in China). The proportion of resistant strains was particularly high among *Salmonella* spp. isolates from foods in Asian countries: 45.5% and 69.7% in Malaysia, 58.1% in Vietnam, 73.3 – 95.0% in China.

The highest incidence of resistance to chloramphenicol was reported by *Yan* et al. (2010) for *Salmonella* strains isolated from chicken samples in China. All of the surveys conducted in European countries reported rates of resistance to

chloramphenicol ranging between 5.3% (chicken in Spain) and 37.5% (lamb in the UK). The frequency of resistance to this antibiotic among isolates from African countries was not higher than 4.8% (various meat products in Algeria), while no resistance to chloramphenicol was detected in *Salmonella* spp. from foods in Ethiopia and Tunisia.

Table 2. Number of resistant *Salmonella* spp. strains isolated in different countries.

| | number of tested strains | number of resistant strains | % of resistant strains | Reference |
|---|---|---|---|---|
| | 19 | 19 | 100 | [5] |
| | 250 | 250 | 100 | [54] |
| | 68 | 68 | 100 | [96] |
| | 27 | 27 | 100 | [70] |
| | 71 | 69 | 97 | [43] |
| | 81 | 76 | 93.8 | [92] |
| | 62 | 56 | 90.3 | [56] |
| | 124 | 105 | 85 | [16] |
| | 88 | 74 | 84 | [79] |
| | 82 | 67 | 82 | [60] |
| | 241 | 189 | 78.4 | [78] |
| | 247 | 193 | 78 | [73] |
| | 83 | 64 | 77 | [48] |
| | 110 | 78 | 71 | [7] |
| | 106 | 73 | 68.9 | [51] |
| | 52 | 30 | 57.7 | [50] |
| | 122 | 52 | 42.6 | [52] |
| | 93 | 32 | 34.4 | [97] |
| | 105 | 30 | 29 | [9] |
| | 80 | 16 | 20 | [2] |
| Total: | 2111 | 1568 | 74.3 | |

Table 2 presents the combined survey results showing the general resistance of *Salmonella* spp. isolates of food origin. The lowest level of antimicrobial resistance was among isolates from raw meat collected from stores in the North African countries of Morocco – 29.0% [9] and Tunisia – 20.0% [2]. Studies conducted on food samples from Spain [5], Brazil [54], Turkey [96] and India [70] reported that all tested *Salmonella* spp. isolates were resistant to at least one antimicrobial compound. The surveys whose results are summarized in Table 2 tested a total of 2111 isolates and 74.3% (1568) showed resistance to at least one antibiotic. This confirms that antimicrobial resistance among *Salmonella* spp. isolated from food is a serious problem for food safety and public health.

## MECHANISMS OF RESISTANCE OF *SALMONELLA* SPP. ISOLATED FROM FOOD

### *Resistance to quinolones and fluoroquinolones*

Quinolone resistance in *Salmonella* spp. is usually associated with point mutations in the quinolone resistance-determining regions (QRDR). Such mutations cause amino acid substitutions that modify the targets gyrase (*gyrA*, *gyrB*) and topoisomerase IV (*parC*, *parE*), and make them less susceptible to quinolone binding. Amino acid substitutions in the target enzymes cause increases in the MIC value that may depend on the *Salmonella* serovar. The following alterations are those most frequently reported: GyrA – Ser83→Phe (MIC=256 μg/mL for nalidixic acid, MIC=0.25 – 2 μg/mL for ciprofloxacin), Asp87→Gly, Tyr (256 – 512 μg/mL for nalidixic acid, MIC=0.12 – 0.5 μg/mL for ciprofloxacin); ParC – Ser80→Ile, Arg. Changes in GyrB are not found in many surveys [15, 26].

A new plasmid-mediated quinolone resistance (PMQR) mechanism to nalidixic acid, ciprofloxacin and other fluoroquinolones was reported by *Martinez-Martinez* et al. [49]. This mechanism is based on protection of a quinolone target. Many related *qnr* genes have since been described, i.e. *qnrA*, *qnrB*, *qnrC*, *qnrD* and *qnrS* [13, 42, 61]. There are also numerous variants within each family, with the differences between them associated with amino acid substitutions, e.g. QnrB1, QnrB7 and QnrB17 [42]. *Qnr* genes are often located on plasmids that carry multiple resistance determinants,

and particularly those that harbor genes encoding extended-spectrum β-lactamases (ESBL) [61]. The genes *qnrA* and sometimes *qnrB* are frequently found as components of complex *sul1*-type integrons. *Qnr* genes and those encoding extended-spectrum or AmpC-type β-lactamases are often present on the same plasmids [65].

Another mechanism of resistance to ciprofloxacin is the production of an modified aminoglycoside acetyltransferase (AAC(6')-Ib-cr) that reduces the activity of this compound by enzymatic modification [66].

Resistance can also be mediated by efflux due to overproduction of the periplasmic protein AcrAB belonging to the AcrAB-TolC efflux pump. This results in a multiple antibiotic resistance (MAR) phenotype [31]. *Baucheron* et al. [8] reported that fluoroquinolone resistance in *Salmonella* Typhimurium DT104 is highly dependent on the AcrAB-TolC efflux system.

A conjugative plasmid conferring resistance to the antibiotic olaquindox was found in *E. coli* strains isolated from swine. The resistance mechanism was identified as a multidrug efflux pump OqxAB [36, 72]. Quinoxalines are sometimes regarded as growth promotors, but they are used mainly in the prevention of swine dysentery [11]. Another efflux pump, QepA, was identified in an *E. coli* strain isolated from a urine specimen from an inpatient in Japan. It was encoded on a plasmid conferring multiple-resistance against aminoglycosides, fluoroquinolones and broad-spectrum β-lactams [95].

Among 13 nalidixic acid-resistant *Salmonella* spp. strains isolated between 2004 – 2007 in Colombia from foods of animal origin (chicken, sausages and ground meat), four (30.8%) were *qnrB* (*qnrB19* in all cases) positive. All of these strains were susceptible to ciprofloxacin. The QnrB gene was identified in *S*. Infantis, and twice in *S*. Uganda and in *Salmonella* 6,7:d:-. No other quinolone resistance genes (*aac(6')-Ib-cr*, *qepA*, *qnrA* or *qnrS*) were detected [44].

In a study of *Salmonella* Schwarzengrund isolates from humans, food and food animals in Denmark, Thailand and the USA, ciprofloxacin resistance was detected in 29 (24%) of 123 nalidixic acid-resistant strains [1]. Ten ciprofloxacin-resistant isolates tested in this study contained a double mutation in *gyrA* at codons 83 (Ser→Phe) and 87 (Asp→Asn), which resulted in high level ciprofloxacin resistance.

An international collaborative study conducted in 13 European countries showed that among isolates of *Salmonella enterica* of various origin (environment, food, humans, pigs, fowl, reptiles, sheep, turkeys), 59% (288/485) carried PMQR genes. Among the food isolates, the *qnrS1* gene was most prevalent, being detected in 6 (along with the *aac(6')-1b-cr* gene in one isolate), while two isolates were *qnrB19* positive and a single strain carried the *qnrD* gene [82].

Thirty multidrug resistant (MDR) *Salmonella* spp. isolates were recovered from retail meat samples (chicken, pork and lamb) taken in Shaanxi Province, China, in 2007 and 2008. A total of 68 mutations in gyrase subunit A (*gyrA*), topoisomerase IV subunit C (*parC*) and topoisomerase IV subunit E (*parE*) were identified in the 30 *Salmonella* spp. isolates, but no mutation was detected in gyrase subunit B (*gyrB*) [94].

*Wong* and *Chen* [90] detected *oqxAB* in *Salmonella* spp. isolated from retail meats in Hong Kong. Importantly, this was the first time that two olaquindox-resistant isolates were found to contain the gene combination *oqxAB*, which confers resistance to olaquindox quinolones and chloramphenicol and reduces susceptibility to other antibiotics. Other isolates characterized in this study carried the *qnrS* and *aac(6=)-Ib-cr* genes.

***Resistance to sulfonamides and trimethoprim***

Due to widespread resistance, the use of sulfonamides is no longer common. The resistance of Gram-negative enteric bacteria to these compounds is mediated by plasmid-borne genes encoding alternative variants of the dihydropteroate synthase (DHPS) that have no affinity for sulfonamides [71]. A second gene encoding "normal" (non-modified) DHPS is present on the chromosome in both resistant and susceptible bacteria. The plasmid-encoded DHPS are 1000-fold less susceptible to sulfonamides compared with that encoded by the chromosomal gene. Plasmid-mediated sulfonamide resistance is often associated with resistance to other chemotherapeutics.

When used in combination with trimethoprim, sulfonamides are bacteriocidal. Like sulphonamides, trimethoprim is a compound which competes with substrates of the essential folic acid pathway in bacteria and inhibits dihydrofolate reductase (DHFR). Raesistance to trimethoprim is mediated by genes encoding dihydrofolate reductase variants (*dhfr* and *dfr*) that have decreased affinity for the antimicrobial agent. This allows folic acid biosynthesis to occur in the presence of trimethoprim [39].

A panel of 73 *Salmonella enterica* strains isolated from food products in Portugal in 2002 and 2003 were screened for the presence of *sul* genes [6]. Of six *sul3*-positive isolates obtained from foods of animal origin, four also carried the *sul1* gene, and one was positive for *sul1*, *sul2* and *sul3*. The association of the *sul3* genes with conjugative plasmids in these isolates could facilitate the spread of this gene to other bacteria. The *sul3* gene was shown to occur in *Salmonella* spp. carrying class 1 integrons with *aadA* and *dfrA* gene cassettes, which allows these strains to survive exposure to a combination of sulfamethoxazole and trimethoprim. Sul3-positive *Salmonella* spp. strains of food origin have also been isolated in Germany [34].

Among *Salmonella* spp. isolates obtained from beef samples collected from retail markets in Vietnam in 2009, resistance to sulfonamides was found in 39.7% (25/63 isolates) and 80.0% of these (20/25) were *sul1* positive [77]. Trimethoprim resistance was detected in 28.6% (18/63) of the isolates and of these, 55.6% (10/18) carried the *dfrA1* gene and 33.3% (6/18) the *dfrA12* gene.

Also in Vietnam, in the years 2007–2009, *Salmonella* spp. strains were isolated from pork and chicken [78]. In this case, 58.1% of isolates were resistant to sulphonamides and 34% to trimethoprim.

Between 2007–2008, 110 *Salmonella* spp. isolates were obtained from meat (chicken, turkey and pork) from retail stores in Canada [7]. Of these, 71% (78/110) showed resistance to sulphonamides. The *sul1* gene was found in 5 isolates, *sul2* in 3 isolates and the *sul3* gene was only found in one (pork) isolate.

Among 88 *Salmonella* spp. strains isolated from retail meats and street foods in Malaysia, 63.6% were sulfonamide-resistant [79]. Of these, 32 were positive for *sul1* and *sul2*, 5 were positive for *sul1*, and 14 were positive for *sul2*. Resistance to trimethoprim-sulfamethoxazole was found in 19.3% of the isolates. The gene cassettes identified in the variable regions included trimethoprim resistance genes *dfrV*, *dfrA1* and *dfrA12*. In addition, the *sul1* gene and *aadA2* gene (encoding resistance to streptomycin) were also identified.

Among *Salmonella* spp. strains isolated from meat products from supermarkets and free markets in Shaanxi Province in China between 2007–2008, 67% were resistant to sulfamethoxazole and 58% to trimethoprim/sulfamethoxazole [93]. Five resistance gene cassettes were identified, which included the determinants *dhfr*, *aadA*, *tetR*, *bla*PSE-1, $bla_{DHA-1}$ and $bla_{VEB-1}$, encoding resistance to trimethoprim, streptomycin, tetracycline and beta-lactams, respectively. One *S*. Enteritidis isolate from chicken contained two integrons (1.2/1.8) carrying three resistance genes ($bla_{PSE-1}$/*dhfr*17-*aad*A5).

*Chen* et al. [14] reported that all sulfonamide-resistant *Salmonella* spp. isolated from retail meats in the USA and in China were *sul1*- and/or *sul2*-positive, and dihydrofolate reductase genes (*dhfr1*, *dhfr12* and *dhfr13*) were detected in each of the trimethoprim-resistant isolates.

***Resistance to β-lactams***

β-lactamases were widespread before penicillin was widely used therapeutically, which suggests that these enzymes are a mechanism to counter antimicrobial substances produced by other species of bacteria or fungi in the environment.

The production of β-lactamases is the main mechanism of resistance to β-lactams in Gram-negative bacteria. In 1965, *Datta* and *Kontomichalou* [18] described a plasmid-encoded β-lactamases, found in an *E. coli* strain isolated in Greece from a patient named Temoneira, and they named this enzyme TEM-1 [18]. Within a few years, TEM-1 had become widespread in many species representing different families of bacteria. SHV-1 is another common plasmid-encoded β-lactamase [10].

The chromosomal *ampC* gene found in many *Enterobacteriaceae* is usually expressed at a low level and is inducible in response to β-lactam exposure. *Salmonella* spp. are naturally $AmpC^-$, but *ampC* genes may occur on transmissible plasmids [41, 63].

The increased use of antibiotics and the introduction of new compounds have resulted in the increasing occurrence of β-lactamases and the appearance of new forms. In the 1980s oxyimino-cephalosporins were introduced to treat infections caused by Gram-negative bacteria. The use of these new β-lactam antibiotics resulted in the appearance of resistant strains producing extended spectrum β-lactamases (ESBLs). ESBLs are able to hydrolyze penicillins, cephalosporins (excluding cephamycins) and monobactams, and can be inhibited by β-lactam inhibitors.The genes $bla_{SHV}$, $bla_{TEM}$, $bla_{CTX}$, $bla_{CMY}$ and $bla_{OXA}$ are responsible for ESBL-mediated resistance in *Salmonella* spp. [10, 89].

Numerous studies have investigated the occurrence of different β-lactamases in Gram-negative bacteria isolated from human infections, including *Salmonella* spp.. There are fewer reports describing these enzymes in isolates from food animals, with only a small number concerning *Salmonella* spp. isolates of food origin [87, 89]. In some countries, ESBL-producing *Salmonella* spp. have yet to be identified in food, but their appearance in food animals makes their eventual isolation from food samples likely.

Among *bla* genes, presence of $bla_{TEM}$ has been reported most often among *Salmonella* spp. isolated from food. However other genes such as $bla_{CTX-M}$ and $bla_{CMY-2}$ have also been found.

*Thai* et al. [77] reported that among 20 ampicillin-resistant strains isolated from retail beef in Vietnam, 90% were $bla_{TEM}$-positive, 5% were $bla_{OXA-1}$-positive and 5% harbored both genes. According to *Aslam* et al. [7], among 110 *Salmonella* spp. isolates from retail meat in Canada, 17 were $bla_{TEM}$-positive and 23 were $bla_{CMY-2}$-positive. The following β-lactamase genes were detected among 7 ceftiofur-resistant *Salmonella* isolates from food in Germany: $bla_{CTX-M-1}$, $bla_{TEM-1}$, $bla_{CMY-2}$, $bla_{TEM-52}$ and $bla_{TEM-20}$ [67].

In the study of *Thong* and *Modarressi* [79], of the 6 types of β-lactamase gene tested for ($bla_{TEM,}$ $bla_{CMY-2}$, $bla_{SHV,}$ $bla_{CTX,}$ $bla_{OXA,}$ $bla_{PSE-1}$), only $bla_{TEM}$ was detected in 3 ampicillin-resistant *Salmonella* spp. isolated from retail meats and street foods in Malaysia.

Among multiple-resistant *Salmonella* spp. isolated in the USA and China, from meat products [14], $bla_{CMY-2}$ was the β-lactamase gene most frequently found in extended-spectrum β-lactam-resistant strains. However, a $bla_{TEM-1}$-like gene was also detected. All ampicillin-resistant isolates from meat products in China contained a $bla_{TEM-1}$-like gene, while a $bla_{PSE-1}$ gene located on a 1.0-kb class 1 integron was identified in two *Salmonella* Typhimurium DT104 isolates displaying the ACSSuT (ampicillin, chloramphenicol, streptomycin, sulphametoxazole, tetracycline) multi-resistant phenotype [14].

***Resistance to aminoglycosides***

There are various mechanisms of aminoglycoside resistance, including alteration of the ribosomal binding sites, decreased uptake, decreased accumulation in bacteria, and the expression of enzymes which modify and inactivate these antibiotics. Of these mechanisms, enzymatic inactivation seems to be the most important and most common type of aminoglycoside resistance among *Salmonella spp.* isolated from food. There are three types of aminoglycoside modifying enzyme: acetyltransferases (AAC), adenylytransferases (ANT) and phosphotransferases (APH). Some *aph* genes are also known as *strA* or *strB* genes conferring resistance to streptomycin. Aminoglycoside nucleotidyltransferases can confer resistance to gentamicin, tobramycin or streptomycin and include the genes *aad* and *ant* [28].

Another resistance mechanism is rRNA methylation, which is employed by actinomycetes as a means of self-protection against the aminoglycosides they produce. Over the last decade, 16S rRNA methyltransferases have emerged in Gram-negative bacteria. A number of different methyltransferase-encoding genes have been identified in *Salmonella* spp. isolates of different origin: *armA*, *rmtA*, *rmtB*, *rmtC*, *rmtD*, *rmtE* and *npmA*. Aminoglycoside inactivating enzymes may be encoded by plasmids or associated with transposons, e.g. *armA* is associated with the transposon Tn*1548* [19; 29].

The majority of aminoglycoside methyltransferases have been identified in clinical isolates, but there are occasional reports of this type of resistance mechanism in *Salmonella* spp. of food origin.

The presence of *Salmonella* spp. carrying 16S rRNA methyltransferases in the East of Africa was confirmed by *Granier* et al. [32] who detected an ArmA methyltransferase in an isolate identified as *S.* enterica I.4,12:i:-, obtained from a sample of chicken meat. *Hopkins* et al. [37] reported a strain of *Salmonella* Virchow bearing *rmtC*, isolated from food in the UK. Among 19 streptomycin-resistant isolates - 78.9% contained the *aadA1* gene and 5.3% *aadA2*. All kanamycin resistant *Salmonella* spp. isolated from beef samples collected in Vietnam harbored the *aphA-1AB* gene, and 88.9% of gentamicin-resistant isolates were *aac(3)-IV*-positive [77]. Of the 30 multiresistant isolates obtained by *Chen* et al. [14] from retail meats in the USA and in China, most carried *aadA1* (60%) and the following genes were also detected: *aph(3')-IIa* (13.3%), *aadA2* (10%), *aacC2* (3.3%) and *aac(3)-IVa* (3.3%). In Canada, 42% of all *Salmonella* spp. strains isolated from meat products were *strA*/*B* positive and these were the most common resistance genes detected in this study [7]. Other genes were detected less frequently among the isolates: *aadA* (5%), *aphA2* (4%) and *aphA1* (2%). In a study on *Salmonella* spp. isolated from retail meats and street foods in Malaysia, 45 of the 51 streptomycin-resistant isolates contained both *strA* and *strB* [79]. Among these, 2 contained only *strA*, 3 *S.* Newport isolates contained only *strB*, while 5 *S.* Typhimurium isolates also had an additional *aadA* gene.

***Resistance to chloramphenicol***

One of the most common mechanisms of resistance against chloramphenicol is its inactivation by chloramphenicol acetyltransferases (CATs). These enzymes are encoded by *cat* determinants that may be chromosomal, carried on a plasmid or associated with a transposon or integron. CatA proteins are encoded by the genes *catA1* and *catA2*. A separate *catB* variant has also been identified in *Salmonella* spp. [3, 14, 83].

Chloramphenicol resistance in *Salmonella* spp. can also be mediated by chloramphenicol efflux pumps encoded by the genes *cmlA* and *floR* [77, 88].

Among *Salmonella* spp. isolates obtained from seafood in India, *Deekshit* et al. [20] identified one chloramphenicol-resistant strain that was positive for the presence of the *catA1* gene. Interestingly, some chloramphenicol-susceptible isolates also possessed this gene.

*Thai* et al. [77] found that all chloramphenicol-resistant *Salmonella* spp. strains isolated from retail beef in Vietnam carried at least one resistance gene. Among these isolates, 57.1% were *floR* positive, 50% were *cmlA1*-positive and 14.3% were *cmlA1+floR* positive, while none carried the *catA1* gene.

*Miko* et al. [58] reported that among 154 chloramphenicol-resistant *Salmonella* spp. isolates obtained from food in Germany, the majority were *floR*-positive (90.9%), whereas the *catA* and *cmlA1*-like genes were found in only 3.2% and 2.6%, respectively.

Neither the *cat1* nor the *cat2* gene was detected in nine chloramphenicol-resistant *Salmonella* spp. isolated from meat products and street food in Malaysia [79]. Instead, the *floR* gene was detected in 7 isolates and *cmlA* was detected in 2 isolates.

***Resistance to tetracyclines***

The most common mechanisms of tetracycline resistance are active efflux and protection of the ribosome. Numerous genetic determinants encoding efflux pumps have been described: *tetA*, *tetB*, *tetC*, *tetD*, *tetE*, *tetG*, *tetH*, *tetI*, *tetJ*, *tetK*, *tetL*, *tetP*, *tetV*, *tetY*, *tetZ*, *tet30*, *tet31*, *tet33*, *tet34*, *tet35*, *otrB* and *tcr3* (*tcrC*). Similarly, multiple tetracycline resistance determinants associated with ribosomal protection have been reported: *tetM*, *tetO*, *tetP*, *tetQ*, *tetS*, *tetT*, *tetW*, *otrA*, *tet32* and *tet36* [46, 57]. Notably, two genes encoding enzymes capable of inactivating tetracyclines have also been identified: *tetX* and *tet37* [21]. However in *Salmonella* spp. isolates, tetracycline resistance is usually mediated by the following determinants: *tetA, tetB, tetC, tetD and tetG* [17].

*Deekshit* et al. [20] found that the phenotypic expression of tetracycline resistance in *Salmonella* spp. isolated from seafood in India was always accompanied by the presence of the corresponding resistance determinant. Among the isolates analyzed, they detected the *tetA* gene located on a plasmid, plus the *tetB* and *tetG* genes, but none carried the *tetC* or *tetD* genes.

The *tetA* and/or *tetB* genes were detected in each tetracycline-resistant isolate obtained from meat samples collected in the USA and China, whereas the genes *tetC*, *tetD*, *tetE* and *tetG* were not found [14].

More than half (54.3%) of the tetracycline-resistant *Salmonella* spp. isolated from food in Germany carried *tetG*, while *tetA* and *tetB* were detected in 28.7% and 14.3%, respectively [58]. The genes *tetC* and *tetD* were detected occasionally (1.5% and 0.8%, respectively) and none of the tetracycline-resistant isolates harbored the *tetE* gene.

Out of 65 tetracycline-resistant *Salmonella* spp. isolated from food in Malaysia, 62 and 3 were positive for *tetA* and *tetB*, respectively [79].

***Resistance and multiresistance among different Salmonella serotypes isolated from food***

The frequency of resistance and multiresistance has been found to vary in different *Salmonella* serotypes. *Singh* et al. [70] and *Yildirim* et al. [96] reported that 100% of tested *S*. Typhimurium isolates were multiresistant, while according to *Thong* and *Modarressi* [79] all *S*. Typhimurium strains isolated from food in Malaysia showed resistance to at least one antimicrobial and 78.9% were multiresistant. Lower but still high levels of resistance/multiresistance among isolates of this serotype were reported by *Little* et al.[48] (91.1%/78%), *Mąka* et al. [52] (91%/70%) and *Zewdu* and *Cornelius* [97] (87.5%/42.9%). All 5 multiresistant *S*. Typhimurium isolates tested by *Bouchrif* et al. [9] were the pentaresistant (ACSSuT) strain DT104.

*Salmonella* Hadar is another serotype which isolates derived from food often display multiresistance profiles. All strains of this serotype isolated by *Dallal* et al. [16] and *Yildirim* et al. [96] were multiresistant. *Bouchrif* et al. [9] and *Thong* and *Modarressi* [79] also reported that 100% of *S*. Hadar isolates were antibiotic resistant, and of these 50% and 28.6% were multiresistant, respectively. *Aslam* et al. [7], *Mąka* et al. [52] and *Zewdu* and *Cornelius* [97] detected similarly high levels of resistance among *S*. Hadar isolates, with respective frequencies of 96.4%, 85.7% and 83.3%.

The resistance profile of *Salmonella* Infantis appears similar to that of the aforementioned serotypes. All strains of this serotype tested by *Zewdu* and *Cornelius* [97] were multiresistant. *Yildirim* et al. [96] found that all *S*. Infantis isolates were resistant to one or more antimicrobial and 90% of them were multiresistant. In contrast, *Bouchrif* et al. [9] reported that among *S*. Infantis isolates, only 16% were resistant.

Although *Salmonella* Enteritidis is considered to be generally susceptible, this has changed in recent years. Studies conducted by *Mąka* et al. [51, 52, 53] have shown the increasing frequency of resistant *S*. Enteritidis isolates in retail foods in Poland. Among strains of this serotype isolated between 2004–2007, the overall percentage of resistance was 13.6% (7% multiresistant) [53]. However, in isolates from the years 2008 – 2012 this value had increased to 54% (5% multiresistant) in strains of this serotype isolated from meat products [51], and to 43.7% (6.7% multiresistant) of strains from foods other than meat [52]. These results are similar to those obtained in Austria by *Mayrhofer* et al. [50] - 36% of *S*. Enteritidis isolates were resistant.

*Álvarez-Fernández* et al. [5] reported that all *S*. Enteritidis strains isolated from retail poultry were multiresistant. In studies conducted in various countries (e.g. Korea, Turkey) poultry has been shown to represent a major reservoir of multiresistant *Salmonella* spp., which suggests that it can be difficult to achieve successful antimicrobial therapy for salmonellosis caused by strains of poultry origin [96].

Strains of *S*. Newport isolated from food are generally characterized by a high frequency of antimicrobial resistance [5, 51,79, 96]. However, *Little* et al. [48] and *Zewdu* and *Cornelius* [97] reported that all *Salmonella* spp. isolates of this serotype were susceptible to all tested antimicrobials.

In the USA and Canada, *Salmonella* Heidelberg represents one of the major serotypes isolated from retail meats. *Zhao* et al. [98] found that 67% of isolates of this serotype were resistant to at least one antimicrobial, and 16.4% were resistant to at least five (one quarter of resistant isolates). *Aslam* et al. [7] reported that among *S*. Heidelberg strains isolated from retail meats in Canada, 80.6% were resistant and 45% displayed a multiresistant profile (i.e. 56% of resistant isolates).

Table 3. Examples of antimicrobial resistance genes detected in *Salmonella* spp. isolated from food

| Resistance gene | Antimicrobial class | Reference |
|---|---|---|
| Point mutation in QRDR of *gyrA*, *parC*, *parE* *qnrB*, *qnrD*, *qnrS, oqxAB* | Quinolones and Fluoroquinolones | [44, 82, 90, 94] |
| *sul1, sul2, sul3* | Sulfonamides | [6, 34] |
| *dfrA1, dfrA12, dfrV, dhfr1, dhfrV, dhfrA7, dhfr12, dhfr13, dhfr17* | Trimethoprim | [14, 20, 77, 93, 79,] |
| $bla_{TEM}$, $bla_{TEM-1}$, $bla_{TEM-20}$, $bla_{TEM-52}$, $bla_{CTX-M-1}$, $bla_{CMY-2}$, $bla_{OXA-1}$, $bla_{PSE-1}$ | β-lactams | [7, 14, 67, 77] |
| *armA*, *rmtC*, *aadA1, aadA2, aadA5, aphA-1AB, aac(3)-IV*, *aph(3')-IIa, aacC2, aac(3)-IVa,aacA4, strA, strB, aadA, aphA2, aphA1* | Aminoglycosides | [7, 14, 32, 37, 77, 79, 80] |
| *catA1*, *floR, cmlA1* | Chloramphenicol | [20, 58, 77] |
| *tetA, tetB, tetC, tetD, tetG* | Tetracyclines | [14, 20, 58] |

## GENETIC ELEMENTS AND ANTIMICROBIAL RESISTANCE IN *SALMONELLA* SPP.

In *Salmonella* spp., resistance genes are often located within mobile genetic elements that participate in horizontal gene transfer, i.e. plasmids, transposons, integrons and gene cassettes.

Plasmids are known to play a role in the transfer of genes in *Salmonella* spp.. *Ferguson* et al. [27] showed that antibiotic resistance plasmids can be transferred by conjugation from plasmid-containing strains of *S*. Typhimurium to plasmid-free strains of the same serotype in human epithelial cells. Moreover, multidrug resistant plasmids may be transferred between bacterial species by conjugation, e.g. from *S*. Typhimurium to *E*. *coli* [30]. Using different combinations of donor and recipient strains, *Van* et al. [80] demonstrated that resistance markers can be readily transferred among the same and different species (e.g. *Salmonella* spp. and *E. coli*). These findings demonstrated the importance of plasmids in the dissemination of antibiotic resistance genes in enteric bacteria isolated from food samples.

*Karczmarczyk* et al. [44] identified a plasmid designated pMK101 (carrying the *qnrB19* gene) in *Salmonella* 6,7:d:- isolated from ground meat in Colombia. This plasmid showed 97% sequence identity to the plasmid pMK100 (also carrying *qnrB19*) found in *S*. Infantis isolated from chicken, and was also highly similar to other *qnrB19*-carrying plasmids, including pSGI15, a small ColE plasmid identified in *S. enterica* serovar Typhimurium isolated in Germany [35], and pPAB19 from an *S*. Infantis clinical isolate recovered in Argentina. The small dissimilarity between pMK101 and the other plasmids is due to the presence of an insertion sequence identical to that found in plasmid pBC633 from *K*. *pneumoniae* strain KN633 (accession number EU176012), a urinary isolate from Colombia displaying carbapenem resistance and containing $bla_{KPC-2}$ [84].

Most of the antimicrobial resistance determinants in the *Salmonella* isolates studied by *Chen* et al. [14], including $bla_{CMY-2}$ and the genes contained in integrons, were present on plasmids and could be transferred to *E. coli* by conjugation. The *E. coli* recipient strain acquired 9 to 11 antimicrobial resistance phenotypes by receiving the plasmid from *Salmonella* Agona and *Salmonella* Typhimurium DT208 via conjugation. This finding indicated that conjugal plasmids can play a significant role in the dissemination of multiple-antimicrobial-resistance.

Of the 23 antibiotic-resistant *Salmonella* spp. isolates tested by *Van* et al. [80], all contained plasmids ranging in size from less than 8 kb to more than 165 kb. Plasmids of > 95 kb were found in 35% of the *Salmonella* spp. isolates, and some contained two large plasmids. These large plasmids were conjugative and carried many antibiotic resistance genes. It was also observed that recipient strains could acquire plasmids from donor strains by conjugation regardless of whether or not the recipients harbored their own plasmids. Antibiotic susceptibility testing of the transconjugants showed that the donors could transfer all or part of their resistance phenotype to the recipients. In addition to antibiotic resistance, high-molecular-weight plasmids are often associated with virulence [68].

The transfer of conjugative plasmids is thought to be the most common mechanism of genetic exchange between bacteria. This process can occur with high frequency, it is capable of co-transferring several resistance genes, and transfer can occur both within and between bacterial species [12].

A recent study of *Salmonella* spp. isolates from India found that the *tetA* gene in tetracycline-resistant strains was located on a plasmid [20]. This gene was identical to *tetA* detected in other *Salmonella* spp. serovars and in other bacterial species including *Escherichia coli*, *Edwardsiella tarda* and *Vibrio*

*cholerae*. Moreover, some isolates also possessed the *catA1* gene mediating chloramphenicol resistance located on a plasmid that was identical to a *catA1* gene found in *E. coli* (FN554766) and other *Salmonella* spp. serovars.

*Deekshit* et al. [20] also showed that the presence of a resistance gene does not necessarily result in resistance to the antibiotic in question. Among tested *Salmonella* spp. isolates, 16 chloramphenicol-sensitive strains possessed *catA1* genes, indicating a lack of expression of this gene. This is one of the few studies to show that environmental nontyphoidal *Salmonella* spp. strains can carry silent antibiotic-resistance genes. Similarly, *Thong* and *Modarressi* [79] reported that an isolate of *Salmonella* Agona containing *aadA2* and *sul1* gene cassettes was susceptible to streptomycin and sulfonamides.

Integrons and gene cassettes also play an important role in the dissemination of antimicrobial resistance. Identical resistance gene cassettes have been found in bacteria of the same species and among different bacterial species [38]. Class 1 integrons are the most prevalent among *Salmonella* spp. of animal, food and human origin, whereas class 2 and 3 integrons are detected rarely or not at all [79, 81].

*Chen* et al. [14] detected integron amplicons in 54% of tested multi-resistant *Salmonella* spp. isolates. The most common antimicrobial resistance genes carried by these integrons were *aadA1* and *aadA2*, conferring resistance to streptomycin, and *dhfrXII*, conferring resistance to trimethoprim. The $bla_{PSE-1}$ gene, located in a 1.0-kb class 1 integron, was amplified in each of two *Salmonella* Typhimurium DT104 isolates with an ACSSuT antibiogram.

Multidrug resistant *S*. Weltevreden and two strains of *S*. Newport isolated from seafood were found to be integron positive [20], and there was an excellent correlation between the presence of gene cassettes and the corresponding antibiotic resistance phenotype of these isolates.

Among resistant *Salmonella* spp. isolated from meat samples taken in Vietnam, 13% were positive for class 1 integrons [80]. This indicated that the majority of the tested resistant isolates contained resistance elements other than integrons. Moreover, restriction fragment length polymorphism analysis of resistance gene PCR products suggested that isolates giving the same amplicon sizes carried identical gene cassettes. Of the MDR *Salmonella* spp. isolates characterized by *Thong and Modarressi* [79], 28.8% harbored class 1 integrons that were mostly located on plasmids (no class 2 or class 3 integrons were detected), which again indicated that the majority of the resistant *Salmonella* spp. isolates probably contained resistance elements other than integrons. Conjugation experiments were carried out with 14 MDR *Salmonella* spp. isolates containing the integrase gene, but only 4 isolates (three *S*. Typhimurium and one *S*. Corvallis) successfully transferred their resistance genes to *E. coli* J53.

## CONCLUSIONS

Antimicrobial resistance in *Salmonella* spp. is a growing problem for food safety. As highlighted in this review, resistant *Salmonella* spp. are becoming more frequent in food in many countries situated in different regions of the world.

To monitor the potential spread and development of resistance, there is the need for further research on antibiotic resistant bacteria in food. Without quantitative estimates it is not possible to increase the quality of risk assessments or develop targeted interventions. In many countries, epidemiological data on antibiotic resistance, from a food safety perspective, are scarce. To permit the comparison of data obtained in many locations around the world, a harmonized approach to monitoring antibiotic resistance should be developed and applied, following international standards and recommendations.

Resistance of *Salmonella* spp. in food is linked to the use of antimicrobials in food animals. The practice of herd treatment of such animals (e.g. broiler chickens) with antimicrobials, leads to their higher exposure to these compounds and consequently promotes the increase in antibiotic resistance. The extensive use of antimicrobials in food production has already resulted in acquiring of resistance by *Salmonella* spp. If current farming practices are not changed, the development and spread of antibiotic resistance will undoubtedly continue.

The use of a single antibiotic may result in the development of resistance to other antimicrobial compounds of the same or different classes. Even in the absence of exposure to a particular antibiotic, resistant bacteria often carry resistance genes for long periods of time and may readily transfer and uptake these genes via horizontal gene transfer. Resistance genes in *Salmonella* spp. are often located on mobile genetic elements like integrons, transposons and sometimes insertion sequences, that promote the spread of resistance determinants.

The potential for the rapid dissemination of resistance among bacteria makes it especially important to monitor antimicrobial susceptibility and mechanisms of resistance of *Salmonella* spp. isolated from food, because new mechanisms of resistance occurring in animals may enter the food chain and be transferred to the consumer. This worrying scenario emphasizes the importance of cooperation between sectors in order to monitor antimicrobial resistance and rapidly identify trends that might further reduce the effectiveness of therapeutic antibiotics.

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***Conflict of intrest***
*The authors declare no conflict of interest.*

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