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Quinolone Resistance in Non-typhoidal *Salmonella*

Siriporn Kongsoi, Chie Nakajima and
Yasuhiko Suzuki

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Abstract

Non-typhoidal *Salmonella* is the primary foodborne zoonotic agent of salmonellosis in many countries. Non-typhoidal *Salmonella* infections are transmitted to humans primarily through consumption of contaminated foods from animal origin, whereas *S.* Typhi and Paratyphi infections are spread directly or indirectly by contact with an infected person. Quinolones exhibit potent antibacterial activity against *Salmonella* and are usually the first choice of treatment for life-threatening salmonellosis due to multidrug-resistant strains. However, by the early 1990s, quinolones have been approved for use in food-producing animals. The increased use of this group of antimicrobials in animal has led to the concomitant emergence of quinolone-resistant non-typhoidal *Salmonella* strains. However, in some countries, there are no legal provisions, which apply to veterinary drugs. This situation provides favorable conditions for spread and persistence of quinolone-resistant bacteria in food-producing animals. The objective of this chapter is to review the current regulatory controls for the use of quinolones in food-producing animals, its effect on development of quinolone resistance, and the potential impact on human and animal health. Moreover, this chapter reviews the current knowledge of quinolone resistance mechanisms and the future directions of research with particular attention to the strategies to control the emergence of quinolone-resistant *Salmonella*.

Keywords: non-typhoidal *Salmonella*, quinolones, resistance

1. Introduction

Non-typhoidal *Salmonella* refers to a group of bacteria that cause diarrheal illness in humans and domestic animals. More than 2500 different serovars of non-typhoidal *Salmonella* have been described: all serovars of *Salmonella* except for Typhi, Paratyphi A, Paratyphi B (tartrate negative), and Paratyphi C. Non-typhoidal *Salmonella* are important causes of foodborne infection because *Salmonella* have a broad host range and are strongly associated with animal

and plant products. Humans are infected by consumption of food or water contaminated with *Salmonella* and direct contact transmission between infected animals and humans in a variety of ways or contaminated environment and directly between humans. The recent outbreaks show that fresh fruits and vegetables can be contaminated with non-typhoidal *Salmonella* especially sprouts, tomatoes, fruits, peanuts, and spinach [1–5]. Non-typhoidal *Salmonella* is commonly found in food products derived from the animal species such as poultry, eggs, dairy products, and contaminated pets such as cats, dogs, rodents, reptiles, or amphibians [6–9].

Non-typhoidal *Salmonella* is a leading cause of bacterial diarrhea worldwide, in contrast to typhoid fever, which remains endemic in developing countries. There are an estimated 93.8 million cases of non-typhoidal *Salmonella* gastroenteritis, resulting in approximately 155,000 deaths globally each year [10]. Gastroenteritis is the most frequent clinical symptom of non-typhoidal *Salmonella* infection. The incubation period of non-typhoidal *Salmonella* gastroenteritis is 6–72 h, usually 12–36 h after initial exposure. The classic presentation in non-typhoidal *Salmonella* gastroenteritis has self-limiting, acute gastroenteritis, watery diarrhea, abdominal pain, fever, nausea, and sometimes vomiting [11]. The gastroenteritis usually lasts 4–7 days, and most people recover with little or no treatment [12]. Non-typhoidal salmonellosis clinical presentations differ significantly by serovars such as *S.* Typhimurium and *S.* Enteritidis, have a broad host range, and can cause gastrointestinal infections with less severity than typhoidal enteric fever which affects both humans and a wide variety of animal hosts. An infection with *S.* Choleraesuis is primarily responsible for the severe systemic illness of salmonellosis in human and swine. Some serotypes such as *S.* Dublin are responsible for the systemic salmonellosis in humans and also cause death in young calves, occasionally death in mature cattle and results in decreased milk production, diarrhea, and abortion in cattle. Rates of invasive systemic salmonellosis and death are generally higher among persons with high-risk conditions, infants aged <3 months, elderly aged ≥60 years, the debilitated, immunosuppressive conditions, and malignant neoplasms.

Antimicrobial therapy can prolong the duration of excretion of non-typhoidal *Salmonella* and, therefore, is only considered for gastroenteritis patients caused by *Salmonella* species with moderate-to-severe diarrhea, high fever, or systemic infection and for gastroenteritis in people at increased risk of invasive disease (persons with high-risk conditions). Current recommendations are that fluoroquinolones (FQs) be reserved for patients with moderate-to-severe diarrhea by non-typhoidal *Salmonella* infection. Resistance among non-typhoidal *Salmonella* serovars to the first-line antibiotics such as chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, and cotrimoxazole has been present for many years, and resistance to FQs has also increased over the last decade.

The emergence of quinolone-resistant non-typhoidal *Salmonella* varies by serotype and geographic location. Therefore, the control of quinolone-resistant non-typhoidal *Salmonella* infection is difficult. There is a high need to understand the quinolone resistance mechanisms for preventing the further quinolone resistance development through the better interventional strategies that prevent spread of quinolone-resistant *Salmonella* between humans and animal reservoirs along the food chain.

2. Quinolone use in food-producing animals

The first quinolone was generated in the early 1960s. The first member of the quinolones is nalidixic acid (NAL), a 1,8-naphthyridine as shown in **Figure 1**, which had a good activity against Gram-negative pathogens and was used to treat urinary tract infections. However, the use of NAL was decreased due to the increasing resistance of this drug and because of the synthesis of new, broad-spectrum, and safer antimicrobials. The molecular modifications of the core quinolone structure significantly affect their antimicrobial activity, allowing the synthesis of various compounds of this drug class.

FQs (fluorinated derivatives of quinolones) were first developed since the 1980s. The presence of fluorine in position 6 of the core quinolone structure provides broad and potent antimicrobial activity against Gram-positive and Gram-negative bacteria because it significantly enhances the antibiotics' penetration into the bacterial cell membrane. Norfloxacin (NOR), launched in 1980, is a first broad-spectrum FQ which consisted of a piperazinyl ring that replaces the methyl group at position 7 (**Figure 1**) results in enhancing activity against Gram-negative bacteria [13]. Ciprofloxacin (CIP) has similar structure to NOR except the ethyl group at N-1 of CIP is replaced by a cyclopropyl group (**Figure 1**) that increasing the spectrum of action which not only active against Gram-negative bacteria but also against Gram-positive bacteria [14]. The structure of enrofloxacin (ENR) is similar to CIP but with an additional ethyl group on the piperazinyl ring (**Figure 1**).
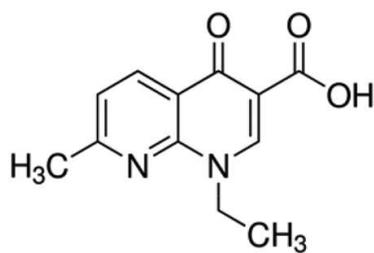
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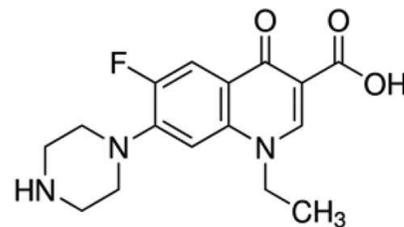
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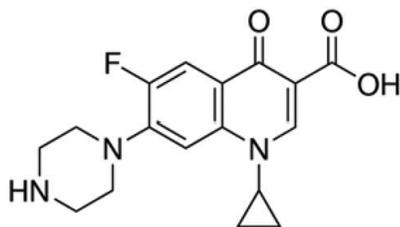
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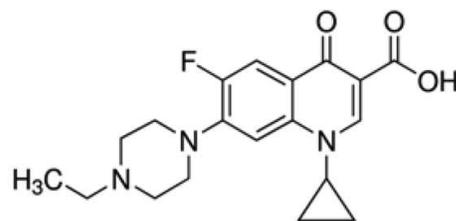
Enrofloxacin

Figure 1. The structural features of four different quinolones.

All these structural modifications in the molecular molecule of quinolones improved a spectrum of drug activity, tissue penetration, long half-life in the body, lower toxicity, and greater capacity to cross bacterial cell membranes and consequently better activity against Gram-negative bacteria and Gram-positive species. Their treatment indications developed from urinary infection to applications against many other systemic diseases. The last generations of quinolones provide the activity against anaerobic bacteria.

FQs have been licensed for use in food animals at the beginning of the 1990s, and subsequently, a new FQs extensively have been authorized, and a large number of different veterinary pharmaceutical products have been launched in the market [15]. ENR exhibits good activity against most Gram-negative bacteria, including *Escherichia coli*, *Campylobacter*, *Enterobacter*, *Serratia*, *Chlamydia*, and *Mycobacterium*, and has a variable effect on *Pseudomonas*, *Enterococcus*, *Clostridium*, *Staphylococcus*, and *Streptococcus*. The efficacies of ENR treatment in food-producing animals have been reported in turkeys against *Pasteurella multocida* infections and in chickens against *E. coli* infections. Danofloxacin (DFX) and ENR are licensed for use in food-producing animals in the United States. ENR and DFX are currently approved to be good choices for therapy of bovine respiratory disease (BRD) in high-risk cattle. ENR is also currently approved for treatment of swine respiratory disease (SRD). DFX and ENR are only available as a sterile injectable solution for animal usage and should be administered under a prescription from a veterinarian. ENR is FQ antimicrobial agent frequently used in poultry production, sold by the Bayer Corporation under the trade name Baytril; however, it is also sold under the various generic names. ENR is a FQ antibiotic that is very similar to the human drug CIP. Under current legislation, if a small number of chickens present the clinical signs and symptoms, ENR can be used to treat the whole flock by adding the drug into the drinking water, even when most of the chickens are not sick. FQs can also be used to treat infections in breeding flocks, and the transmission of drug-resistant organisms may occur among chicks.

Finland and Denmark ban all the uses of FQs in poultry; however, they are used in other species of farm livestock. Australia has never approved the use of FQs in poultry and any farm animals, and consequently, resistance to FQs in zoonotic bacteria such as *Campylobacter* and *Salmonella* has a low prevalence in farm animals. The prevalence in human infected with resistant bacteria is also much lower than in many other countries. Resistant *Campylobacter* infections were low just 0% in 2003 and 2.6% in 2006; however, nearly all of these cases were returning travelers [16]. Human infections with resistant *E. coli* were also low in prevalence at 4–5% [16]. Finland does not approve the use of FQs in poultry result in no resistant *Campylobacter* from poultry productions in 2007, and the resistance in *Campylobacter* was found only 1% in 2008 and 2009. Resistant *Campylobacter* infections of Finnish patients who had not traveled abroad were found 2–3% and 61% were investigated from the patients who have traveled abroad within 2 weeks [17].

In September 2005, the U.S. Food and Drug Administration (FDA) banned the use of FQs for treating bacterial infections in U.S. poultry result from concerns about increasing in FQ resistance among *Campylobacter* isolates of poultry and humans. Although the FQs were banned in the US in 2005, the impact of the ban on resistance in human *C. jejuni* is not clear because the resistant isolates in 2013 remained at the same level as in 2005 (22%). In retail chicken,

CIP resistance in *C. coli* has decreased to 13.5% in 2010 from 29% in 2005; however, resistance in *C. jejuni* significantly increased from 15.2 to 22.5% from 2002 to 2010. It may be caused by the illegal use of FQs in the U.S. poultry industry.

3. A contribution of veterinary usage of quinolones to resistance in human non-typhoidal *Salmonella* isolates

Multidrug resistance in non-typhoidal *Salmonella* is a global problem, and these strains are linked to more severe disease outcome. Serovars Typhimurium and Newport, two of most common serotypes, are more resistant to multiple antimicrobial agents than the other serotypes [18]. Multidrug-resistant *S.* Typhimurium definitive type (DT) 104, was first detected in 1980s, emerged as a public health concern because of its global distribution in diseases among animal species such as poultry, pigs, and sheep and humans [19, 20]. The emergence and worldwide spread of multidrug-resistant *S.* Typhimurium DT104 isolates are associated with the intake of contaminated meat and meat products. Many strains of *S.* Typhimurium DT104 are generally resistant to ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracycline [21]. Moreover, new resistant strains of non-typhoidal *Salmonella* are constantly rising worldwide and resistant against ampicillin, chloramphenicol, kanamycin, streptomycin, trimethoprim, and cotrimoxazole [22–24], for example, a multidrug-resistant strains of serovars Virchow [25], Heidelberg [26], and Infantis [27, 28].

Quinolones were introduced for veterinary use in various countries, and subsequent use has been followed by the development of quinolone resistance in bacteria of food-producing animals and consequently transmits the resistant zoonotic bacteria to humans [29]. In many countries, FQs are drug of first choice for prescription in acute gastrointestinal symptoms caused by *Salmonella* infection, and resistance to this drug group has often been described, particularly to NAL [15]. In a study performed between 1996 and 2003, *Salmonella* isolates were investigated for quinolone susceptibility; the results revealed that NAL and CIP resistances were 1.6 and 7%, respectively. A significant upward trend in resistance was observed for NAL from 0.4% in 1996 to 2.3% in 2003 [30]. In Germany, an increase in the frequency of NAL-resistant *Salmonella* strains was discovered after the approval and use of ENR [31]. Concurrent increase in resistance was observed in France among *Salmonella* isolates from animals and humans, and the same clones were determined among the different hosts [32]. In the United Kingdom, also in Spain, the incidence of NAL-resistant *Salmonella* illnesses in humans was increased followed the introduction for veterinary use of FQs in 1993 [33, 34]. A study from Denmark and Taiwan described the emergence of salmonellosis caused by multidrug and quinolone-resistant *S.* Typhimurium DT104 linked to a swine herd and the subsequent spread of those isolates to humans [35–37]. In European countries, similar associations between FQ resistance development in *Salmonella* infecting humans and retail poultry products have been described. Therefore, the FQ-resistant *Salmonella* in poultry has reached alarming proportions in some countries [38]. In the United States, there was an increase in the proportion of FQ resistance development in *Salmonella* infections following the first approved use of FQs in food-producing animals in 1995 [39].

The data indicate that it would be reasonable to assume that the veterinary usage of FQs will have made a remarkable contribution to FQ resistance in human *Salmonella* infections.

4. The potential impact on human health

FQ resistance in *Salmonella* is clearly associated with FQ use in food-producing animals, and foodborne infections caused by such resistant bacteria are well investigated in human. FQ resistance in *S.* Typhimurium DT104 has been associated with increased hospitalization, more frequent and longer illness, treatment failures, and a higher risk of death [40]. Many studies also investigated that infections with multidrug-resistant *Salmonella* were associated with longer hospitalization and a higher death rate than infections with susceptible isolates [41–43]. Previous study has found a 3.15 times increased mortality when patients infected with NAL-resistant *S.* Typhimurium compared to patients infected with susceptible isolates [44]. For treatment of the infections with FQ-resistant *Salmonella,* alternative antimicrobials are the third or fourth generation cephalosporin. Nevertheless, it should be considered contraindications for treatment of uncomplicated non-typhoidal *Salmonella* infection because FQ treatment can induce prolonged excretion of *Salmonella* and increased frequency of relapses [45]. However, for patients at risk such as immunocompromised, severely infected and elderly, FQs are considered first choice drugs and effective in reducing the disease length if the treatment starts early in the infection.

5. The potential impact on animal health

FQs are highly potent antimicrobial agents rapidly absorbed after oral administration and have a long half-life and widespread distribution to most body tissues, which made them suitable for using in herd treatment of food-producing animals. FQs are effective for serious infections in food-producing animals such as systematic gastroenteritis and severe respiratory diseases and are also used to treat urinary tract, skin, and soft-tissue infections caused by Gram-negative or some Gram-positive aerobic bacteria. Moreover, they also have potential for treatment of infections caused by *Mycoplasma*, *Mycobacterium*, *Chlamydia*, *Ehrlichia*, and *Rickettsia*. However, documentation about authorized dosages and the effectiveness of FQs to treat all these infections in animals have not been determined on the base of the pharmacokinetic and pharmacodynamics properties. Sufficient knowledge about the selecting optimal dose and duration of FQs could help to develop appropriate dosing regimens to maximize the clinical efficacy, avoid therapeutic failure, and decrease the selection of resistance which would ensure for the benefit of animals and their future use.

However, the potential clinical disadvantage associated with FQ use was a rapid selection for resistance. Several pathogenic bacteria of food-producing animals have been investigated the increasing of resistance to FQs following the introduction of ENR [46]. If FQ resistance emerges in animal pathogenic bacteria, this may result in treatment failure and increased mortality. This is a risk for poor animal welfare conditions and will result in economical

losses. Consequently, for some animal infectious diseases, antimicrobial therapeutic use will be complicated if FQs lose their efficacy. As described in a previous study, multidrug-resistant *S.* Typhimurium infections in veal calves were resistant to most conventionally used antimicrobials and also resistant to ENR resulted in a mortality exceeding 90%. FQs are also considered effective in other infections such as pneumonia, neonatal diarrhea, and mastitis caused by Gram-negative organisms in piglets and calves. However, there were insufficient data to support the animal health or welfare problems when diseases cannot be treated result from FQ resistance during treatment.

6. The current state of knowledge of quinolone resistance mechanisms

FQs are strong inhibitors of bacterial enzymes, which are necessary enzymes associated in major biological processes including DNA replication [47–49]. In prokaryotes, DNA is known as a double helix because there are two strands that intertwine around each other. However, additional complexity comes from the further twisting (supercoiling) of the double-strand structure to put the double helix under torsion stress [50]. This supercoiling process that enables the long strands of DNA is condensed into compact supercoils permitting large amounts of DNA to be packed into the cell [51].

Topoisomerase I and topoisomerase II enzymes are enzymes that regulate the overwinding or underwinding of DNA and control the level of twisting within DNA. Topoisomerase I removes the number of negative supercoils, in contrast to topoisomerase II, which introduces negative supercoils that facilitate the unwinding of the over-twisted DNA and can further change the DNA topology into an under-twisted DNA [50]. DNA gyrase and DNA topoisomerase IV are type II topoisomerase comprising 2 A subunits and 2 B subunits encoded by the *gyrA* and *gyrB* genes or 2 C subunits and 2 E subunits encoded by the *parC* and *parE* genes, respectively [52]. DNA gyrase and topoisomerase IV have distinct roles although both enzymes have homologous action to relax positively supercoiled DNA. DNA gyrase decatenates replicating DNA by introducing negative supercoils into relaxed DNA while topoisomerase IV unlinks the newly replicated daughter chromosomes during cell division [52–54].

FQs are direct inhibitors of bacterial DNA synthesis by inhibiting two enzymes, DNA gyrase and topoisomerase IV, which have important roles in DNA replication. The quinolones bind to these enzymes with DNA to form drug-enzyme-DNA complexes (known as a ternary complex) subsequently induces double-strand DNA breaks and blocks replication, therefore, results in damage to bacterial DNA and bacterial cell death [55–58]. However, the primary target enzyme, either DNA gyrase or topoisomerase IV, of FQs varies depending on the bacterial species. The preferential target of FQs in Gram-negative bacteria is DNA gyrase, whereas in Gram-positive microorganisms, topoisomerase IV is the primary target [58].

Resistance to quinolones occurs by different ways. The major mechanisms of bacterial resistance to FQs are altered target enzymes, expression of an active efflux, and altered membrane permeability.

6.1. Target-site mutation

The main mechanism of FQ resistance is due to mutation in target genes (*gyrA*, *gyrB*, *parC*, and *parE*) that encode the primary and secondary target enzymes of these drugs. The mutations in quinolone resistance-determining region (QRDR) of target genes alter the target enzyme conformation by amino acid substitutions and subsequently decrease in the drug binding affinity of the target enzyme, leading to FQ resistance [59–62].

In *Salmonella*, quinolone resistance was firstly investigated in the *gyrA* gene coding for the A subunit of gyrase. Mutations associated with FQ resistance in GyrA have been clustered between amino acids 67 and 106, termed the QRDR region. Amino acid substitutions of GyrA at Ser83 (to Phe, Tyr, or Ala) or at Asp87 (to Gly, Asn, or Tyr) are most usually identified in NAL-resistant *Salmonella* strains. Previous studies have observed that single point mutation in QRDR of *gyrA* led to reduced sensitivity to CIP in *Salmonella* isolates [63]. Similar decreasing in CIP susceptibility was also found in three amino acid mutations of *parC* at Ser67 (to Cys), Arg76 (to Cys), and Cys80 (to Arg) in *S.* Enteritidis [64, 65]. Nevertheless, less frequently, the previous study detected novel mutations inside QRDR of GyrA at codon Asp72, Asp82, and Ala119 and also outside the QRDR [66]. Moreover, in another studies, the authors found double mutations in GyrA at both Ser83 and Asp87 in *S.* Typhimurium DT204 [67] and a single mutation at Asp87 (to Tyr) in all *Salmonella* strains [68] showing high-level resistance to FQs. A *gyrB* gene mutation has also been observed in a quinolone-resistant *S.* Typhimurium at Ser463 (to Tyr) [69].

These target-site mutations show that different mutations of FQ-resistant *Salmonella* isolates can result in very different resistance levels of quinolones, and this is not the same for all strains and all resistance mutations. Therefore, amino acid substitutions in topoisomerases are inadequate to clarify the level of resistance to quinolones in *S. enterica*. Nevertheless, it remains to be investigated what the specific role of these mutations on quinolone resistance in *Salmonella*.

6.2. Transmissible quinolone-resistance mechanisms

Plasmid-mediated quinolone resistance (PMQR) genes on mobile genetic elements are able to reduce susceptibility of quinolone or FQ antimicrobials. The PMQR gene, *qnr*, encodes a pentapeptide repeat motif protein (Qnr) that protects the target enzyme DNA gyrase and topoisomerase IV by blocking the quinolone inhibition [70]. Recently, several Qnr proteins were investigated in Enterobacteriaceae (QnrA, QnrB, QnrC, QnrD, QnrS) [71, 72]. A recent study reported six variants of *qnrB* genes in *Salmonella* and *E. coli* isolates of human and animal isolates [73]. Nonetheless, the prevalence of *qnrS* genes is higher than the other *qnr* genes in *Salmonella*. A study from different European countries investigated a *qnrS* gene in 10% of the *Salmonella* isolates [73]. Moreover, *qnrS* gene has been identified in non-typhoidal *Salmonella* clinical isolate from the USA [74]. The *qnrD* gene also has been investigated in eight different *Salmonella* serovars from 13 European countries [73].

Another plasmid-encoded quinolone resistance determinant is a variant of an aminoglycoside acetyl transferase gene, *aac(6')-Ib-cr*, which is able to acetylate the amino nitrogen on the piperazinyl substituent in aminoglycoside, and FQ drug classes lead to decreased

susceptibility of these drugs [75–77]. However, the variant enzyme is not able to acetylate moxifloxacin and levofloxacin due to the absence of a piperazinyl substituent at position C-7. Recently, this *aac(6')-Ib-cr* gene has been reported in *Salmonella* isolated from chickens in China [78]. Plasmid-mediated quinolone resistance determinants in *Salmonella* isolated from food-producing animals are serious public health concern. Continuous surveillance of quinolone resistance determinants at national and international levels needs for limiting the dissemination of quinolone-resistant *Salmonella* strains.

6.3. Membrane permeability

The membrane permeability and the ability of FQs to enter the bacterial cells are an important determinant of the potency of these drugs that have intracellular targets [79]. The outer-membrane proteins (OMPs) of Gram-negative bacteria consist of pore-forming outer-membrane proteins which serve as a particular barrier for the entry of hydrophilic molecules into the cell. It has been shown that CIP (hydrophilic quinolones) preferentially entry into the cells via porin pathway [80]. Down-regulation of OMPs results in reduced FQ susceptibility in FQ-resistant isolates of different species [81–84]. Very few researches have investigated on alterations of OMP expression or the role of lipopolysaccharide composition in quinolone-resistant *Salmonella* isolates [68, 85–89]. The lengthening of the O chains has been studied in quinolone-resistant *Salmonella* that could also lead to a lower level in the permeability of the outer membrane [85]. The previous studies have found the lack of OmpF porin expression result from SoxS up-regulates micF transcription in quinolone-resistant *Salmonella* strains [86–88, 90]. However, it remains unclear whether such alterations contributed to significant reduction of outer-membrane permeability and reduced susceptibility of quinolones in *Salmonella* isolates.

6.4. Efflux

Chromosomal multidrug efflux pumps are capable of actively removing FQs and a broad range of antimicrobial agents from the bacterial cell and are mostly encoded by chromosomal genes. These efflux systems consist of different classes of transporters such as the resistance nodulation division (RND) family of tripartite transporters of Gram-negative pathogens [91, 92]. These systems are mainly responsible for the intrinsic pattern of reduced susceptibility to FQs and other antimicrobial agents but are also responsible for increased resistance resulting from derepression of the transporter. Previous studies showed the evidence for the participation of active efflux in quinolone-resistant *Salmonella* isolates [85, 93]. It was concluded that the overproduction of the AcrAB-TolC efflux pump appeared prior to *gyrA* mutations in *in vitro* selected quinolone-resistant *Salmonella* mutants [85]; therefore, the AcrAB-TolC efflux system is the major mechanism that involved in quinolone resistance in *S.* Typhimurium DT104 strains. However, both target gene mutations and active efflux mediated by AcrAB-TolC are necessary to obtain high-level FQ resistance for *S.* Typhimurium DT204 strains [94]. Nevertheless, there is no direct evidence to demonstrate the role of the AcrAB-TolC efflux system in quinolone-resistant *Salmonella*; therefore, substantial work remains to be done in order to understand the role of efflux and its regulation in *Salmonella*.

6.5. The fitness costs

Mechanisms associated with high-level FQ resistance are multiple mutations in the type II topoisomerase-encoding genes and the over-expression of multidrug resistance efflux pumps. The presence of mutations in these structural or regulatory genes not only increases resistance to quinolones but also affects fitness costs such as reduced growth rates and virulence of the bacterial cell in a lack of antibiotic selective pressure [95–99]. However, maintenance of resistance can arise through the development of second-site compensatory mutations that restore fitness and virulence without loss of resistance [100].

The fitness cost of the genes responsible for quinolone resistance traits has not been fully elucidated in high-level FQ-resistant *Salmonella*. Nevertheless, results from previous studies suggest that high-level CIP resistance mechanisms in *Salmonella* lead to restrictive conditions of fitness costs and minimizing the emergence and spread of highly resistant clones in the absence of drug selection pressure [101, 102]. As demonstrated in previous study [103], high-level CIP-resistant *S*. Enteritidis *in vitro* derived mutants in the absence of antibiotic selective pressure result in compensatory evolution favoring a reversion back to a more sensitive phenotype associated with lesser fitness costs, rather than the compensatory mutations that would restore resistance. However, under *in vivo* conditions, a previous study has found that chromosomal mutations of *S*. Typhimurium that confer resistance to NAL, streptomycin, or rifampicin decrease growth rate and ability to colonize in mice rather than a reversion to the susceptible phenotype and restore virulence [104]. In contrast to the high-level FQ resistance, an intermediate level of resistance to CIP of *S*. Typhimurium mutants apparently favored a partial reversion to a susceptible level and a normal growth rate with successfully colonized the gut of chickens, rather than the acquisition of resistance to FQs [101].

Quinolone resistance of non-typhoidal *Salmonella* is complicated. The understanding of the various mechanisms of quinolone resistance, the fitness costs of each *Salmonella* strain, and the interplay between different quinolone resistance mechanisms has increased in recent years. Increased resistance to quinolones could be selected under a wide range of selective conditions even in the absence of quinolone selective pressure. Therefore, minimizing the emergence and spread of quinolone resistance will not be as simple as limiting the use of these drugs.

7. To decrease the emergence and spread of quinolone resistance

FQs are intensively used in animal production and have allowed better treatment of several animal infectious diseases. The risks of the overuse and misuse of FQs in food-animal production can contribute to higher levels of resistance in human *Salmonella* infections. Therefore, the FQ resistance of *Salmonella* should be taken into account and prevented as resistant bacteria or resistance genes may be transferred to humans through the food chain. Given the importance of FQ resistance as a global health concern, many researchers have reviewed the existing scientific literatures and developed guidelines to limit all compounds of FQ use, including use in food-producing animals. FQs should be banned for all preventive use and mass medication, but only used as life-saving therapeutic treatment of individual sick animals.

Priority setting of agendas for research on minimizing the emergence of FQ resistance in *Salmonella* is needed to identify missing scientific data and to specify research designs and methods to address these resistance problems in food-producing animals and human medicine. The priorities identified by the research agenda must include contributions by different experts in basic genetics and microbiology sciences, veterinary medicine, human medicine, public health organization, social sciences, economics sciences, and public policy.

Furthermore, sufficient research funding for minimizing the FQ resistance of *Salmonella* in human and food-producing animals has likely contributed to the adequate scientific evidence which necessary for informing public health decisions. Given the scale of the FQ resistance problem and the demonstrated role of FQ uses in food-producing animals in this public health crisis, adequate support for research specific to the role of food-producing animal uses of FQs in the development of resistance must be a national priority.

Urgently address complex barriers that limit the quality of data on the use of FQs in food-producing animals and human medicine. Currently, such data from human and veterinary medicine are provided on a voluntary basis, and the methods used to collect, analyze, and report are not standardized because of political, economic, and social barriers. Effective surveillance of FQ use in food-producing animals and humans is a key first step toward for estimating the full scope of FQ resistance in *Salmonella*. Despite increasingly widespread recognition that FQ use in food-producing animals is a major factor of human infections with FQ-resistant *Salmonella*, there remains a significant need for scientific evidence of the FQ use practices that affect the human health risk.

8. Conclusion

Infections in humans with quinolone-resistant *Salmonella* resulted in increased risk of hospitalization and mortality. FQs are efficient and valuable antimicrobials in some serious animal indications because FQs are the only alternative available. Therefore, if FQs lose their ability for the treatment of animal diseases, the therapeutic effect of some diseases will be complicated and may result in poor animal welfare and economical losses. Recently, it is now critical that food-producing animal use of FQs be recognized as one of the major contributors to the development of resistant *Salmonella* strains that result in life-threatening human infections and included as part of the strategy to control the public health crisis of FQ resistance.

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