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Review Paper

Sub-minimal inhibitory concentrations of fluoroquinolones in the environment: A trigger for the emergence of drug-resistant bacteria

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ABSTRACT

Fluoroquinolones represent a significant class of antimicrobial agents. These compounds are effective in the treatment of various enteric infections in veterinary medicine. The primary bacterial targets of quinolones are topoisomerase IV and DNA gyrase, enzymes essential for DNA replication and repair. A major public health concern is the potential transmission of fluoroquinolone-resistant bacteria from livestock to humans. The development of antimicrobial resistance in both animals and humans is interconnected. Multiple observational studies and randomized trials have established an association between the use of antibiotics in food animals and the emergence of antimicrobial-resistant bacteria. Fluoroquinolones induce DNA damage, leading to DNA strand breaks that activate the SOS response and various DNA repair pathways. The SOS system, a key component of the DNA repair machinery, plays a critical role in cell cycle regulation. Activation of this system initiates a cascade of signals within bacteria, resulting in enhanced pathogenicity. Through these signaling pathways, bacteria have evolved diverse mechanisms such as pathogenicity islands, biofilm formation, and toxin production. The presence of residual fluoroquinolones in livestock environments and animal production systems following veterinary use is associated with increased bacterial virulence. This review focuses on the impact of fluoroquinolone exposure at sub-minimal inhibitory concentrations on bacterial virulence and pathogenicity.

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1. Introduction

Antibiotics are considered an indispensable element of contemporary medicine; therefore, antimicrobial resistance is a major concern globally. Antibiotic therapy is the primary step in managing critically ill patients diagnosed with infectious diseases [1]. The treatment of infections caused by drug-resistant pathogens is becoming more challenging. High drug resistance rates lead to fewer treatment options, prolonged hospital stays, higher rates of morbidity and mortality, and higher health care costs. Antimicrobial resistance genes are rapidly disseminated within and between species through genetic recombination [2].

There are a wide range of compounds that are fluoroquinolones that are effective against complicated urinary tract infections, gastrointestinal infections, respiratory tract infections, sexually transmitted diseases, and chronic osteomyelitis. In both human medicine and the food industry, consumption of fluoroquinolones has increased rapidly because they are excellent antibiotics for a variety of clinical indications [3]. DNA gyrase and topoisomerase IV are genes involved in fluoroquinolone resistance, as are the regulatory factors controlling bacterial permeability and efflux capacity [4].

Over-prescription or misuse of antibiotics for infections that may not be caused by bacteria increases pressure on populations of bacteria. The combination of this selective pressure and the ability of bacteria to acquire antibiotic-resistance genes (ARGs) led to drug-resistant bacteria [5]. The sewage treatment plants, industrial facilities, and hospitals produce most ARG emissions but they can also occur in natural environments, including agriculture, aquaculture, and livestock [6]. In the presence of antibiotic pressure, ARGs can provide a substantial fitness advantage to drug-resistant strains compared to drug-sensitive strains. Moreover, their ability to interchange genes across species, known as horizontal gene transfer (HGT), raises more significant concerns [7]. It allows bacteria to become resistant to multiple antibiotics, including last-resort antibiotics. Multiple Drug Resistance (MDR) refers to the emergence of resistance to at least one agent from three or more categories of antimicrobials. Across the globe, clinically relevant genes can frequently be found in the environment, despite previously being believed only to be prevalent in healthcare facilities.

Non-human bacterial species, transferring ARGs into the host species, can serve as incubators for potential pathogens [8,9]. There is a connection between the development of antimicrobial drug resistance in animals and humans. It requires a monitoring system, helping the physician select the most appropriate medication for the patient and protect them from drug-resistant bacteria [10]. Antimicrobial treatments for animals primarily target veterinary pathogens, subject to the most significant selective pressure [11]. Developing an alert system to detect newly emerging or developing resistance patterns is a crucial aspect of surveillance in this group of bacteria. Because intensively managed livestock operations have a high population density, bacteria and pathogens are likely to share, which can cause the rapid spread of infections [12]. As a result, animals raised in these environments often require antibiotic therapy as part of aggressive infection management strategies. This review addresses the effect of fluoroquinolone exposure at sub-minimal inhibitory concentrations on bacterial virulence/pathogenicity.

2. The mode of action of fluoroquinolones

The main applications of antibiotics in animals are therapeutic, prophylactic, and enhancing animal growth. However, these applications are frequently indistinct, and often, both approaches are used simultaneously in livestock populations [12]. For instance, 16% of all milking cows are treated with antibiotics for clinical mastitis annually. Still, nearly all dairy cows get prophylactic antibiotic infusions after each lactation to avert and manage possible mastitis [13,14].

Quinolones have been among the most prominent classes of antimicrobial drugs available for the past 50 years [15]. This family started with the introduction of nalidixic acid in the 1960s, followed by the development of fluoroquinolones (FQs) some years later, with a broader spectrum of activity compared to nonfluorinated quinolones [16]. As a quinolone prototype for the first time, the US Food and Drug Administration (FDA) approved Nalidixic acid for adults in the early 1960s. It was available for children three months and older over two decades [17]. Despite its promising therapeutic potential as a first-generation quinolone, nalidixic acid quickly lost popularity due to its limited antimicrobial spectrum, the rapid development of resistance, and poor pharmacokinetics [18].

The first quinolone was modified to develop improved agents with better pharmacokinetic and antimicrobial activity [19]. Fluoroquinolones have been shown to exhibit good antimicrobial activity against both Gram-positive and Gram-negative pathogens and have pharmacokinetic characteristics suitable for managing complicated community-acquired and nosocomial infections [20]. In the early 1980s, Norfloxacin and Ciprofloxacin, Pefloxacin, Levofloxacin, Ofloxacin, Lomefloxacin, Enoxacin, Fleroxacin, and Rufloxacin were introduced as the second-generation quinolones with enhanced antimicrobial activity against aerobic Gram-positive and Gram-negative bacteria compared with the first-generation [15]. Additional modifications resulted in the third generation advent, which included Gatifloxacin, Grepafloxacin, Sparfloxacin, Temafloxacin, Tosufloxacin, and Pazufloxacin which had an enhanced activity against Gram-positive and anaerobic bacteria [21]. Finally, newer Fluoroquinolones, termed fourth-

generation, developed under Trovafloxacin, Clinafloxacin, Sitafloxacin, Moxifloxacin, and Gemifloxacin with increased activity against anaerobes [22]. Fluoroquinolones are prominent drugs that prevent and treat animal and human infections [23]. Clinical trials have illustrated that Levofloxacin, Ciprofloxacin, Gatifloxacin, and Moxifloxacin can treat complicated urinary tract infections, gastroenteritis, sexually transmitted diseases, and respiratory tract infections [24].

The main targets for quinolones in the bacterial cell are the topoisomerase IV and DNA gyrase, critical enzymes involved in the replication, transcription, recombination, and repair of DNA [25]. DNA gyrase is a necessary bacterial enzyme that transports negative supercoils into DNA during chromosome replication [26]. Negatively supercoiled DNA is essential to trigger DNA replication. DNA gyrase facilitates replication by removing supercoils that accumulate before the replication split or as a result of gene transcription [27].

Quinolones reversibly bind to these cleavage complexes at the enzyme–DNA interface in the cleavage–active ligation site, preventing DNA strand re-ligation and increasing steady-state concentrations of cleavage complexes [25]. As a result of interactions between replication forks, transcription complexes, or other DNA tracking systems and drug-stabilized cleavage complexes, permanent chromosomal breaks are formed [28]. Consequently, these DNA breaks initiate the SOS response and different DNA repair pathways [29]. Complex formation inhibits DNA and cell growth reversibly. Quinolones are also catalytic inhibitors affecting topoisomerase IV and overall gyrase functions [30].

3. Bacterial resistance to fluoroquinolones

Quinolone resistance can be attributed to three mechanisms: mutations that change drug targets, drug concentration reduction, and plasmids that protect DNA gyrase and topoisomerase IV. Mutations in DNA gyrase and topoisomerase IV genes are the most frequent mechanisms of quinolone resistance [31]. Quinolones have two primary targets: gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria [32]. Interestingly, quinolones show a greater affinity for gyrase from Gram-positive bacteria than for gyrase from Gram-negative bacteria; however, it has been demonstrated that quinolone structure influences target affinity [33]. There are mutations in the GyrA or ParC subunits that confer resistance by introducing amino acid substitutions called the "quinolone-resistance-determining region" (QRDR) [34]. There are different "hot spots" for mutation in Gram-positive and Gram-negative organisms in this region of the enzyme's DNA-binding surface [35].

In addition, both Gram-negative and Gram-positive bacteria collectively express nonspecific, energy-dependent efflux systems. Some of these systems are constitutively expressed, while others are inducible through mutations or global regulatory mechanisms [36]. For example, *Escherichia coli* exhibits multiple regulatory pathways controlling the AcrAB-TolC efflux pump, which plays a central role in quinolone efflux. The activation of this pump is enhanced by mutations in the acrR repressor gene, which modulates the expression of acrAB [37]. Other Gram-negative bacteria have also been found to possess efflux pumps, including *Stenotrophomonas maltophilia* [38], *Pseudomonas aeruginosa* [39], and *Acinetobacter baumannii* [40]. In Gram-positive bacteria, efflux systems such as NorA mediate *Staphylococcus aureus* resistance to fluoroquinolones, antiseptics, and disinfectants [41]. Additionally, *Streptococcus pneumoniae*, other Gram-positive species, and mycobacteria exhibit antibiotic resistance through efflux mechanisms; clinical isolates often display both target-site modifications and efflux activation [42]. Notably, *E. coli* mutations in GyrA do not substantially elevate quinolone minimum inhibitory concentrations (MICs) in the absence of functional AcrAB efflux pumps [31].

Plasmid-mediated quinolone resistance (PMQR) genes have been implicated in both human and animal infections [43]. To date, six PMQR genes, qnrA, qnrB, qnrC, qnrD, qnrVC, and qnrS have been identified; these genes encode repetitive peptides that protect DNA gyrase and topoisomerase IV from inhibition by ciprofloxacin [44]. Additional PMQR mechanisms include efflux pumps encoded by oqxAB, qepA, and qacBIII, as well as the aac(6′)-Ib-cr gene, which encodes an aminoglycoside and quinolone-inactivating acetyltransferase [45]. This resistance has been spread worldwide with multiple plasmids of different sizes, incompatibilities, and specificities [44]. PMQR genes are often located near or within integrons on plasmids and chromosomes [46]. Through transposition, they may become associated with multiple ARG cassettes within integrons, thereby enhancing their mobility and facilitating the spread of resistance [47].

4. Fluoroquinolones used in industrial poultry production

Several enteric infections and respiratory diseases can be effectively treated with fluoroquinolones in veterinary medicine. In addition to their antimicrobial properties, they have beneficial pharmacokinetic features and low toxicity making them suitable for farm animals [48]. Since the 1980s, the farming industry has extensively utilized fluoroquinolones as the selected antimicrobials in food-producing animals [49]. Fluoroquinolones have been the preferred antimicrobials in the farming industry since the 1980s [50]. Also, have another mechanism of action than those used in veterinary medicine since the late 1980s. A public health concern is the potential transmission of bacterial resistance from livestock to humans via fluoroquinolones [48]. Antibiotics application in

animals may affect human health both directly and indirectly. Due to the application of antibiotics in food animals, direct products can be causally linked to antibiotic-resistant bacteria, and antibiotic use in food animals can lead to indirect effects, which result in contact with resistant organisms spreading to various ecosystem components (such as water and soil) [51]. Several observational studies and randomized trials have confirmed a link between utilizing antibiotics in food animals and antimicrobial-resistant bacteria [12]. It has been observed that animal-originated bacteria with antibiotic resistance occur in the environment nearby livestock farming operations, in retail stores selling meat products, and in humans who suffer clinical infections or subclinical colonization [52].

The amount of antimicrobials used in the animal production system strongly correlates with human and animal antimicrobial resistance [12]. Schulz et al. recently analyzed 125 samples of sedimentation dust originating from 14 sampled barns in Northern Germany and revealed fluoroquinolones in 47% of the dust samples. These concentrations range from 0.01 ng/mg to 46 ng/mg. The first finding was from a sample obtained in 2003, while samples from the 1980s and 1990s were below the limit of detection (LOD). Marbofloxacin was the most commonly detected fluoroquinolone present over a broad sampling period, followed by Enrofloxacin and Ciprofloxacin.

Additionally, Ciprofloxacin concentrations were lower than Enrofloxacin, indicating that Ciprofloxacin is the primary metabolite. *E. coli* was detected in 43% of the analyzed dust samples. Statistical analysis showed a significant correlation between the presence of resistant isolates of *E. coli* and fluoroquinolones found in the dust samples. Also, the odds of finding resistant Ciprofloxacin *E. coli* in dust samples were approximately four times higher in the presence of fluoroquinolones than in the absence of them [48]. Moniri et al. studied the antibacterial resistance of E. coli to quinolones and its relation to fluoroquinolones previously used in Iran. Totally from 190 healthy broilers, 181 *E. coli* isolates were collected. About fifty-two percent (52.5%) of chickens had used Flumequine and Enrofloxacin before the study. In a statistical analysis, Ciprofloxacin-resistant strains were significantly more prevalent among chickens previously exposed to fluoroquinolones than chickens with no previous exposure [53]. Humphrey et al. showed that treatment with fluoroquinolones (Difloxacin or Enrofloxacin) increases Ciprofloxacin-resistant *Campylobacter* rapidly. A tiny proportion of *Campylobacter* was Ciprofloxacin-resistant during pretreatment, compared to nearly 100% during treatment. Also, resistant strains persisted in some flocks for up to four weeks after treatment [54]. Another study was performed by Xu et al. at Shenyang City in northeast China to evaluate the correlation between fluoroquinolone residues and fluoroquinolone resistance levels from manured soil samples in swine farms. Individual fluoroquinolone concentrations ranged from the limit of quantification (LOQ) to 27.2 g kg-1 in manured soil, with higher concentrations with a higher swine manure application rate. In contrast, they were below the LOQ in control samples, suggesting swine manure could be a source of fluoroquinolone contamination.

Moreover, fluoroquinolone concentrations were associated with fluoroquinolone resistance levels [55]. Animal products such as muscles, liver, and eggs may contain antimicrobial residues and pose inherent risks if consumed by humans. Another concern is the antimicrobial application in the production of livestock [56]. A study by Goetting et al. suggests that Some drugs have been found to leave detectable residues in eggs laid days or weeks after treatment has stopped when administered to laying hens. In eggs, fluoroquinolone residues are evident 24 hours after the first dose, and they persist for days in the yolk and albumen [57].

5. SOS response, triggers, and effects

The SOS system is part of the DNA repair system and is crucial in the cell cycle checkpoint. Generally, SOS response in bacteria, especially *E. coli*, involves cell cycle arrest, DNA repair, and mutagenesis [58]. Two pivotal proteins control SOS response. Without stress and DNA damage, LexA dimers bind to SOS and suppress more than 50 included genes. Upon stress and DNA damage, a single-strand DNA (ssDNA) binds to RecA and activates it. RecA then induces self-cleavage and lowers LexA levels, triggering SOS [59].

Additionally, two horizontal gene transfer methods involve the transient presence of ssDNA: conjugation, in which double-stranded DNA is transferred directly between donor and recipient bacterial cells, and transformation, in which double-stranded DNA is taken up from an exogenous source. A conjugative plasmid DNA transfer and a transformation induce SOS. SOS can also be triggered by exogenous factors, such as oxidative components, UV radiation, physical stress, and antibiotics [59,60].

6. SOS and bacterial pathogenesis

SOS can increase the virulence of bacteria and is crucial to developing antibiotic resistance in bacteria. For example, by integrating conjugative elements (ICEs), *Vibrio cholerae*-derived sulfamethoxazole-trimethoprim (SXT) encodes genes to resist Sulfamethoxazole, Chloramphenicol, Trimethoprim, and Streptomycin [61]. DNA damage triggers the 'SOS response,' which makes genes more likely to be expressed for SXT transfer, such as mitomycin C [62]. Generally, SOS induces SXT transfer by mitomycin C expression. Fluoroquinolone antibiotics, such as Ciprofloxacin, which activate the SOS response, also increase SXT activity [63].

Furthermore, the formation of certain types of biofilms has been linked to the SOS response. For instance, biofilms produced by *Listeria monocytogenes* exhibit an elongated cell network surrounded by spherical microcolonies [64]. Cell elongation was observed following the induction of YneA by SOS response factors in *L. monocytogenes*. Recent studies have demonstrated a clear association between the SOS response and the formation of knitted chain biofilms under continuous flow conditions (Figure 1). YneA has been identified as a key mediator of biofilm formation triggered by the SOS response [65,66].

Additionally, by downregulating pchE, the SOS response likely enhances curli-mediated adhesion, rendering it more robust and intimate through the upregulation of pch group 1 genes [67]. Furthermore, the SOS response may induce the expression of genes within pathogenicity islands, thereby increasing bacterial virulence [68]. Mobile genetic elements, such as bacteriophages and phage-associated pathogenicity islands, frequently carry toxin-encoding genes. For example, a prophage encodes the Shiga toxin [69,70]. Additionally, SOS induction by commonly administered fluoroquinolone antibiotics can promote the replication and transfer of SaPI1, the prototypical pathogenicity island of *S. aureus* [70].

7. Conclusion

Sub-MICs of fluoroquinolones present in the environment, particularly within livestock and animal production settings, represent a significant and underappreciated driver of bacterial resistance and virulence. Exposure to these low-level antimicrobial residues not only selects for drug-resistant bacterial populations but also triggers complex cellular responses, such as the SOS DNA repair system, which facilitates genetic adaptation and enhances pathogenic potential. The SOS response mediates multiple mechanisms that contribute to bacterial survival and virulence, including the induction of biofilm formation, activation of mobile genetic elements carrying resistance and toxin genes, and upregulation of pathogenicity islands.

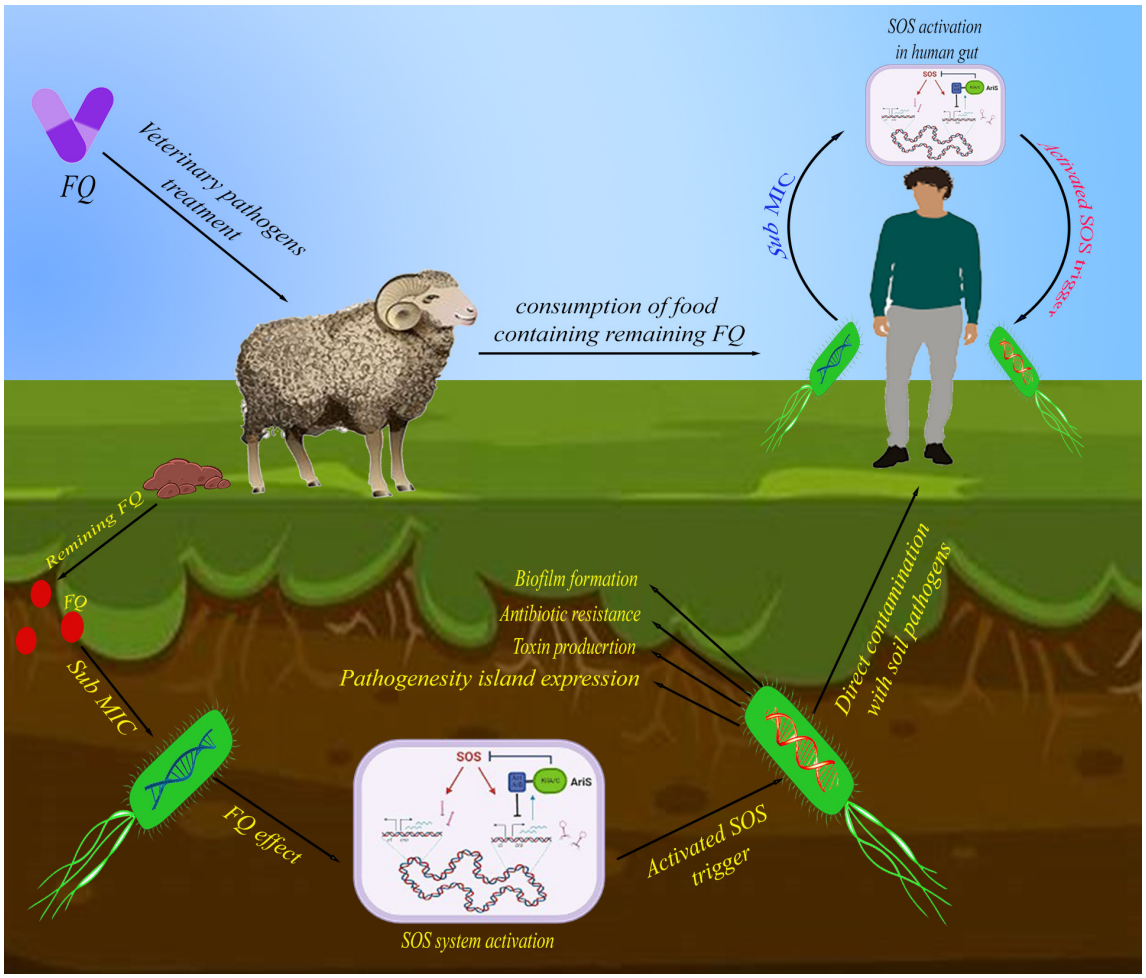

Figure 1. Activation of the SOS response and transmission of resistant bacterial isolates to humans. The use of quinolones in veterinary medicine leads to the introduction of low-dose quinolones into animal waste and food products. Residual quinolones present in soil and food can affect bacterial populations by triggering the SOS response in bacteria residing in the soil or gastrointestinal tract. In addition to promoting antibiotic resistance, SOS activation can induce biofilm formation, toxin production, and the expression of virulence factors. These SOS-activated bacterial isolates may be transmitted to humans through the consumption of contaminated food or direct contact with soil-borne pathogens.

These adaptive strategies increase the fitness of resistant bacteria, promoting their persistence and dissemination within agricultural environments and beyond. Given the demonstrated transmission of resistance determinants from animal-associated bacteria to human pathogens, the ecological and public health implications of environmental fluoroquinolone contamination are profound.

Consequently, stringent monitoring of fluoroquinolone residues in agricultural ecosystems, prudent antimicrobial stewardship in veterinary practices, and continued research into the molecular pathways activated by sub-MIC exposure are essential to mitigate the emergence and spread of drug-resistant bacteria. Addressing these challenges will be critical to safeguarding both animal and human health in the face of escalating antimicrobial resistance.

Authors' contributions

Conceptualization, Validation, Methodology, Review and Editing, Visualization, Project administration: HS. Literature search, Investigation, Data Curation, Drafting: FS, MEA, AS, AB. All authors read and approved the final version of manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

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