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Review article

MECHANISMS OF RESISTANCE TO QUINOLONES AND EPIDEMIOLOGICAL SIGNIFICANCE OF *Salmonella* spp.

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Bacteria develop resistance to antimicrobial agents by a number of different mechanisms. The resistance to (fluoro)quinolones in *Salmonella* is of particular importance especially if therapy in humans is required. For decades there has been a significant interest in studying the biology of *Salmonella* because these bacteria are among the leading causes of foodborne illnesses around the globe. To this date, two main mechanisms of quinolone resistance have been established: alteration in the targets for quinolones, decreased accumulation inside bacteria due to impermeability of the membrane and/or an over expression of the efflux pump systems. Both of these mechanisms are chromosomally mediated. Furthermore, mobile elements have been described carrying the *qnr* gene which confers resistance to quinolones. The plasmid encoded QNR proteins belong to the pentapeptide repeat family of proteins. The plasmid mediated quinolone resistance (PMQR) is often associated with the resistance to beta lactam antibiotics. It was noticed that PMQR is backing up chromosomal mutations for quinolone resistance, hence becoming an important resistance mechanism worldwide. Even with our knowledge expanding over the years, it is not possible to predict how bacteria will respond in the future, if they are exposed to new external challenges. The possibility that they will find a way to survive by introducing new mutations or by exchanging mobile genetic elements and subsequently developing resistance to survive in the environment should not be underestimated.

Key words: salmonella, resistance, quinolones, efflux pump, PMQR

INTRODUCTION

Foodborne diseases are one of the most important concerns worldwide. The global surveillance coordinated by the World Health Organization (WHO) has documented that *Salmonella* Enteritidis (*S*. Enteritidis) is a frequent cause of alimentary infections. The most prominent was the pandemic outbreak of human salmonellosis in the late 1980 caused by the consumption of table eggs. The highly prevalent *Salmonellae* in humans are also: *Salmonella* Infantis (*S*. Infantis), *Salmonella* Typhi (*S*. Typhi) and *Salmonella* Montevideo (*S*. Montevideo). In the year 2002, *Salmonella* Typhimurum (*S*.

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Typhimurium) was most commonly isolated from nonhuman specimens, while *S*. Enteritidis was ranked in third place [1]. Even if the numbers of outbreaks caused by *S*. Enteritidis and *S*. Typhimurium are declining in developed countries, because of the comprehensive eradication campaign in the veterinary sector, problems regarding *Salmonella* infections are still very relevant.

The next growing problem is the occurrences of resistance in *Salmonella*, especially in cases when young children, elderly people or patients with immune deficiencies require therapy. Because treatment with antibiotics is a frequent practice in veterinary medicine, foods of animal origin present a source of infection with resistant bacteria in humans. The application of antibiotics in developed countries is restricted and more careful, comparing to the practice of antibiotic use in developing countries. However, traveling and trade impair the ecological barriers and because of that, infections with resistant bacteria are not limited only to certain areas or smaller communities [1].

Fluoroquinolones (FQ) and beta lactam antibiotics are a broad class of antibiotics, used for the therapy of humans in cases of foodborne infections. Resistance to both classes of antibiotics has been documented in the emerging multiple resistant bacteria [2]. Monitoring of the antimicrobial resistance (AMR) is supported by the National legislatives and is being authorized by International Committees, which specify annually, the recommendations for clinical and epidemiological breakpoints of target antibiotics and associated guidelines for AMR testing. The recommendations from the Clinical and Laboratory Standard Institute (CLSI) [3,4] and the European Committee on Antimicrobial Susceptibility Testing [5] are often used as interpretative criteria.

In recognition of worldwide problems of AMR, the goal of this work was to briefly summarize the research that contributed to the understanding of the major mechanism of resistance to FQ in *Salmonella* spp., and their epidemiological significance.

Chromosomally mediated resistance to fluoroquinolones

Resistance to FQ in *Salmonella* occurs due to the point mutation on genes encoding topoisomerase enzymes. These enzymes act to regulate DNA supercoiling by catalyzing the winding and unwinding of the DNA strands. Therefore topoisomerase enzymes are essential for the replication of bacteria. The GyraseA is the primary target in Gram-negative bacteria. It consists of two subunits, the GyrA and GyrB, encoded by their complementary genes (*gyrA* and *gyrB*). Topoisomerase IV is the main target in Gram-positive bacteria and a secondary target in Gram negative microorganisms. The *parC* and *parE* genes encode two subunits (ParC and ParE) of the topoisomerase IV and they are homologous to the GyrA and GyrB subunits. Mutations induced by (fluoro)quinolones occur in the Quinolone resistance determining region (QRDR). This region encompasses amino acids from Ala67-Gln106 in the *gyrA* and Asp426-Lys447 in the *gyrB* [6,7]. In *Salmonella* the most frequent mutations are introduced on codons Ser83 and Phe87. The Ser83→Phe substitution is favored by enrofloxacin (a fluoroqunolone antibiotic), while nalidixic acid and ciprofloxacin, induce mutations

on codon 87 more often [8]. The increasing rate of FQ resistance is associated with the two point mutations in the *gyrA* gene in *Salmonella*. The most frequent double substitutions are Ser83→Phe and Asp87→Asn. Common mutations on the *parC* gene correspond to codons 78, 80 and 84 while the most frequent mutation on the *gyrB* and *parE* gene are at the codons 464 and 458 respectively. Concomitant mutations on the *gyrA*, *gyrB*, *parC* and *parE* genes in *Salmonella* spp, *Escherichia coli* (*E. coli*) and *Campylobacter* spp isolates from all around the globe have been summarized recently [9]. Particularly, double, triple and quadruplet FQ mutants in *Salmonella* are reported more frequently in isolates from developing countries. Hence, easy access and uncontrolled use of antibiotics in human and veterinary medicine contributes to the development of mutational polymorphism in *Salmonella* spp. [10]. *Salmonella* which are resistant to FQ usually attain a multidrug resistant phenotype (MDR), but the occurrence of such isolates in food producing animals and humans is not common.

The evidence of a clonal spread of *Salmonella* Typhimurium definite phage type 204 (STDT204), harboring the resistance to FQ, presents an important example of the occurrence of FQ resistant strains of *Salmonella* in humans and animals. Point mutations which are found in the topoisomerase genes of the STDT204, are associated with the following amino acid transitions: *gyrA* (Ser83→Ala, Asp87→Asn); *gyrB* Ser464→Phe and *parC* gene (Ser80→Ile). The STDT204 is also resistant to ampicillin, kanamycin, tetracycline, chloramphenicol and trimethoprim [11]. The related strain, *Salmonella* Typhimuirum DT104 harbors resistance to ampicillin, chloramphenicol, streptomycin, sulphonamides and tetracycline (ACSSuT, R type) and acquires a decreased susceptibility to FQ. The Asp87→Asn amino acid substitution is most frequently found on the *gyrA* gene [12].

The clonal spread of multidrug resistant *Salmonella* Kentucky (*S*. Kentucky) is today the most prominent example of new, well established, clones of *Salmonella*. The first multidrug resistant strain of *S*. Kentucky was isolated from French travelers returning from Africa, and soon after that, it was diagnosed worldwide. The emerging clones are highly resistant to ciprofloxacin but also to amoxicillin, streptomycin, spectinomycin, gentamycin, sulfametoxazole and tetracycline. Chromosomal mutations on topoismorease genes play a major role in the resistance to FQ in *S*. Kentucky. The following point mutations are responsible for this type of resistance: Ser83→Phe and Asp87→Asn or Tyr, Gly on the *gyrA* gene and Ser80→Ile on the *parC* gene. Clonal strains are a multi locus sequence type 198. After the DNA digestion with the restriction enzyme *Xba*I, the pulsed gel electrophoresis type is established as X1, [13]. Because the strains producing the extended spectrum cephalosporins (ESCs) and carbapenems were identified recently, it is important to report the occurrence of multiple resistant strains of *S*. Kentucky [14].

The emergency of quinolone resistant clones of *S*. Infantis in humans and food animals is also taking an important place in the epidemiology of *Salmonella*. The FQ resistance in *S*. Infanits is reported in multiple resistant strains in Hungary [15] and recently in Serbia [16, 17]. Multiple resistance phenotypes of *S*. Infantis are also being

recorded in Japan, Israel, Germany and Argentina [18,19,20]. Perhaps, *S*. Infanits has "accommodated" to the animal farms and along the food chain and is considered as a clonal strain [19]. The sharp increase in the incidence of multidrug resistant *S*. Infantis in Israel was noticed in 2007 [21]. The new strains of *S*. Infants were resistant to NAL, nitrofurantoin, tetracycline (TET) and trimethprim-sulfamethoxazole (SXT). Resistance to TET and SXT is encoded from a single-large mosaic, self-transmissible plasmid, of 280 kb (pESI). Resistance to NAL and nitrofurantoin is associated with chromosomal mutations. The emerging strains are also tolerant to a toxic concentration of inorganic mercury and are increasingly tolerant to hydrogen peroxide. The next very important discovery in the existing *S*. Infantis clones from Israel, is the presence of genetically related, previously uncharacterized, chaperon-usher fimbria operons, the K88-like and the Ipf fimbria, from the pESI. The presence of virulence factors, such as fimbriae, is responsible for higher pathogenicity, increased inflammation, and prominent adhesion to mammalian host cells, and for the high ability of the biofilm formation. The conjugative transfer revealed that the new plasmid is transferable to a plasmid free *S*. Infantis and *E. coli,* implicating the possibility of a broad dissemination of the pESI plasmid in microbiota. Successive passages in the antibiotic free medium have shown that the plasmid is stable in the absence of selective pressure. Resistance to quinolones is attributed to a single nucleotide substitution at position 259 where guanine is replaced with thymine, causing the Asp87→Tyr transition. For the first time it was shown that an adenine-guanine substitution, resulting in a nonsense mutation at a position 159 in the nitroreductase gene *nfsA*, introduces a premature stop codon and that this genetic event causes the resistance to nitrofurantoin in *S*. Infantis. The sharp increase of the FQ resistance in clinical isolates of *Salmonella enterica* serovar Choleresuis (*S*. Choleresuis) was recorded in two teaching hospitals in Taiwan from the year 2001 to 2003. The hospital patients with the acquired infection from the CIP^r clone of *S*. Choleresuis did not receive therapy with the fluoroquinolones before admission to the hospital. It was observed that the resistance to FQ is related to the mutations on the *gyrA* gene, generating the following amino acid substitutions: Ser83→Phe and Asp87→Asn. The pork meat was identified as the source of human infection with *S*. Cholersuis in Taiwan [22].

Mutations on the topoisomerase genes do not occur suddenly, but as a consequence of the persistent use of FQ antibiotics in clinical practice or livestock production. Hence, the occurrence of antimicrobial resistance in *Salmonella* develops in either longer or shorter timeframe. Decreased susceptibility to CIP has to be reported in every country and consequent measures should be taken to reduce the use of antibiotics in veterinary and human medicine.

The efflux mechanism of resistance to FQ in Salmonella

A very important mechanism of resistance to FQ in *Salmonella* is associated with the Resistance-nodulation-division (RND) family of proteinaceous transporters, localized in the cytoplasmic membrane. The most important efflux system is represented by a

tripartite efflux pump - the AcrAB-TolC. The AcrAB-TolC efflux pump is activated as a consequence of an overexpression of the *acrB* gene. The transporter protein AcrB has the ability to extrude a number of unrelated compounds from the bacterial cells and it is responsible for the development of a multiresistant phenotype in *Salmonella*. The AcrB forms a tripartite complex with the periplasmic adaptor protein (PAP) and with the outer membrane channel protein TolC [6,7]. The efflux mechanism is driven by the proton-motive force energy. It was established that the efflux system plays a major role in the resistance to FQ but also to unrelated antibiotics in STDT204. Hence, the inactivation of the *acrB* gene induces the 16-32 fold decrease in the resistance to fluoroquinolones, regardless of the several mutations on the topoisomerase genes. [23]. Genetic regulation of the AcrAB-TolC relies on the repressor protein named AcrR. Thus mutations on the *acr*R gene have an influence on the overexpression of *acrAB*. The mutations in *acr*R gene have been studied and it was found that a 6 bp duplication of the nucleotides 223-228 which caused the duplication of amino acids Ile75 and Glu76 in quinolone resistant mutants of *S*. Typhimurum, selected *in vitro*, were responsible for the lower activity of the repressor protein and subsequently increased efflux pump mechanism. Complemenation experiments of laboratory derived mutants with a plasmid borne, wild type *acr*R gene, have shown a decreased resistance to several unrelated antibiotics. Hence, the multidrug resistance phenotype is attributed to mutations on the *acr*R [24]. It is interesting to note that STDT204 also activates the alternative efflux mechanism, the AcrEF, in cases when *acrB* gene is inactivated. The integration of the IS*1* or IS*10* transposable elements creates a new and stronger promoter sequence, upstream of the *acrE*, and consequently activates the transcription of the *acrEF* efflux pump[25]. At a global level, the expression of the AcrAB-TolC system is regulated by the family of AraC/XylS transcriptional activators, MarA, SoxS, Rob and RamA in *Salmonella* or *E. coli* [26]. The repressor gene *ram*R of the ram regulon was shown to regulate the *ramA* gene expression in *Salmonella* Typhimurium strains. Several point mutations leading to amino acid exchanges, frameshift mutations or the insertion of the IS*1* element within *ram*R have been detected experimentally in *S*. Typhimurium and have caused interruption of the repressor gene. In the STDT104 isolate, deletions of two nucleotides from the putative binding site of the RamR protein were also detected. Complementation experiments with the wild type *ram*R gene or inactivation of the *ramA* gene has shown that particular mutation is indeed involved in the MDR phenotype in *S*. Typhimurium [27].

S. Typhimurium mutants obtained *in vitro* were used to examine the occurrence of genetic alterations in the *ramA* gene and *sox*R*S* region. It was found that a 9 bp deletion in the promoter region of the *ramA* gene (LTL strain), probably representing the RamR binding site, has an effect on the constitutive expression of the *ramA* gene and the *acrAB*. The replacement of the wild type *ramA* allele with the mutant allele *ramA*^{c} has shown a significantly higher MICs to fluoroquinolones, chloramphenicol and tetracycline, in laboratory mutants, expressing multiple mutations on the toposiomerase genes (LTH mutant), or in LT2 isolate without chromosomal mutations on the topoisomerase

genes. An increased *soxS* expression was associated with an in frame 3bp insertion creating two amino acid exchanges and an alanine insertion at the C terminus. Genetic alterations on the *soxS* gene were found to be associated with an in frame 12 bp deletions as well as eight residue alterations at the C terminus. The deletion of thymine which has caused a frameshift mutation at the stop codon -153, probably delaying the termination of the transcription in laboratory mutants of *S*. Typhimurium, was also found. However, the introduction of the *soxRS* allele from LTH to LT2 (having susceptible phenotype) did not induce changes in drug susceptibility. This means that the constitutive *ramA* transcription but not of the *soxS*, activates the MDR phenotype in *S*. Typhimuirum mutants, with or without chromosomal mutations in the QRDR [28].

Genetic alterations on the *ram*R gene were identified also in *Salmonellae* other than Typhimurium obtaining a decreased susceptibility to fluoroquinolones, tetracycline, florfenicol and chloramphenicol. After *Salmonella* were exposed to increased concentrations of ciprofloxacin *in vitro*, the following mutations in the global regulators were induced: the R46P amino acid exchange in the RamR was detected in *Salmonella* Livingstone 3 (mutant 2), in *S*. Infantis and *S*. Paratyphi B 10 (mutant 2), a 10 or 15 bp deletion was found in the *ram*R gene, causing a generation of an early stop codon and a loss of five amino acids respectively, in *Salmonella* Paratyphi B10 (mutant 2) a single base pair exchange GAA→GAC has resulted in an amino acid exchange E160D generating a stop codon at 160. These genetic events have increased the *ramA* gene expression and minor increase in *acrA* and *tolC* gene expression. In *Salmonella* Paratyphi B5 (mutant 3), a point mutation (C→A) was found between the *ramA* gene and the repressor gene (presenting the repressor gene binding site) and this mutation has increased the *ramA* expression to a moderate level (10 fold comparing to the aforementioned alterations that induced the increase of the *ramA* gene expression of 34.3, 41.6 and 94.8 fold). For the first time an insertion of 49 bp in the *soxR* gene has been identified introducing an early stop codon which resulted in the up regulation of the soxS gene in *Salmonella* Virchow mutant 2 (strain1). This research work has shown that alterations on the *ram*R-*ramA* and the *soxS* gene can activate the efflux mechanism by an upregulaton of the AcrAB system in salmonellas other than Typhimurium [29].

In Gram-negative bacteria, the resistance-nodulation-division families of proteinaceous transporters play an important role in transferring various compounds out of the cell. In *Salmonella,* two global regulatory mechanisms (Ram and Sox) seem to play a major role in the efflux pump activity but also, the local mechanisms of regulation of the AcrAB and AcrEF pump are very important. Inactivation of the RND efflux systems by specific inhibitors was shown to alter the expression of virulence genes as well. Such compounds are becoming attractive targets for a new generation of antimicrobial drugs in the future [26].

Plasmid mediated resistance to FQ in Salmonella spp

The Plasmid mediated resistance (PMQR) was first reported in clinical isolates of *Klebsiella pneumonie* exhibiting reduced susceptibility quinolones by Martinez-Martinez and colleagues in 1998 [30]. The plasmid borne gene was named *qnrA*. QnrA protein protect Gyrase (the subunits and the holoenzyme) by inhibiting the Gyraze enzyme/DNA interactions. After initial discovery of the *qnrA* gene an array of *qnr* variants were recognized over the years. The *qnrS* gene was identified by Hata and colleagues in 2005 [31] from *Shigella flexneri* 2b, which was isolated during an outbreak of food poisoning in Aici Prefecture, Japan. The *qnrB* gene was detected from a clinical isolate of *Klebsiella pneumoniae* from South of India by Jacoby and colleagues in 2006 [32]. Comparison of the *qnrB* gene with the *qnrA* and *qnrS* genes has shown 39.5 and 37.4% of the amino acid identity respectively. This QnrB protein belongs to the pentapeptide repeat family of proteins and it protects the gyraze from quinolones in a similar manner like other Qnr proteins. The *qnrC* gene was detected from an isolate of *Proteus mirabilis* 06-489, from an outpatient in China experiencing urinary tract infection. The isolate conferred a low level resistance to ciprofloxacin (MIC 0.25 mg/L). Upstream of the *qnrC* gene a new member of the IS*3* family of insertion sequences was discovered and therefore the *qnrC* gene presents a mobile genetic element [33]. The *qnrD* gene was found by Cavaco and colleagues in 2009 [34], from *Salmonella enterica* serovar Kentucky and Bovismorbificans isolated from human infection in China. In transformants, obtained after the conjugation experiment, a small plasmid of an approximate size of 4.3 kb was identified. Cloning and sequencing of the 3.2 kb fragment has shown that an open reading frame (ORF) encodes a protein of 214 amino acids and the sequence identity with other members of the *qnr* family was as follows: 45% of identity is with the *qnrA1* gene, 65% with the *qnrB1* gene and 38% of identity is with the *qnrS1* gene. Integron structures or other resistance determinants were not found in those isolates.

To summarize, the Qnr-type proteins have approximately 30% variations in their nucleotide sequences, and several amino acid differences [35]. The QNR proteins do not induce a high resistance to FQ but their respective genes are frequently detected in the ESBL producing strains and multi drug resistant Gram negative bacteria [6, 36].

Enzymatic drug modification is probably the most widespread plasmid encoded resistance to FQ in Gram negative bacteria. The responsible gene *aac(6)-Ib-cr,* encodes an aminoglycoside acetyltransferase variant, which enables the N-acetylation of the piperazinyl amine in the molecule of the CIP, conferring the resistance to CIP and norfloxacin. This gene originates from a common aminoglycoside acetyltransferase enzyme, conferring resistance to tobramycin, amikacin and kanamycin which is associated with mobile genetic elements-the integron cassette. The *aac(6)-Ib-cr* variant was detected for the first time in transconjugants from clinical isolates of *E. coli* which were isolated during the years 2000-2001, most of which were from hospitalized patients in Shanghai China. The transconjugants exhibited MIC to CIP of 0.125-2 mg/L. The amino acid substitutions Trp102→Arg and Asp179→Tyr were found to be responsible for the acetylation of the CIP by the respective enzyme. Concomitant detection of the

aac(6)-Ib-cr gene and the *qnrA* gene is identified occasionally but a strong association with these two genes or other *qnr* determinants is not evident. However, the presence of the *aac(6)-Ib-cr gene* facilitates the selection of chromosomal mutations in the presence of the FQ [37, 38, 39]. The *qepA* gene was first described in clinical isolates of *E. coli* displaying a multidrug resistant phenotype to aminoglycosides, FQ, as well as to a broad spectrum of β-lactam antibiotics (except for ceftazidime and imipenem). The *qepA* gene encodes protein that operates as a proton antiporter efflux pump mechanism. The QepA protein resembles a high similarity to multidrug transporters from the major facilitator superfamily of transporters. It may have incorporated via the transposition mechanisms to *E. coli* from environmental bacteria which utilize their own mechanisms for extruding antibiotics structurally similar to FQ [40]. Recently discovered *oqxA* and *oqxB* genes, encode the multidrug transporters of the RND-family and are included for screening of the PMQR genes in Enterobacteriaceae [41]. It was discovered that clinical isolates of *S*. Typhimurum from China carry on a same plasmid the *oqxAB* and the *aac(6)-Ib-cr* genes, which accelerate the resistance to CIP. Namely, when both genes were extracted from the clinical isolates and electroporated into a negative *S*. Typhimuirum LT2, the fourfold increase of the resistance to CIP was obtained. The *oqxAB* gene is associated with the *IS*26 element which means that this gene was excised from the plasmid pOLA52 and transferred to a different plasmid of *Salmonella* which harbors also the *aac(6)-Ib-cr* [42]. The worldwide distribution of the PMQR is well documented. Often strains highly resistant to FQ do not posses PMQR genes. However, Kehrenberg et al., 2006, [43] have found the *qnrS* gene in *S*. Infantis with an increased MIC to NAL (512 mg/L), which also indicates the necessity of PMQR identification in isolates with an increased resistance to FQ.

Concluding remarks

The research work in the field of antimicrobial resistance is constantly growing and for that reason the opportunity was taken to outline very briefly, the recent developments in molecular mechanisms of resistance to fluroquinolones and epidemiological aspects of *Salmonella* infections. A small review of mechanisms of resistance to FQ in *Salmonella* with a special concern towards the efflux pump system of resistance was presented just a while ago in Archives of Veterinary Medicine [44]. From the epidemiological standpoint, *S*. Infantis and *S*. Enteritidis are most frequently isolated from poultry flocks in southern Bačka and Srem region. Next but not so frequently isolated serovars in both counties are *S*. Typhimurium and *S*. Newport. It is interesting to note that *S*. Infantis was resistant only to NAL and TET and an unexpectedly, susceptible phenotype in *S*. Typhimurium was recorded [45]. *S*. Infantis clones isolated in poultry specimens from Serbia have a truncated Tn*1721* transposon with the *tetA* gene, which is responsible for resistance to tetracycline [46] The occurrence of multidrug resistant *S*. Kentucky isolated from one flock of turkey pullets was also evident. *S*. Kentucky in Serbia harbors a multidrug resistance phenotype and an increased resistance to FQ. Point mutations on chromosomal topoisomerase genes are major mechanisms of

resistance in *S*. Infantis and *S*. Kentucky in Serbia. The preliminary investigation has shown that the efflux pump mechanisms play a role in the resistance development to FQ in *S*. Infantis but it was not confirmed in the existing collection of *S*. Kentucky isolates (from human and turkey specimens). The PMQR resistance genes were not found in *S*. Infantis from Serbia. Because of the epidemiological importance of *Salmonella*, especially serovars with an acquired resistance to FQ, we emphasized the need for compulsory monitoring of *Salmonella* spp. serovars but also for regular recording of the occurrence of *S*. Kentucky in Serbia [47].

The research on antimicrobial resistance is always challenging. One moment we think that a new drug or a combination of drugs will help in combating persistent or invasive infections caused by bacteria, and the next moment microbial communities acquire or recruit new genetic mechanisms to eliminate antibiotics out of the cell or prevent their responses. The question remains, is it possible to prevent the occurrence of multidrug resistant bacteria in the future and to predict genetic models which they will use to survive in the environment.

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Authors' contributions

MV has design the paper, selected reference for the presentation and wrote the manuscript. MV takes responsibilities for all aspects of the work and accuracy of the quoted data in the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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MEHANIZMI REZISTENCIJE NA HINOLONE I EPIDEMIOLOŠKI ZNAČAJ *SALMONELLA* SPP.

VELHNER Maja

Bakterije razvijaju mnogobrojne mehanizme rezistencije na antimikrobne agense. Od posebnog značaja je rezistencija na (fluoro)hinolone kod Salmonella spp. posebno u slučajevima kada je indikovana terapija kod ljudi. Decenijama postoji veliko interesovanje za izučavanjem biologije salmonela zato što su one najčešći uzročnici bolesti koje se prenose namirnicama animalnog porekla u celom svetu. Do danas su ustanovljena dva najvažnija mehanizma rezistencije odnosno, alteracije na ciljnim genima za hinolone, smanjena akumulacija koja nastaje zbog smanjene propustljivosti ćelijskog zida i/ili prekomerne ekspresije sistema efluks pumpe. Oba mehanizma su kodirana sa hromozoma. Takođe su opisani mobilni elementi na kojima se nalaze qnr geni koji uzrokuju rezistenciju na hinolone. QNR proteini pripadaju familiji proteina koji su organizovani u pentapeptidne ponovke i kodirani su sa plazmida. Rezistencija koja nastaje preko plazmida (PMQR) obično je povezana sa rezistencijom na prošireni spektar beta laktama. Takođe je ustanovljeno da PMQR, podržava mutacije na hromozomu bakterija, uzrokujući rezistenciju na hinolone, tako da spada u veoma važne mehanizme rezistencije širom sveta. Iako se tokom godina sve više saznaje o mehanizmima rezistencije, nemoguće je predvideti kako će bakterije da reaguju u budućnosti ukoliko budu izložene novim uticajima iz životine sredine. Velika je verovatnoća da će putem novih mutacija ili izmenom mobilnih genetičkih elemenata razviti rezistenciju kako bi preživele u okruženju.