

Review article

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THE GLOBAL SPREAD AND EPIDEMIOLOGICAL CHARACTERISTICS OF *SALMONELLA* SPP., *ESCHERICHIA COLI* AND METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA): RELATED RESEARCH STUDIES IN SERBIA

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Abstract

It has been established that some clones of pathogenic bacteria such as *Salmonella* spp., *Escherichia coli* ST131, and methicillin-resistant *Staphylococcus aureus* (MRSA) tend to spread worldwide. Therefore, epidemiological surveys have been conducted to identify the source of infection and to break the chain of infection. In this article, it was pointed out that common international clones of *Salmonella* are represented with the serotypes Typhimurium, Kentucky, Infantis and Enteritidis. Serovars Typhimurium and Kentucky display multidrug-resistant phenotypes more frequently. Several sequence types of *E. coli* and the international clone ST131 are described, including clades C1 and C2 with the extended-spectrum cephalosporin-resistance genes (*bla*CTX-M-15 or *bla*CTX-M-27). These pathogens are often found in both humans and animals. It is noted that *Staphylococcus aureus* became resistant to methicillin almost instantly after its introduction into clinical practice. Soon afterwards, MRSA found its way to farm animals and wildlife. The cycles of infection are bidirectional: humans can disseminate MRSA in the environment but animals may also be sources of infection for humans. Comprehensive work has been done by epidemiologists to introduce all necessary measures to eliminate MRSA from hospitals. Also, much effort has been made in MRSA control to prevent infections on animal farms and contamination in the primary food production chain. As the struggle with pathogenic bacteria continues, we face the incessant

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threat of new resistance and virulence mechanisms, which bacteria use to resist the hostile environment and enhance their survival in their natural habitats including humans and animals. Therefore, the capacity of certain bacteria to spread due to their virulence mechanisms and resistance phenotypes is presented, and a brief description of the research conducted in Serbia is included.

Key words: *Salmonella*, *E. coli*, MRSA, virulence, epidemiology, clonal spread

GLOBALNA RASPROSTRANJENOST I EPIDEMIOLOŠKE KARAKTERISTIKE POJEDINIH KLONOVA *SALMONELLA* SPP., *ESCHERICHIA COLI* I METICILIN- REZISTENTNIH *STAPHYLOCOCCUS AUREUS* (MRSA) I PRIKAZ SLIČNIH ISTRAŽIVANJA U SRBIJI

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Kratak sadržaj

Pojedine vrsta bakterija, kao što su *Salmonella* spp., *Escherichia coli* ST131 i meticilin-rezistentni *Staphylococcus aureus* (MRSA), rasprostranjene su širom sveta. Zbog se sprovode brojna epidemiološka istraživanja s ciljem otkrivanja izvora i prekida lanca infekcija koje izazivaju. Istaknuto je da su serovarijete Typhimurium, Kentucky, Infantis i Enteritidis, najznačajniji globalno rasprostranjeni klonovi *Salmonella* spp. kao i da su Typhimurium i Kentucky češće od drugih serovarijete, rezistentni na više klasa antibiotika. Opisano je nekoliko različitih vrsta *Escherichia coli* uključujući i podvrste *E. coli* ST131, i to C1 i C2 sa genima rezistencije na cefalosporine proširenog spektra (*bla*CTX-M-15 or *bla*CTX-M-27). Navedene bakterije izolovane su i od ljudi i od životinja. Meticilin rezistentni sojevi *Staphylococcus aureus* (MRSA) ustanovljeni su vrlo brzo nakon uvođenja meticilina u kliničku praksu. Ubrzo su MRSA nađeni i kod domaćih životinja i divljači. Ciklusi infekcije ovom vrstom bakterija odvijaju se u oba pravca: ljudi mogu izlučivati MRSA u životnu sredinu, a životinje mogu biti rezervoari infekcije za ljude. Sveobuhvatan rad epidemi-

ologa doprineo je primeni strogih mera za kontrolu i eliminaciju MRSA u bolničkim sredinama, a značajna pažnja je usmerena i na otkrivanje MRSA infekcija kod farmaski gajenih životinja, u cilju sprečavanja kontaminacije u lancu proizvodnje hrane. Uprkos naporima koji se ulažu u kontroli širenja patogenih vrsta bakterija i prevenciji infekcija koje izazivaju, suočeni smo sa konstantnom pretnjom od pojave novih mehanizama rezistencije i virulencije koje bakterije koriste da bi preživele u nepovoljnim uslovima životne sredine, uključujući tu i organizme ljudi i životinja. Iz navedenih razloga u ovom radu prikazani su mehanizmi virulencije i rezistencije za koje se smatra da značajno doprinose globalnoj rasprostranjenosti pojedinih klonova navedenih vrsta bakterija, uz kratak opis sličnih istraživanja u Srbiji.

Ključne reči: *Salmonella*, *E. coli*, MRSA, virulencija, epidemiologija, klonalna

INTRODUCTION

Coping with multidrug-resistant bacteria has been among the ultimate goals of medicine. Apart from having intrinsic resistance, bacteria can also acquire antibiotic resistance genes and mobile genetic elements and induce the exchange of genetic material within their counterparts. The long-lasting bacterial evolution prompts the question whether it is possible to create efficient therapy for humans and animals in the future (Dandekar et al., 2015). Bacteria use specific metabolic pathways to increase their fitness, colonize the gut and organize themselves in biofilm communities. For example, even highly pathogenic bacteria with prominent virulence and resistance mechanisms, which may present a burden to themselves, tend to become well-established in natural environments (Beceiro et al., 2013). All these features together result in the endless dissemination of resistant and virulent clones worldwide (Pitout and Finn, 2020). Therefore, it is very important to detect and prevent the dissemination of pathogenic and multidrug-resistant bacteria in hospital settings and food production chains. Control strategies aiming to deal with bacterial infections are more comprehensive in more economically developed countries as compared to developing countries. However, mass primary production and utilization of antibiotic feed additives as growth promoters has led to an increase in resistance to antibiotics, even in developed countries (Silbergeld et al., 2008). Those were the reasons why as early as since 1970 some antibiotics have been sequentially banned as feed additives in the EU and from 1 January 2006 antibiotics may no longer be used as growth promoters (Castanon,

2007). Consequently, we have witnessed a decrease in antimicrobial resistance in pathogenic and commensal bacteria which originate from the environment and food-producing animals in some European countries (Aarestrup et al., 2001). However, the antibiotic withdrawal from food-producing animals has not significantly changed the resistance levels in human pathogens (Pradella et al., 2006). The fear of continuous development of new mechanisms of resistance in bacteria is still an important global issue, while trade and travel continuously increase the risk from dissemination of multidrug-resistant and virulent bacteria with limited fitness cost. In this brief review, some of the prominent examples of the worldwide spread of bacterial pathogens are discussed and the brief presentation of related research in Serbia is included as well.

CLONAL SPREAD OF *SALMONELLA* SPP.

There are several examples of the successful clonal spread of pathogenic bacteria from food to humans. Non typhoidal *Salmonella* spp. is at the top of the list of foodborne pathogens (Majowicz et al., 2010). Poultry meat and products including table eggs have long been recognized as the main reservoirs of non-typhoidal *Salmonella* (Antunes et al., 2016). The diseases are manifested as a self-limiting food poisoning or take a course of severe infection that requires antibiotic therapy. These are the reasons why *Salmonella* spp. is targeted in countless studies aiming to discover epidemiological trends in infection especially in serovars that become well-established international clones. The most prominent examples of the successful clonal spread in *Salmonella enteric* serovars are *Salmonella* Typhimurium DT104 (Threlfall, 2000), *Salmonella* Kentucky ST198 (Le Hello et al., 2013), *Salmonella* Infantis (Aviv et al., 2014) and *Salmonella* Enteritidis (Pijnacker et al., 2019, Li et al., 2021). It is important to bring up the fact that serovar Enteritidis can also be vertically transmitted, which renders them even more dangerous for public health due to the increased potential for dissemination across the food chain and subsequent increase of their spread in communities. Therefore, one of the important goals of contemporary agricultural production is to eliminate dangerous *Salmonella* serovars from poultry and other food-producing animals around the globe. Subsequently, the implementation of enforced biosecurity measures in the entire food chain including pre-harvest has become important both in developed and developing countries (EFSA, 2019).

Epidemiologists who are focused to trace back the source of *Salmonella* spp. outbreaks, to minimize the likelihood of infection in humans, are trying to help to break the chain of infection at the very bottom of the production

pyramid (Pijnacker et al., 2019). Indeed, a comprehensive genome analysis of *Salmonella* originating from poultry has revealed that *S. Enteritidis* from breeder flocks has been spreading through global trade for decades (Li et al., 2021). The exact reasons for persistent infection with serovars *Enteritidis* and *Typhimurium* can be revealed using experimental animals. It was shown that invasive serovars have more virulence factors, invade internal organs of the host more efficiently and possess mechanisms prompting their survival inside the macrophages of the host (Velhner et al., 2018). For instance, the global spread of *Salmonella* *Enteritidis* phage type 4 (PT4) was attributed to successful infection of the hens' reproductive tract most likely by inheriting additional virulence factors which facilitate internal contamination of eggs (Velge et al., 2005). Therefore, the enhanced management practice, vaccination and utilization of prebiotics and probiotics have been enforced in many countries of the world, which has led to a much better epidemiological situation regarding *Salmonella* spp. infection of food-producing animals. Many of these strategies have helped to eliminate some other serovars besides *Enteritidis* and *Typhimurium* (two serovars that are primarily targeted by vaccines) and thus reduce the burden of infection at the farms worldwide.

The clonal spread of *Salmonella* *Infantis* in Serbia was in part attributed to strains which become resistant to ciprofloxacin (Velhner et al., 2014). However, in 2018, it was established that strain *Infantis* continues to be resistant to nalidixic acid but not longer to ciprofloxacin, which is possibly due to restrictions on the use of enrofloxacin for the therapy of day-old chickens. It is interesting to note that brief monitoring of antimicrobial resistance in *Salmonella* isolates in Serbia reveals that *Salmonella* *Typhimurium* is frequently susceptible to antibiotics unlike the isolates reported in other European countries (Jovčić et al., 2020). In Serbia, *Salmonella* *Enteritidis* (SE) was not examined by any of the available genetic methods including phage typing and the whole-genome sequencing approach. Thus, factual information about the possible clonal spread of SE from humans and animals is still lacking.

GENETIC BASIS OF THE PROGRESSION OF THE *E. COLI* WITH THE DISTINCTIVE SEQUENCE TYPES AND PHENOTYPE

E. coli sequence type-ST131 is primarily a human pathogen often causing urinary infection (Giedraitiene et al., 2016). However, due to the high dissemination rate, it can infect all animal species and contaminate the environment. The exact reasons for the successful global spread of the clone ST131 have not been entirely elucidated. Namely, the virulence factors, including their

resistance determinants, could be assumed as moderate, while the transmission rates could be minimized with proper hygiene and disinfection in hospital facilities. Therefore, the combination of all virulence properties perhaps contributes to the good fitness and widespread nature of the ST131 clone but none of these factors alone is significantly pronounced to cause such persistent infection and significant contamination rates (Pitout and Finn, 2020). There are several well-established *E. coli* ST131 clades. The clades A and B comprise strains susceptible to antibiotics but possess different *fimH* genes, which are a part of a *fim* operon. The *fim* operon encodes fimbria which determines the success of bacterial attachment to the host tissue receptors (Pitout and Finn, 2020). Clade C is represented by three major groups: C0, C1 and C2. The major differences between these are the resistance to fluoroquinolones, which is present in isolates belonging to clades C1 and C2 but absent in those from clade C0. Fluoroquinolone resistance has been developed due to the multiple mutations in topoisomerase genes (the *gyrA* and the *parC* gene). During genomic evolution of the *E. coli* ST131 isolates from the clades C1 and C2, the acquisition of the extended-spectrum beta-lactamase resistance genes took place, also. All of these genetic changes are attributed to the new plasmid or the presence of insertion elements required for the successful integration of other genes in already existing plasmids. However, even if these properties have helped scientists with the phylogenetic classification of the ST131 clones, none of them is the key reason for the successful spread of these bacteria. The following additional factors are further influencing the abundant pathways of the *E. coli* ST131 strains: the level of compensatory mutations required to obtain plasmid stability and decreased fitness cost, the horizontal integration of genomic islands and prophages including a variety of virulence genes carried on by chromosomes and plasmids (Beceiro et al., 2013; Pitout and Finn, 2020).

The ESBL resistance gene *bla*CTX-M-15 becomes one of the most distinctive and worldwide spread genes in *E. coli* clones of various sequence types. However, the CTX-M-15 carriers are more prevalent in humans than in animals or the environment (Irrgang et al., 2017). The *bla*CTX-M-15 gene is often found in the multireplicon IncF plasmids or, in some rare cases, it could be integrated into the chromosome owing to the occurrence of several independent events (Irrgang et al., 2017). The CTX-M-15-producing *E. coli* encompasses 5.2% of all ESBL/AmpC producing *E. coli* isolates from food animals and products in Germany. The most frequent sequence types were ST167 and ST410. Four ST410 isolates except one carried the *bla*CTX-M-15 gene on a chromosome, while in strains ST167, the *bla*CTX-M-15 gene was found on IncF multireplicon plasmids. In both the chromosome and the plasmid,

*bla*CTX-M-15 gene was associated with the *ISEcp1* element, confirming the high tendency of the transferability. The *E. coli* sequence type ST410 was also detected in humans, implicating the possibility of clonal transfer (Irrgang et al., 2017).

The recent increase in infections caused by the extra intestinal pathogenic *E. coli* in Japan, in human patients, was attributed to the worldwide clone ST131, resistant to extended-spectrum cephalosporins due to the inheritance of the *bla*CTX-M-27 gene (Matsumura et al., 2016). Based on a core genome sequence analysis this clone is genetically distinctive and forms the C1-M27 clade. The pangenome analysis identified a specific region in the clade C1-M27 that closely resembles a prophage-like genomic island originally identified in an *E. coli* isolate from a pig. This region was termed M27PP1. Upstream the M27PP1, in the two C1-M27 isolates, an additional insertion region was identified showing homology to a prophage sequence found in a chromosome of the *g*-proteobacterium HdN1 (Matsumura et al., 2016). The reservoirs of the CTX-M27 are found worldwide in non-human and environmental specimens and thus present an important clade among the ST131 variants with the capacity of further global spread.

Unlike *Salmonella*, which tends to disseminate as a common clone, *E. coli* is genetically quite diverse. The exceptions are the above-mentioned sequence types, which persist in various niches and disseminate thanks to their enhanced fitness. During the investigation of the diverse, multidrug-resistant commensal *E. coli* from a poultry farm practicing frequent use of antibiotics in Serbia, three independent clones with the common virulence type and resistotype were determined by pulse-field gel electrophoresis (Velhner et al., 2018). The multilocus sequence type of only a small number of *E. coli* isolates from gulls was done as well. It was discovered that isolates resistant to extended-spectrum cephalosporins were ST38, ST2307, ST224 or ST162 while ST131 was not detected (Velhner et al., 2021). However, more comprehensive multilocus sequence typing of commensal and pathogenic *E. coli* isolates from animals was not performed, and therefore, the data on the existence of particular ST is not available.

EVOLUTION OF THE METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important human pathogen. This worldwide epidemic clone emerged in 1961, soon after methicillin had been introduced for the therapy of infections caused by peni-

cillin-resistant *Staphylococcus aureus*. MRSA is characterized by the *mecA* gene that is incorporated in a staphylococcal cassette chromosome *SCCmec*, which differs in size and genetic composition. The *mecA* gene encodes the penicillin-binding protein PBP2a of the bacterial cell wall, which has a low affinity for beta-lactam antibiotics (Enright et al., 2002). MRSA isolates are multidrug-resistant and often only glycopeptide antibiotics such as vancomycin are effective against them. However, some strains became resistant also to these antibiotic classes (such isolates are called GISA), which renders successful treatment impossible (Enright et al., 2002). MRSA emerged primarily as a hospital pathogen, but it is now widespread in the community and can be isolated from animals and the environment. The evolution of MRSA is still a puzzle. Since genetic analysis has confirmed genetic divergence between strains, it has been proposed that independent inheritance of the *mecA* gene contributed to the evolution of MRSA rather than the diverse inheritance of genetic material that has arisen in a single clone (Enright et al., 2002). The multilocus sequence typing (MLST) utilizes analysis of the seven housekeeping genes to obtain the specific allelic profile. This method is beneficial in the classification of various MRSA lineages that have appeared in the past decades and more recently. It was elucidated that early MRSA strains evolve from the ST250 ancestor, who in turn arose from the methicillin-susceptible (MSSA) ST8 lineage. The ST247 clone that emerged independently from ST250 is currently circulating in European hospitals. Several MRSA clones have the same allelic composition as their methicillin-susceptible (MSSA) counterparts indicating the independent horizontal acquisition of the *mecA* gene. This fact is in a way supported by the independent introduction of the four *SCCmec* types within MRSA strains of the same sequence type (Enright et al., 2002).

The community-acquired MRSA strains (CA-MRSA) possess more virulence determinants than hospital strains. The production of the Panton-Valentine leucocidin (PVL) exotoxin is pronounced in community-acquired strains and its detection could be used to distinguish CA-MRSA from the healthcare MRSA (HA-MRSA). PVL toxin is recognized in those strains that cause necrotizing pneumonia and invasive skin diseases although the mechanism of these virulence factors is not known. Other toxins produced primarily by the CA-MRSA are toxic shock syndrome toxin-1, staphylococcal enterotoxin B or C, α -haemolysin and phenol-soluble modulins (Hassoun et al., 2017).

Livestock-associated MRSA (LA-MRSA) are also very important pathogens (Deiters et al., 2015). Not only may farm workers or those in contact with raw meat become infected with LA-MRSA but they might also transmit this pathogen to hospitals. In the vice versa manner, humans infected with LA-

MRSA can transfer the pathogens to animals. This type of two-way directional transmission makes it even more difficult to keep infections under control in both human and veterinary medicine. However, with the proper treatment and management in hospitals and on farms it is possible to eliminate and prevent the spread of MRSA. The principle “search and destroy” is very effective in healthcare settings in eliminating this pathogen. Firstly, the MRSA carriers are to be detected, and then the medical treatment is to be applied to eliminate the pathogen and interrupt its transmission pathways. A similar principle is applied on farms, but there it is also important to prevent the purchase of positive herds to keep the MRSA infection under control (Crespo-Piazuelo and Lawor, 2021). Therefore, effective management programmes are required to be rewarded with a healthier environment and better treatment options for both human and animal patients.

It was shown that MRSA isolates among patients and health care workers from the Serbian University Clinical Hospital were mostly of the CC-5-SCC-*mec* type I. These isolates were predominantly found in patients from emergency departments and medical departments. In addition, various genetic lineages were found in isolates from healthcare workers in surgical departments. MRSA isolates from healthcare workers carried mostly smaller SCC elements of type IV and V. This was the most comprehensive MRSA detection in Serbia and, as noted, has shown the increased risk of MRSA carriage not only among patients but also among the healthcare workers (Cirkovic et al., 2015). The presence of MRSA in pigs was estimated on one farm from the north of Serbia, revealing that out of 84 nasal swabs, six tested positive for MRSA. Those isolates belonged to the ST45, *spa* type t015 and in addition possessed SCC*mec* IVa. The MRSA sequence type 45 is a global MRSA lineage of particular strain diversity and common nosocomial isolate in Europe (Velebit et al., 2010).

CONCLUSION

The important goal in human and veterinary medicine is to follow up the work of epidemiologists to break the infection cycles of all persistent and dangerous pathogens. If collective efforts in improving management are introduced in everyday practice, it will be possible to reduce the burden of infections with pathogenic bacteria.

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Author's Contribution:

MV wrote the manuscript and reviews the literature, DM reviewed the manuscript, NA reviewed the manuscript and did the English editing.

Competing interest

The authors declare that they have no competing interests.

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