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Original article

PREVALENCE OF POULTRY *ESCHERICHIA COLI* ISOLATES PRODUCING EXTENDED-SPECTRUM BETA-LACTAMASES AND THEIR PUBLIC HEALTH IMPORTANCE

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Summary

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Recently, different reports highlighted the problem with dissemination of *Escherichia coli* producing extended spectrum beta-lactamases (ESBL) in poultry farms in Europe. The high incidence of *Escherichia coli* among poultry in Europe harbouring $bla_{\text{CTX-M-1}}$ and the occurrence of ESBL and AmpC-producing *Escherichia coli* in raw meat samples collected from slaughterhouses in Europe have been discussed. ESBL-producing *Enterobacteriaceae* can be transmitted along the broiler production chain. Plasmids responsible for ESBL production frequently carry genes coding resistance to other antimicrobial classes, such as fluoroquinolones, aminoglycosides, sulphonamides. Resistance to cephalosporins in *Enterobacteriaceae* is of special concern for public health, because these antimicrobial agents are critically important. The aim of this mini review was to describe the mechanisms of resistance and prevalence of ESBL-producing *E. coli*. It is important to investigate the spread of these bacteria among poultry, the role of farm birds as reservoir of *E. coli* and the risk for people.

Key words: *E. coli*, public health, poultry, resistance to beta-lactams

INTRODUCTION

The wide prevalence of resistance to antibiotics is a global concern for both human and animal health (Roth *et al*., 2019). *E. coli* are commensal bacteria with exceptional flexibility of genetic platforms associated to determination of resistance to various groups of chemotherapeutics (Thenmozhi *et al*., 2014). *E. coli,* similarly to other members of the commensal microflora could be reservoir for genes encoding resistance to chemotherapeutics, which are transferred among different bacterial species, including those of zoonotic relevance (Thenmozhi *et al*., 2014). Enterobacteria producing beta-lactamases could play an important role in the etiology of polymicrobial infections. Such infections are usually associated with higher morbidity and mortality rates

and more severe clinical course (Rupp & Fey, 2003; Paterson, 2007).

In domestic poultry, antibiotics and chemotherapeutics are most commonly used on population level both for therapy and metaphylaxis of bacterial infections. The use of chemotherapeutics as growth promoters in livestock was prohibited in EC in 2006, and in the USA – in 2017; nowadays they are used in Brazil and China (Casewell *et al*., 2003; Anonymous, 2005; 2018).

The commonest mechanism determining resistance to β-lactam antibiotics is associated with expression of β-lactamase enzymes that hydrolyse the beta-lactam ring (Ambler, 1980). The first extended-spectrum β-lactamases (ESBL) are expressed as a result of point mutations in $bla_{\text{TEM-1}}$ and $bla_{\text{SHV-1}}$ genes (Bush *et al*., 1995). During the last decade, another ESBL type, encoded by bla_{CTXM} genes was reported (Livermore *et al*., 2007).

In the mid 1980s, a new group of ESBL was discovered (Kliebe *et al*., 1985; Bradford *et al*., 2001). ESBL are β-lactamases that hydrolyse cephalosporins with extended spectrum, cefotaxime, ceftriaxone, ceftazidime, as well as monobactams.

CLASSIFICATION OF BETA-LACTAMASES

One of classifications of β-lactamases, that of Ambler (1980), groups enzymes in 4 classes (A, B, C and D) on the basis of their structural features, respectively amino acid sequences. Classes A, C and D include serine-containing beta- lactamases whereas class B includes zinc-containing metallo-β-lactamases.

Plasmids determining the genetic profile of ESBL types often carry genes encoding also resistance against other classes of chemotherapeutics (aminoglycosides and fluoroquinolones) (Rios *et al*., 2015).

The functional classification of beta-lactamases was published in 1989 by Bush *et al*. and then, updated in 1995, 2010 and 2018 (Bush *et al*., 1995; 2010; 2018). It is created on the basis of functional features and substrate profiles of enzymes, and later, a combined scheme including also their molecular features was published (Bush & Jacoby, 2010). In this scheme, enzymes are divided into three main groups: cephalosporinases from Group 1, which are not inhibited by clavulanic acid, extended-spectrum enzymes from Group 2, which are usually inhibited by clavulanic acid (with the exception of groups 2d and 2f) and metallo-β-lactamases from Group 3. Most ESBL belong to group 2be, and are able to hydrolyse penicillins, cephalosporins and monobactams.

Now, about 17 functional groups are associated with the four molecular classes. Beta- lactamases are grouped depending on the variety of their substrate profiles – penicillins, cephalosporins, monobactams, carbapenems respectively, and their sensitivity to beta-lactamase inhibitors, clavulanic acid, avibactam and EDTA (Bush, 2018). Naas *et al*., (2017) proposed another scheme for classification of beta-lactamases, especially with regard to enzymes from class A, Group 2, on the basis of their three-dimensional structure and functional features.

The most important extended spectrum beta-lactamases producedg by *Escherichia coli* isolates from poultry are:

TEM β-lactamases (class A)

Substitutions of amino acids in the vicinity to the active site of the enzyme, which are responsible for ESBL phenotype, alter its configuration allowing access to vari-

ous substrates e.g. oxyimino-β-lactams. In general, opening of the active site to β-lactam substrates increases the sensitivity of enzymes to inhibitors of beta-lactamases, such as clavulanic acid. Clasen *et al.* (2019) reported that single nucleotide polymorphisms (SNPs) in *bla* $_{TEM}$ genes may lead to amino acid substitutions in the TEM enzyme. Single amino acid substitutions in positions 104, 164, 238 and 240 induce the emergence of a variable range of extended-spectrum beta-lactamases. Some authors reported about several hundred variants of TEM β-lactamases which are widely spread worldwide. They can be found in different species such as *E. coli*, *P. aeruginosa*, *Haemophilus influenzae* and *Neisseria gonorrheae* (Bradford, 2001). On the basis of various combinations of mutational changes, about 223 TEM enzymes with extended spectrum are now described (Rahman *et al*., 2018). All of described variants of TEM β-lactamases have derived from TEM-1 and TEM-2 β-lactamases (Pleiss, 2020).

SHV β-lactamases (class A)

SHV-1 structure is similar to that of TEM-1, as about 68% of amino acid sequences are concerned (Zhao *et al*., 2013). *Klebsiella ozaenae* strain isolated from human which produced SHV-2 ESBL was established in Germany (1983). SHV-2 sequence is similar to that of SHV-1 with substitution of glycine by serine at position 238 with extension of its hydrolytic substrate profile to include cefotaxime and ceftazidime. Plasmid determined SHV-1 β-lactamases are most commonly encountered in *Klebsiella* spp. and exhibit resistance to cefotaxime and ceftazidime. Also, SHV-5 and SHV-12 are frequently reported in enterobacteria (Perilli *et al*., 2011).

CTX-M β-lactamases (class A)

CTX-M β-lactamases have an extended spectrum of activity and are closely associated to chromosomally determined beta-lactamases of *Kluyvera* spp. (Poirel *et al*., 2002). They were mainly detected in *Salmonella enterica* serovar Typhimurium and *E. coli* strains, but also in other *Enterobacteriaceae* species. CTX-M-15 is considered to be one of the commonly prevalent types in *E. coli* strains (Lopez-Cerero *et al*., 2013).

AmpC β-lactamases (class C)

The genes determining production of AmpC β-lactamases (class C or Group 1) are usually located in the chromosome of a number of Gram-negative bacteria, for example *Citrobacter* spp., *Serratia* spp., and *Enterobacter* spp. AmpC β-lactamases could be also plasmid-determined (Papanicolaou *et al*., 1990). AmpC β-lactamases hydrolyse cephalosporins with extended spectrum but are not inhibited by β-lactamase inhibitors such as clavulanic acid (Monnaie & Frere, 1993). CMY-2 enzymes have a broad geographic areal among non-typhoid salmonellae isolated from humans and animals (Winokur *et al*., 2000).

PREVALENCE OF EXTENDED-SPECTRUM BETA-LACTAMASES AMONG AVIAN *E. COLI* STRAINS

Prevalence of ESBL-producing E. coli in Europe

According to the EFSA report from 2016 (EFSA, 2016), the prevalence of resident *E. coli* isolates from broilers resistant to ampicillin, tetracycline and ciprofloxacin exceeded 50% (58.7%; 65.7%; 50.1%). It also noted that *E. coli* isolates resistant to ciprofloxacin and cefotaxime demon-

strated 1.9% resistance as interpreted on the basis of clinical critical values (Giovanardi *et al.,* 2013). Higher percentages were noted for resistant *E. coli* isolates from turkeys. For example, the resistance in commensal *E. coli* strains to ampicillin was 69.0% compared to other antimicrobials such as ciprofloxacin and tetracycline that showed 50.3% and 70.9% resistance respectively. The resistance to cefotaxime and ceftazidime was 2.3% and 2.2% respectively. Co-resistance is resistance to more than one class of antibiotics in the same bacterial strain as it might occur by mutations in genes. Co-resistance to ciprofloxacin and cefotaxime was about 0.8%. About 5% of *E. coli* isolates from broilers and turkeys demonstrated a phenotype profile corresponding to ESBL, and the combination of ESBL and AmpC phenotypes was found out in 0.5% of broiler *E. coli* isolates.

The latest EFSA report (EFSA, 2020) outlines that the combined resistance to cefotaxime and ciprofloxacin in indicator *E. coli* bacteria from broilers and turkeys was 2.1% and 1.5%, respectively according to interpretation criteria of EUCAST. The data evidenced higher prevalence (14.8%–16.2%) of resistant *E. coli* strains to third-generation cephalosporins that were isolated from broilers in Belgium. Phenotypically determined ESBL producers (Anonymous, 2018) among isolates from broiler and turkeys were 2.0% and 1.9% respectively. Producers of AmpC beta-lactamases were 0.9% and 0.3%, respectively.

In Poland, data from the national monitoring programme for prevalence of commensal *E. coli* from broilers indicated high prevalence of resistance to ampicillin (from 70 to 90%) (Wasyl *et al*., 2012). Trends for increasing resistance to ampicillin and cefotaxime were also reported in *E. coli* isolates from poultry by Wasyl *et al*. (2013) who also commented on the incidence of ceftazidime-resistant *E. coli* strains. The highest percentage was that of resistant isolates from broiler chickens (54.5%), followed by those from turkeys (48.0%) while the lowest percentage of resistance was detected among strains from layer hens (2.3%). Strains producing CTX-M-1 and AmpC were predominating.

Data from two monitoring programmes in the United Kingdom also demonstrated high prevalence of *E. coli* bacteria resistant to ampicillin and tetracycline (Bywater, 2004; Randall *et al*., 2011). Randall *et al*. (2011) discussed the predominant spread of CTX-M-1 producing *E. coli* isolates from broilers (3.6%) and isolates producing CTX-M-1,-14 in turkeys (6.9%).

In the Czech Republic, Kolar *et al*. (2010) established a wide spread of ESBL producers from CTX-M-1 and SHV-12 types, as well as of AmpC enzymes type CMY-2 in commensal *E. coli* bacteria isolated from broiler chickens and from turkeys.

In Germany, a higher prevalence of *E. coli* bacteria resistant to ampicillin and sulfamethoxazole compared to other groups of chemotherapeutics was reported (Roth *et al*., 2019). Dahms *et al*. (2015) have established a predominance of SHV enzymes in resident *E. coli* strains from broilers. The studies of Kaesbohrer *et al*. (2019) also provided proofs for a high prevalence of ESBL-producing *E. coli* isolated from chicken and turkey meat (74.9%; 40.1%). The highest prevalence (10.1%) was observed with respect to strains producing CTX-M. Saliu *et al*. (2017) also discussed higher prevalence of *E. coli* producing ESBL in poultry and $bla_{\text{CTX-M-1}}$, $bla_{\text{SHV-12}}$ as the commonest genes.

In France, the spread of amoxicillin-resistant *E. coli* bacteria for the period 2006–2016 was estimated to be about 40%. Casella *et al*. (2017) reported a superior occurrence of CTX-M-1, TEM-52, SHV-12 and CMY-2 among *E. coli* bacteria from poultry meat. The authors discussed the results in the context of the hypothesis that the surveyed period was outlined with drastic restriction of ceftiofur application in poultry farming. Again Geser *et al*. (2012) reported a broader spread of CTX-M-1 producers among commensal *E. coli* bacteria from broiler chickens.

The study of Giovanardi *et al*. (2013) conducted in Italy showed data on the wide spread of pathogenic *E. coli* strains from turkeys, which were resistant to ampicillin (96%) and tetracycline. Beninati *et al*. (2015) also found out a substantial prevalence of ESBL producers among *E. coli* isolates from poultry and turkey meat (81.3%). In Spain, Abreu *et al*. (2014) confirmed a high prevalence (59.1%) of CTX-M producing *E. coli* bacteria isolated from broiler chickens.

A study carried out in Czech Republic and Slovakia examined the resistance to ampicillin (72%), cephalothin (89%), and to tetracycline (22%) (Holko *et al.,* 2019).

Global epidemiology of ESBLs

Hasan *et al*. (2012) reported that about 30% of *E. coli* strains isolated from poultry in Bangladesh produced ESBL. The commonest enzymes from this group belonged to types CTX-M-1, CTX-M-9 and CTX-M-14. The combination of *bla* $_{\text{CTX-M-15}}$ or *bla* $_{\text{CTX-M-1}}$ и *bla* $_{\text{TEM-1}}$ was detected in 50% of poultry isolates. What is more, the authors observed a similar ESBL profile in *E. coli* strains from wild birds.

In Egypt, the survey on 50 multidrug resistant *E. coli* strains from broilers demonstrated prevalence of genes *bla* $_{\text{TEM-57}}$, *bla* $_{\text{SHV-12}}$, *bla* $_{\text{CTX-M-14}}$ and *bla* $_{\text{CMY-2}}$ (El-Shazly *et al*., 2017). High MIC values (≥4; ≥16 mg/ L) were observed in cefotaxime- and ceftazidime-resistant *E. coli* isolates. In 12% of AmpC enzymes producers, higher MICs to cefoxitin were established (≥32 mg /L).

Yang *et al*. (2004) and Lin *et al*. (2016) reported the prevalence of class 1 integrons among poultry *E. coli* strains possessing genes determining resistance to beta-lactams, aminoglycosides, trimethoprim and quinolones. Machado *et al*. (2008) discussed the wide prevalence of class 1 integrons (100%), containing bla_{TEM}, bla_{SHV} or $bla_{\text{CTX-M}}$ or bla_{CMY} genes in various enterobacteria and affirmed that these genetic platforms were essential for the distribution of genes conferring drug resistance.

In China, research was carried out to evaluate the significance of biofilm formation on the prevalence of resistance to chemotherapeutics in poultry *E. coli* strains. A wide spread of biofilm-forming *E. coli* bacteria resistant to penicillins (78.5%) and aztreonam (69.5%) was found out. The authors confirmed that 92.1% strains from poultry were multidrug resistant and that 81.6% of strains formed biofilm (Wang *et al*., 2016).

In Canada Moffat *et al.* (2020) established resistance to exended-spectrum cephalosporins (ESC) in *E. coli* from turkeys. 93% of the positive enrichment cultures (67% of total samples) were recognised as *E. coli*. Of the ESC-resistant Enterobacterales isolates from selective enrichments, 71%, 18%, 14%, and 8% were positive for *bla* $_{\text{CMY}}$, *bla* $_{\text{TEM}}$, *bla* $_{\text{CTX-M}}$, and *bla* $_{\text{SHV,}}$ respectively.

In Canada, Varga *et al*. (2019) confirmed frequent prevalence of multidrug-resistant *E. coli*. A total of 433 faecal *E.*

coli isolates from chickens, turkeys, ducks and game bird were recovered. *E. coli* isolates were resistant to tetracycline (43% chicken, 81% turkey, 42% duck, and 38% game bird isolates), streptomycin (29% chicken, 37% turkey, and 33% game bird isolates), sulfonamides (17% chicken, 37% turkey, and 21% duck isolates), and ampicillin (16% chicken and 41% turkey isolates). Multidrug resistance was found in 37% of turkey, 20% of chicken, 13% of duck, and 8% of game bird *E. coli* isolates.

The possibility that domestic fowl could serve as reservoir of *E. coli* strains producing extended-spectrum beta-lactamases and CTX-M in particular, poses risks for the transfer of such strains along the food chain. That is why Randall *et al*. (2011) discussed this risk on the basis of data on identity of Inc plasmids and sequence profiles of CTX-M enzymes in poultry *E. coli* strains isolated from broilers and humans. On the other hand, the direct contact between birds and farmers is a pre-requisite for transfer of resistant *E. coli* bacteria (Dierikx *et al*., 2013; Huijbers *et al*., 2014). Although repeatedly commented from the point of view of their public health relevance, these issues require a particular attention having in mind data from monitoring programmes and epidemiological surveys on commensal ESBL-producing enterobacteria confirming their wide prevalence among domestic livestock species. According to Madec *et al*. (2017) the importance of animal reservoirs on human health remains unclear, which is prerequisite for collecting and analyzing information in this area from different regions of the world.

Prevalence of ESBL E. coli among humans

In Ghana, Falgenhauer *et al.* (2019) reported the prevalence of ESBL *E. coli,* isolated form children and broilers. Forty-one of 140 broilers (29%) and 33/54 children (61%) harboured ESBL *E. coli*, respectively. ST10 was the most prevalent among broilers (n=31, 69%) but ST sequences were not detected among humans. $Bla_{CTX\text{-}M\text{-}15}$ gene was predominant among broilers (n=43, 96%) and humans (n=32, 97%). Whole-genome-based phylogenetic analysis revealed three very closely related broiler/human isolate clusters (10% of ESBL isolates) with chromosomal and plasmid-mediated ESBL genes.

In Thailand, Tansawai *et al.* (2019) discussed the spread of ESBL *E. coli* among poultry, farmers and environment. During the study 587 samples have been collected and 27.1% ESBL-producing *E. coli* isolates were obtained (159/587). Among these, ESBL-producing *E. coli* was isolated from 50% of faecal samples from farmers, 25.9% from poultry (24.9% of chickens and 36.6% of ducks), and 25.0% of the environmental samples. All isolates demonstrated multidrug resistance, most frequently to ≥ 10 different antimicrobial agents. Molecular analysis of ESBL-encoding genes showed that the predominant gene was $bla_{\text{CTX-M-55}}$ (54.1%), $bla_{\text{CTX-M-14}}$ (28.3%), $bla_{\text{CTX-M-15}}$ (8.8%). $bla_{\text{CTX-M-27}}$ (3.8%) and $bla_{\text{CTX-M-65}}$ (0.6%) were detected at low frequencies.

Teklu *et al.* (2019) determined the frequency of ESBL-producing *Enterobacteriaceae* from clinical specimens in Ethiopia. The most widespread species of *Enterobacteriaceae* were *E. coli* (53.5%) and *K.* pneumoniae (24.1%). The quantity of ESBLs-E was 57.7%. The highest resistance level was established to sulfamethoxazole-trimethoprim (77.0%), amoxicillin

with clavulanic acid (71.6%), cefotaxime (62.2%), cefepime (60.3%) and ceftazidime (60.8%).

From the point of view of public health relevance, data from monitoring programmes and epidemiological surveys on commensal ESBL-producing enterobacteria with respect to their prevalence among domestic livestock species require a particular attention.

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