ANTIBIOTIC RESISTANCE IN LIVESTOCK BREEDING: A REVIEW*

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Antibiotic resistance represents a serious threat worldwide. When considering the increasing ability of bacteria to effectively resist antibacterial agents, it is necessary to reduce the consumption of antibiotic substances in animal production in order to preserve their effectiveness in the future. Attention should be paid to the multidrug resistant microorganisms' occurrence, which can be very exhausting for the breeder not only from the economic point of view. Therefore, alternative sources of antibacterials should be considered due to the limited possibilities of using conventional antibiotics in animal breeding, e.g. application of various substances including organic acids, clay minerals, etc. Nowadays, the research in this field also focuses on the combinatory effect of such compounds, which can also find the perspective for use in animal breeding. This article provides an overview of problems connected with the resistance of diverse bacteria to antibiotic treatment in livestock breeding. It emphasises the need for alternate resources usage with the aim to lower the environmental burden caused by overuse of antimicrobials used in subclinical doses in the past and with the expanding bacterial resistance.

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INTRODUCTION

The occurrence of alimentary diseases is a serious threat for inhabitants of both developed (Havelaar et al., 2010) and developing (Byarugaba, 2004) countries connected primarily to inappropriate dealing with products of animal origin, their further modifications, and consumption. Since the undesirable bacterial contamination is one of the agents causing food-borne diseases (Levin, Antia, 2001), its eradication is sought already at the beginning of food-production process: in animal breeding. This can be achieved by using various antimicrobials, such as antibiotics. These are anti-effective drugs discovered from natural and chemical products and derived semi-synthetically with phenotypic methods during the second half of the 20th century (Power, 2006). Generally, three periods of bacterial diseases' therapy are distinguished: pre-antibiotic, antibiotic, and period of antibiotic resistance's development that is happening right now (with possible transition back to the principles of pre-antibiotic period in certain countries). Antibiotics have been used to decrease the infectious pressure causing difficulties in animal husbandry and across human population since their discovery (Aminov, 2010). Antibiotics for treating diseases, and in prevention as prophylactic agents against bacterial infections and as antibiotic growth promoters (AGPs) have been used in animal production (Table 1) since the very beginnings of antibiotic therapy with the aim to maximise production and to get the highest possible profit (Moore et al., 1946; Jukes et al., 1950). Using AGPs for longer

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Table 1. Types of antimicrobials use in food animals (McEwen, Fedorka-Cray, 2002)

Type of antibiotic use	Purpose	Route or vehicle of administration	Administration to individuals or group	Diseased animals
Therapeutic	therapy	injection, feed, water	individual or group	diseased individuals; in groups, may include some animals that are not diseased or are subclinical
Metaphylactic	disease prophylaxis, therapy	injection (feedlot calves), feed, water	group	some
Prophylactic	disease prevention	feed	group	none evident, although some animals may be subclinical
Subtherapeutic	growth promotion	feed	group	none
	feed efficiency	feed	group	none
	disease prophylaxis	feed	group	none

term may lead to the natural selection of surviving resistant bacteria and strains able to transport such an ability to other bacterium and make them resistant (Aarestrup, 1999). The ability of microorganisms to conquer antibiotic treatment by different mechanisms is called antibiotic resistance (Ronquillo, Hernandez, 2017). This property is not a novel phenomenon – contrariwise is true: healthcare systems worldwide are facing this situation both in human and veterinary medicine since the very beginnings of antibiotic's treatment applications (Barbosa, Levy, 2000). For example, just two years after penicillin has been introduced in 1941 as an anti-staphylococcal treatment, the resistance level increased to 6% and after a decade even to 50% in hospital-acquired infections (Barber, Rozwadowska-Dowzenko, 1948). This makes antibiotic resistance an issue targeting not only medicine, but different fields – politics, economics, biology, sociology and ecology – with unknown result and solution (Balsalobre et al., 2014).

Increasing number of inhabitants and economic prosperity is globally connected with rising demand for proteins of animal origins resulting in the estimated increase of animal production by 70% to feed the population of 9.6 billion of people living on the Earth by 2050 (Gerber et al., 2013). The rise of animal production is logically connected (especially in developing countries) with higher production and usage of antimicrobials in food-producing species according to its above mentioned (sub)therapeutical and growth-promotory activity. This occurrence is supposed to lead to the estimated growth of antibiotic production by 67%, meaning 105.596 (± 3.605) t by 2030. Approximately 2/3 of increase is expected to be due to higher numbers of reared animals, and 1/3 because of the shift towards intensified animal breeding (Van Boeckel et al., 2015). Nowadays, approximately 60% of nation's annual consumption of medically important antimicrobials in the USA are used for disease prevention and growth promotion in food-producing animals (FDA, 2017). According to previously stated data of production and consumption of antibacterial compounds (more than 1 t per day in various European countries), it is rational to mention that the progression of bacterial resistance against antibiotics is going to evolve further, and is one of the best documented cases of biological evolution in progress even nowadays (Baquero, Blazquez, 1997).

To understand the resistance of bacteria against antimicrobials, it is necessary to know the bacterial mechanisms of resistance and to clarify the impact of resistant bacteria on humans. This is going to be described further in next paragraphs altogether with the summary of possible precautions that can be made in order to preserve the ability of antibiotics to effectively act against bacteria in the future.

Mechanisms of resistance

Both mutation and selection for the growth when higher concentrations of antibiotics are used, contribute to the increase in profound ability of microorganisms to resist the antimicrobial effect of various compounds, as well as acquiring other factors of resistance (Berger-Bachi, 2005). Rich variability of mechanisms that cause resistance gains an ability to defeat antibiotics in microorganisms, increases their chance to survive in environment containing antibiotics, and allows researchers even to predict a probability of resistance's origins itself. The resistance is believed to be originating out of so-called 'pre-resistant molecules' that arose during different evolutionary processes – e.g. appearance of thirty genes able to modify aminoglycosides (Payie et al., 1995), or seventeen genes for resistance against

tetracycline that has developed among diverse bacterial species (Johnson, Adams, 1992). Basically, five targets of antibiotic therapy include: cell wall synthesis, protein synthesis, DNA synthesis, DNA-directed RNA polymerase, and essential metabolic enzymes (Coates et al., 2002). Bacterial resistance to antibiotics is caused by various mechanisms that can be divided into two groups: (A) direct attribute of the bacterial cell causing antibiotics resistance: (a) genetic modification – e.g. ADP-ribosyl transferases mutation making bacteria resistant to rifampicin (Mazel, Davies, 1999), (b) enzymatic modification – e.g. methylation of adenine residuals in 23S rRNA causing resistance to macrolides (Zalacain, Cundliffe, 1990), (c) replacement – e.g. ribosomal protection to antibiotic binding through Tet(O) protein causing tetracycline resistance (Li et al., 2013), (d) protection on cellular or population level – e.g. ability to secrete big amount of exopolysaccharides that creates a barrier impeding antibiotic binding (Nwodo et al., 2012); and (B) bacterium initiated change of antibiotic causing its deactivation: (a) antibiotic modification – e.g. aminoglycoside's acetylation (Ramirez, Tolmasky, 2010), (b) antibiotic destruction – e.g. beta-lactamases influence on beta-lactam antibiotics (Sandanayaka, Prashad, 2002), and (c) elimination of antibiotic out of the cell – e.g. elimination by efflux pump (Soto, 2013). Generally, this categorisation is artificial, and not every mechanism is possible to sort into mentioned groups. As an example, so-called 'kin selection' can be used. This mechanism of resistance roots in an ability of drug resistant mutants of bacteria to shield the less resistant isolates by production of certain metabolite under antibiotic stress (Lee et al., 2010). Therefore, kin selection can cause difficulties when trying to eradicate populations of diverse bacterial strains or species as in biofilms.

Health-threatening bacteria

Nowadays, there are no commercially available antibiotics at disposal that do not exhibit any bacterial resistance pattern against at least a single microorganism (Brachman, Abrutyn, 2009; Cushnie, Lamb, 2011). The European Centre for Disease Control and Prevention (ECDC) oversees resistant microorganisms within the EARS-Net Surveillance Network on Antibiotic Resistance (EARS-Net) in the European Union. ECDC sets sensitivity/resistance criteria of microorganisms to antibiotics and settles rules for detection methods of resistance for these microorganisms: *Acinetobacter* spp., *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae* (ECDC, 2016). Multidrug-resistant microorganisms represent the most serious threat to public health (Nicasio et al., 2008; Kumarasamy et al., 2010) among which are listed, for example: vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), extended-spectrum β-lactamase (ESBL) producing Gram-negative bacteria, carbapenemases producing *Klebsiella pneumoniae* (KPC), and multi-drug resistant Gram-negative rod-shaped bacteria: *Acinetobacter baumannii, Enterobacter spp.*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* (Boucher et al., 2009). The nature of multiresistance (resistance of microorganisms to more than three groups of antibiotics) is often derived from genetically mobile organelles, such as plasmids, transposons, and integrons (Dessen et al., 2001), therefore its reduction is a major challenge for researchers and an important concern for the community (Byarugaba, 2010). According to the World Health Organization (WHO), many of these multi-drug resistant bacteria are pathogens of the digestive tract (WHO, 2015), causing considerable economic losses in animal breeding (Graham et al., 2007). Above that, some resistant bacteria of animal origin may be indirectly transmissible to humans through the outside environment (Graham et al., 2009), and products of animal origin (Price et al., 2005), or directly by contact of farm workers with animals (Smith et al., 2013) (Fig. 1). In the case of *Clostridium perfringens*, the world's most widespread pathogen, which produces many endotoxins and exotoxins, the acquisition of resistance properties is gradually being started, and this problem needs to be taken into consideration in a timely manner (Rainey et al., 2009). Another important factor contributing to the increase of bacterial resistance to antibiotics is the ability of some of the above-mentioned to form a biofilm (Parsek, Singh, 2003; Kong et al.,

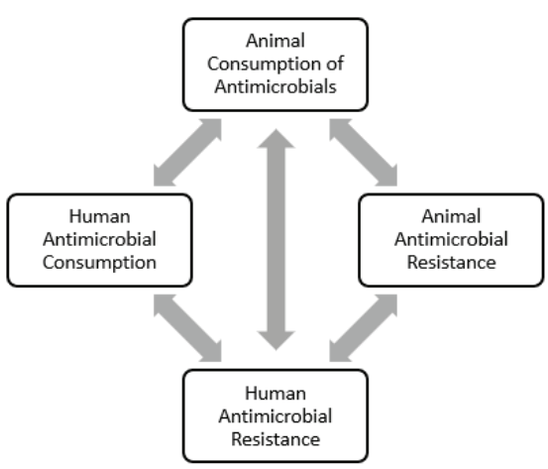

Fig. 1. Formation and transmission of antimicrobial resistance in microorganisms (EFSA, 2016)

Table 2. Restrictions on the use of antibiotics in livestock in OECD countries (Laxminarayan et al., 2015)

OECD member country	Legislative status of country in terms of animal use of antibiotics	
	ban on antibiotic growth-promoters (AGPs)	prescription requirement to use antibiotics in animals
Australia	no, but some AGPs are banned (fluoroquinolones, avoparcin, virginiamycin, etc.) (Australian Commission on Safety and Quality in Health Care, 2013)	nearly all veterinary antibiotics can only be sold on a veterinarian prescription
Canada	no, the Canadian government released a notice in April 2014 to stakeholders mimicking the FDA approach to voluntarily phase out use of medically important antibiotics as growth promoters (Government of Canada, 2014)	no, plan to develop options to strengthen the veterinary oversight of antibiotic use in food animals in line with the FDA approach
EU member states	yes, all AGPs banned in 2006 (EU, 2003)	yes
Japan	no	yes
Mexico	yes, AGPs were banned in 2007 with some exceptions (avoparcin, vancomycin, bacitracin, tylosin, virginiamycin, etc.)	yes
New Zealand	yes, for the critically and highly important antibiotics listed by both WHO and OIE (MAF New Zealand, 2011)	yes, for antibiotics identified with the potential or resistance problems
South Korea	yes, since 2011 AGP use has been discontinued until a veterinary oversight system can be put in place (USDA, 2011)	yes, the veterinary oversight system is currently being developed
USA	no, the FDA released voluntary guidelines for the industry to withdraw the use of medically important antibiotics as growth promoters (U.S. Food and Drug Administration, 2013)	no, under the new FDA guidance for industry, use of medically important antibiotics will be under the oversight of licensed veterinarians

2006) – a generic and species-diverse society of to the substrate adhered microorganisms surrounded by a layer of exopolysaccharides that are produced by these bacteria (Davies, 2003). This phenomenon can be encountered not only in *S. aureus*, but also in other pathogens, e.g. in the oral cavity (Jenkinson, Lamont, 2005).

Monitoring of resistance

Globally used antimicrobial agents include 27 antibacterial classes, 9 of which are used exclusively in animals (Pagel, Gautier, 2012). Highest consumption of antibiotics can be observed in poultry and pig farms, but the increasing trend in aquaculture consumption cannot be overlooked. The consumption of antibiotics as growth promoters in the United States, Brazil and Argentina is also not negligible (Gelband et al., 2015). Macrolides, penicillins and tetracyclines, which are the world's best-selling antibiotic groups, are classified as critical in human medicine (WHO, 2011). The highest resistance is described in poultry among the European Union – from 0.9% in the case of aminoglycosides, 6% in macrolides, and up to 59.6% in tetracyclines. The most significant is the resistance of salmonellas and campylobacters to tetracyclines (5.6–82.4% and 1–87.5%, respectively) and quinolones (3.6–94.1% and 3.96–96.3%, respectively) in broiler breeds (EFSA, 2016). In the United States, 22% resistance to fluoroquinolones and 95.4% to gentamycin is reported in poultry with the highest numbers in salmonella strains resistant to tetracyclines (41–46%) being consistent with the EU, the decreasing trend of resistance is then reported in salmonellas with relation to cephalosporins (decrease from 38 to 18%) within chickens in the retail network (CDC, 2014). From 2011 to 2014, reported overall sales of veterinary antimicrobials (in mg/PCU) decreased in 14 European countries and sales of the 3rd and 4th-generation cephalosporins and fluoroquinolones decreased in 10 and 11 European countries, respectively (ECDC et al., 2017). Such a decline in sales of veterinary antimicrobials among EU countries correlates also with the average annual change (between years 2012–2016) showing a slight decline (–0.01) in consumption of antibiotics for systemic use in the community in EU/EEA countries (ECDC, 2017).

Antimicrobial resistance precautions

It is well known that antibiotic pressure will boost the resistance because of the selection allowing only the fittest bacteria to survive even more in the future (Martinez et al., 2007). Such a circumstance may have a negative impact on profound resistance in multi-drug resistant microorganisms. According to the above-mentioned danger of overuse of antibiotics, there is a need to act – one of the attempts to reduce their overuse has become the awareness of the use of antibiotics in human medicine, and in agriculture the ban on antibiotic growth stimulators (EU, 2003) (Table 2). Options to reduce the consumption of classical antibiotics and prevent the associated development of resistance include alternative sources of substances with antibiotic effects, e. g. prebiotics (Abd El-Khalek et al., 2010), probiotics (Marinho et al., 2007), enzymes (Shim et al., 2005), organic acids (Marounek et al., 2007), synbiotics (Bomba et al., 2002), bacteriocins, bacteriophages (Caly et al., 2015), plant extracts (Jouany, Morgavi, 2007), zinc oxide (Ou et al., 2007), or clay minerals (Phillips et al., 2002). In relation with the previous list of non-antibiotic growth promoters, it is necessary to mention, that also in this group of antimicrobials, restrictions of usage will apply in the future. As an example, the zinc oxide can be used: it has recently been stated that overall benefit–risk balance for veterinary medicinal products containing zinc oxide to be administered orally to food-producing species is negative. This is due to the fact, that the zinc's antidiarrhoeal effect value is not exceeding the value of its accumulation rate in the environment and its potential contribution in increase of the bacterial resistance. According to these findings, no more new marketing authorisations will be issued and the withdrawals of the existing marketing authorisations for veterinary medicinal products containing zinc oxide will be implemented in the European Union (EMEA, 2017). Therefore, another possibility to reduce bacterial antibiotic resistance due to reduced dosage of antibiotics is the use of the combinatory effect of various plants (Garvey et al., 2011; Pervaiz et al., 2016), or synthetic substances (Lefebvre et al., 2016) both with each other and in combination with antibiotics. Synergistic reactions of two compounds are clearly beneficial for combating bacterial infections, bringing into treatment a perspective of not only reduction of antibacterial resistance, but also a potential in reduced dosage of individual substances used in the combination; extension of antimicrobial treatment; reduced side effects of individual substances; and lowered environmental burden (Aktas, Derbentli, 2016). On the other hand, antagonistic interaction between two solely active agents is able to bring undesirable circumstances into treatment that can be even life-threatening (Cascorbi, 2012). Nevertheless, by theoretical models, antagonism could be useful in reducing the potential for evolving resistance more than synergism that is enhancing it by the selection pressure allowing very strongly resistant bacteria to outlast (Michel et al., 2008).

CONCLUSION

Given the general concerns about the progress of antimicrobial resistance in microorganisms to an extent that is not compatible with available drugs, it is highly desirable to limit the consumption of these pharmaceuticals especially in food-producing animals such as poultry and pigs to the lowest acceptable level. Such a minimisation can be achieved not only through legislative interventions, but also by the prevention of disease or using alternative sources of antibacterial agents and also by the combinatory effect of various compounds.

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