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Review article

IMPACT OF ANTIBIOTICS USED AS GROWTH PROMOTERS ON BACTERIAL RESISTANCE

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ABSTRACT: For decades intensive husbandry has more or less been based on the use of antibiotics in sub-minimum inhibitory concentrations (sub-MIC) aimed at growth promotion. Continuous exposure of animal intestinal microbiota, including opportunistic zoonotic pathogens, to sub-MIC poses a pressure to selection and spread of bacteria strains with developed mechanism of antibiotic resistance. These bacteria may be transferred to people either by direct contact with farm animals or indirectly, via the food chain. Although in the EU a ban on the use of antibiotics as growth promoters was imposed in 2006, in many countries, including the largest producers and consumers of antibiotics in the world, it has yet to be done. Given that we are faced with a global problem of the loss of the efficacy of several antibiotic classes which are available for the treatment of human bacterial infections, it is unacceptable that antibiotic use in husbandry is not under global control. Reduction in antibiotic use in clinical practice in human medicine remains in dispute, but non-therapeutic use in husbandry remains a field in which much can be done to contribute substantially to the extension of antibiotic effectiveness and health care of future generations.

Keywords: *antibiotics, feed supplement, bacterial resistance*

INTRODUCTION

The discovery of antibiotics is one of the greatest successes in medicine, which enabled the cure of infectious diseases and preserved millions of human lives. However, not much time has passed between the beginning of their use, and the emergence of resistance in bacteria, even Alexander Fleming, 70 years ago, warned that it would happen in a short time (Calderone, 2015). Researchers make considerable efforts to produce novel classes of antibiotics, but with rapid evolution of resistance factors bacteria have an advantage in this race. For example, *Acinetobacter baumannii,* an opportunistic human pathogen, evolved in 30 years from a bacterium species susceptible to all antibiotics into the one which has a genomic island of 45 resistance genes which it acquired from various genera of bacteria by horizontal transfer (Foumier et al., 2006). Nowadays, the situation concerning antimicrobial resistance is alarming and points to the entry into a post-antibiotic era.

The hospital environment is a major selective environment of antibiotic-resistant bacteria, which has clearly been confirmed in

clinical practice. The use of antibiotics is of huge importance in human health protection, although not necessarily justifiable. It is estimated that approximately 50% of antibiotics used in US hospitals was not essential, as well as that about 45% of prescribed antibiotics were aimed for illnesses that antibiotics cannot help (Calderone, 2015). Even more worrying is the fact that the same or similar antibiotics are used in vast quantities in food-producing animals and agriculture. In addition, intensive animal farming has mainly been based on continuous antibiotic administration in subtherapeutic doses as growth promoters, to increase feed efficiency, and in disease prevention (Katsunuma et al., 2007; Modi et al., 2011; Schmieder and Edwards, 2012; Wang and Yu, 2012). This practice has been maintained in many countries despite the fact that repeated exposure of bacteria to subminimum inhibitory concentrations was identified as a key factor which induces resistance (Kemper, 2008; EMEA, 1999; Ambrožič Avguštin, 2012). More than half of the total annual antibiotic production in the US and some other countries is spent in food-animal production (Wang and Yu, 2012), and as much as 60-80% of the total is used for non-therapeutic purposes (Chapin et al., 2005). Excessive use of antibiotics in animal husbandry is connected to high risks of the selection, spread and the persistence of antimicrobial-resistant bacteria. The consequences are the transfer of multiple-resistant bacteria to people in farms and slaughterhouses or indirectly, via the food chain and the spread in the ecosystem, water and soil (Landers et al. 2012; Wang and Yu, 2012; Zhu et al. 2013; Wichmann et al. 2014).The ultimate consequence is the loss of antibiotic efficacy against bacteria with multiple resistances to antibiotics and 'pan-resistant' gram-negative strains (Livermore, 2004; Nikaido, 2009). Only in the US, antibiotic-resistant bacteria cause more than 2 million illnesses and at least 23,000 deaths each year (FDA, 2016). The Chancellor of the Exchequer UK, George Osborne, claimed that '*resistance to antibiotics will become an even greater threat to mankind than cancer'* explaining that even 10 million people could die worldwide each year by 2050, as a result of ineffective antibiotic therapy (Hughes, 2016).

In this paper the consequences of deployment of antibiotics as growth promoters are discussed when taking into consideration the development of resistance in zoonotic bacteria and the health protection of people and domestic animals.

USE OF ANTIBIOTICS AS GROWTH PROMOTERS IN FOOD-PRODUCING ANIMALS

Historical data and mechanisms of action

The use of antibiotics in subtherapeutic concentrations as growth promoters, was approved of in the 1950s (Becker, 2010; Schmieder and Edwards, 2012). Several antibiotic classes have been used as growth promoters: penicillins, macrolides, sulphonamides, tetracyclines, pleuromutilins, polypeptides, streptogramins, carbadox, bambermycin (Becker, 2010). Penicillins and tetracyclines were the first to be used as feed supplements in swine, poultry and beef cattle in concentrations which correspond to 10% or 1% of therapeutic doses (EMEA, 1999; Marshall and Levy, 2011). Tetracycline, chlortetracycline and oxytetracycline are most frequently used in poultry, and ampicillin, bacitracin, erythromycin, lincomycin, virginiamycin and tetracycline in swine production (Chapin et al., 2005; Abrožič Avguštin, 2012).

It has been proven in practice that the addition of antibiotics to feed for animals increases animal weight gains and feed utilisation efficacy (EMEA, 1999). The average weight gain may increase by 4-8% and feed utilisation by 2-5% (Butaye et al., 2003). The precise mechanisms of action of antibiotics as growth stimulators have yet to be completely elucidated (Becker, 2010). However, the influence of the gastrointestinal (GI) microbiota undoubtedly plays a vital role in the process. In monogastric animals the GI tract is usually colonised by 400 to 500 different bacterial species, primarily obligate anaerobes such as the members of genera of *Bacteroides*, *Bifidobacterium* and *Clostridium*, but also

some aerobes and facultative anaerobes (lactobacilli, streptococci, *Escherichia coli*) (Richards et al., 2005). The number of bacteria increases along the GI tube: in the proximal parts there are 10^3-10^5 CFU per gram of digesta and in the colonic contents as many as 10^{10}-10^{12} CFU g^{-1} (Richards et al. 2005; Dibner and Richards, 2005). The composition of microbiota varies depending on the animal species and age, but is not entirely known due to the presence of uncultivable species. GI microbiota performs important functions in the metabolic processes, synthesis of short-chain fatty acids and essential vitamins (B and K), and influences the health and performance of the monogastric animal host (Richards et al., 2005; Dibner and Richards, 2005).

The proportion of GI bacteria to the number of host gut cells is 10:1 on average, which is why GI microbiota competes with the host cells in feed utilisation. Thus, oral administration of antibiotics and a consequent reduction in the number of bacteria result in more feed components available to the host. In addition, research has suggested that in germ-free animals the absorption of amino acids is twice the normal extent (Visek, 1978). The reduction of in bacteria number leads to increased utilisation of fat ingested with feed because of the intestinal bacteria catabolise bile salts, which results in decreased fat digestibility (Richards et al., 2005; Modi et al., 2011). Some of the metabolic products of GI microbiota are toxic compounds, such as ammonia, amines, phenols and indole, which all may stunt animal growth. Moreover, microbiota contributes to the thickening of the lamina propria in the gut wall and the length of the villi, which decrease nutrient digestibility (Anderson et al., 1999; Gaskins et al., 2002; Richards et al., 2005; Dibner and Richards, 2005; Modi et al., 2011).

In addition, bacterial antigenic determinants continually encourage local immune response and the production of immunoglobulins (IgA and IgG), which utilises proteins necessary for growth. It is estimated that a human adult secretes more than 5g of IgA each day, which binds to GI bacteria and food antigens; there is no reason to not suppose that an analogy can be drawn with the adult pig (Richards et al., 2005). Bacteria also stimulate mucus secretion by intestinal goblet cell and the turnover rates of the epithelial cells.

The drawback of this practice is in connection with the fact that GI microbiota is one of the most powerful non-specific protective mechanisms against infections, known as colonisation resistance (EMEA, 1999), or competitive exclusion (Richards et al., 2005). Continuous oral antibiotic administration, especially those which are non-absorbable or broad-spectrum, does irreversible damage to GI microbiota. Thus, animals highly susceptible to infections are recruited. If the antibiotic treatment is ceased, these animals usually contract infective diseases, chickens especially necrotic enteritis, and pigs *E. coli* and *Lawsonia intracellularis* colitis (Marshall and Levy, 2011; Casewell et al., 2003). Having considered these claims, it seems almost paradoxical that the principal reason which supports the continuation of antibiotic use as growth promoters it is stated that otherwise the use of antibiotics for therapeutic purposes will follow inevitably. In states where antibiotics are still in use as growth stimulators researchers suggest that the benefits from the prohibition of these for this purpose must be carefully weight against the consequences (Katsunuma et al., 2007).

Denmark is a state where the most accurate data on the antibiotic expenditure in food animals are gathered, thanks to the Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP). Research conducted from 1992 to 2008 indicated that despite a transient increase in antibiotic deployment for therapeutic uses in swine, no persistent consecutive negative effects of the ceased antibiotic feed supplementation have been observed (Aarestrup et al., 2010).

Moreover, no increase in the mortality of poultry occurred due to necrotic enteritis, but the use of salinomycin was on increase, which is an anticoccidial active against *Clostridium perfringens* (Dibner and Richards, 2005).

growth promoters and for therapeutic reasons in food animals (Xiao et al., 2008).

Antibiotics which are not used in humans, such as monensin, salinomycin, virginiamycin, tylosin, spiramycin, avilamycin, avoparcin, ardacin, olaquindox and carbadox have also been used as growth promoters (Butaye et al., 2003).

However, it has been confirmed that due to the chemical similarity of these with those used in humans and the fact that they are aimed at the same bacterial targets, the use of veterinary products can produce cross-resistance (Marshall and Levy, 2011). For these reasons it is possible to detect bacteria with resistance genes to antibiotics which have never been used in animals on a particular farm. The classic example is avoparcin (a glycopeptide), which started being used as feed supplement at the beginning of 1970s and was in use in the EU for nearly 20 years. It led to the selection of vancomycin-resistant enterococci (VRE), which were first detected in Europe in 1986 and in the following year in the USA (EMEA, 1999). VRE strains exhibit partial cross-resistance with teicoplanin (Butaye et al., 2003).

In people who were in direct contact with these animals the same clones of vancomycin-resistant enterococci (VRE) were found (Stobberingh et al., 1999). A link between the resistance in animal and human hospital isolates of avoparcin- and vancomycin-coresistant *Enterococcus* spp. was also confirmed using ribotyping methods (Bates et al., 1994). Multi/methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci (VRE) are the most common causes of nosocomial infections, and the genes coding resistance to vancomycin can be transferred via plasmids to *S. aureus* (Noble et al., 1992).

It is even more concerning given that vancomycin is the major drug for the therapy of human infections caused by multidrug-resistant (MDR) *Enterococcus* and frequently a drug of last resort. Human infection with VRE strains, especially in liver-transplant patients and those with hematologic malignancies, could be life-threatening (Rice, 2001).

One reasonable means of combat against resistance seems to be the termination of antibiotic use for non-therapeutic purposes. The prohibition of avoparcin in the EU resulted in the decrease in the number of VRE in broilers, but not in pigs. In the latter, there was a clone expansion of VRE with resistance genes for glycopeptides (*vanA*) and macrolides (*ermB*) located on the same mobile DNA (Aarestrup, 2005). Moreover, two years after the decrease in the use of tylosin for growth promotion and therapy in pigs, a considerable decline in VRE among *Enterococcus faecium* isolates occurred (Aarestrup, 2005). The ban of tylosine use in Denmark led to the decrease in the resistance of *Enterococcus faecium* not only to this antibiotic, but also to erythromycin, a chemically related macrolide (DANMAP, 2008). Following the prohibition of avoparcin use as feed supplement in Denmark (Bager et al., 1997), Italy (Pantosti et al., 1999), Hungary (Kaszanyitzky et al., 2007) and Germany (Klare et al., 1999), a considerable decline in the prevalence of vancomycin-resistant *Enterococcus* strains in poultry, pigs and cattle was detected. Commission of the EU banned avoparcin in all member states in 1997 (Dibner and Richards, 2005). Investigation into the resistance of *Enterococcus* from the gut microbiota of healthy people towards vancomycin showed decreased VRE colonisation (Klare et al., 1999).

Large quantities of antibiotics used in intensive animal husbandry influence the selection of resistant bacteria in animals and their secretions. Given that bacteria account for about 50% of the faeces, the annual quantity of 180 million dry tons of livestock and poultry manure merely in the US represents 90 dry tons of bacteria with developed resistance mechanisms against antibiotics (Wang and Yu, 2012).

Moreover, antibiotics used as growth promoters are usually poorly absorbed and 30-80% may be excreted as waste (Ambrožič Avguštin, 2012). Both antibiotics and resistant bacterial strains are spread by fertilisation to agricultural areas,

which is why people are indirectly exposed to risk of infections with resistant bacteria via the food chain.

Rules and regulations

Soon after the beginning of the use of antibiotics as feed supplements, the justification of this decision was questioned in Europe. In Denmark in 1969 the recommendation of the Swann committee was issued, which stated that antibiotics which were used in therapy of infections in humans and animals should not be used as growth promoters (Aarestrup, 2005). In 1969, in accordance with the recommendations of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, the use of penicillin, tetracyclines and sulphonamides as feed supplements was banned in the EU, but macrolides such as tylosin and spiramycin were used in the next 30 years, despite the importance of erythromycin, a related antibiotic, for human infections (EMEA, 1999). In 1985 in Sweden the Feeding Stuffs Act was issued, which was the first one to outlaw the use of antibiotics as animal growth promoters (Dibner and Richard, 2005).

From 1995, avoparcin (glycopeptide) has been banned in animals in Denmark, and from 1997 in the other member countries of the EU (Aarestrup, 2005; Ambrožič Avguštin, 2012). In 1999 the EU banned the use of bacitracin, spiramycin, tylosin and virginiamycin for growth promotion (Katsunuma et al., 2007). From 1 January 2006 all growth promoters have been banned from European agriculture by Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 (Regulation (EC) No 1831/2003; Kemper, 2008; Becker, 2010). In Serbia, the complete feed for animals must not contain antibiotics and sulfonamides (Pravilnik o kvalitetu hrane za životinje, 2010).

However, the use of antibiotics as growth promoters is still a practice in many countries, including large drug producers and consumers, such as the USA, China and Japan. For instance, in the USA, in 1951 a total of 100 tons of antibiotics were spent in animal husbandry, mostly as feed supplements, but 27 years later as much as 5,580 tons (Aarestrup, 2005). In 2009, 80% of total antibiotics used in the US were spent for non-human use, and 64% of these were administered to healthy animals (FDA, 2014). It is estimated that in the US up to eight times higher quantities of antibiotics are used for non-therapeutic purposes than for animal therapy (Marshall and Levy, 2011). In Australia 55.8% of antibiotics were used in stock feeds (Modi et al., 2011). China is the world's largest producer and consumer of antibiotics and in its industrial pig farms all major classes of antibiotics are used as growth promoters or for therapeutic reasons (Zhu et al., 2013). In Japan six synthetic antimicrobials and 19 antibiotics are approved for growth promotion (Katsunuma et al., 2007).

It has been claimed that the consumption of medically important antimicrobials approved for use in food-producing animals increased by 23% from 2009 to 2014 (FDA, 2015). In May 2016, FDA requested from drug-producing companies precise data on the quantities of antibiotics used annually in the four major food-producing animal species: pigs, cattle, chickens and turkeys. One of the objectives of this request is to remove growth promotion as an approved use for antibiotics (Pew Charitable Trusts website, 2016). The goal is to administer antibiotics in feed only when medically necessary, that is, for the therapy of sick, and not all animals.

In Japan in 1999 a Veterinary Antimicrobial Resistance Monitoring System was established. Its main focus is the investigation into the influence of antibiotics administered to animals via feed on the emergence of antimicrobial resistance, primarily in *Enterococcus* and *E. coli*; the ultimate goal is to assess the necessity of the withdrawal of antibiotics as growth promoters in the whole country (Katsunuma et al., 2007).

In the EU experts agree that non-therapeutic use of antibiotics in food-producing animals pose a high risk to the development of resistance and transfer of multiple-resistant bacteria strains to people. By contrast, in some other coun-

tries the relationship between the use of antibiotics in food-producing animals and drug-resistant bacteria in humans is still a contentious issue (Marshall and Levy, 2011).

CONCLUDING REMARKS

Public health experts warn that a strict control or a total ban on the use of antibiotics as growth promoters is inevitable, particularly of those which are associated with human medical treatments. Agricultural producers, however, claim that, firstly, without antibiotics many phases in animal production would not be commercially sustainable, and secondly, that there are no sufficiently strong scientific proofs of the connection between the use of antibiotics as growth stimulators and the bacterial resistance. Until a final agreement is achieved, profound consequences on animal health keep arising, the mechanisms of resistance towards antibiotics are emerging and spreading among both commensals and pathogens, and these disseminate into the environment and eventually, affect human health.

The use of antibiotics is inevitable to maintain domestic animals' health, particularly in intensive animal production, but it cannot act as a substitution for good hygiene management The termination of continuous antibiotic use requires considerable changes in animal husbandry management, reduction in stock density, higher standards of hygiene, accurate, precise and timely antibiotic therapy, deployment of alternative substances for disease prevention (such as enzymes, prebiotics, organic acids, probiotics, trace minerals or herbs) and vaccines (Kemper, 2008).

Humans are capable only of preventing the emergence of additional reasons which may powerfully influence the increase in the number and the spread of resistance genes in bacteria. Facing the danger which the diseases caused by bacteria strains resistant to available antibiotics may threaten, it is incomprehensive that the use of antibiotics in veterinary medicine in the majority of countries is still not under strict control. Feed and foods of animal origin are distributed across the world, which makes the resistance which emerged in any country the problem for all (Aarestrup, 2005). Today, on the threshold of the post-antibiotic era, the use of antibiotics for non-therapeutic purposes is unacceptable. Still remains the open question when the measures for strict control of antibiotic use in animal husbandry will be taken on a global level, which is of utmost importance for the maintenance of their effectiveness and health protection of future generations.

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УТИЦАЈ АНТИБИОТИКА КОЈИ СЕ КОРИСТЕ КАО СТИМУЛАТОРИ РАСТА КОД ЖИВОТИЊА НА РЕЗИСТЕНЦИЈУ БАКТЕРИЈА

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Сажетак: Интензивна сточарска производња се деценијама у већој или мањој мери базира на употреби антибиотика у субинхибиторним концентрацијама за промоцију раста. Континуирано излагање микробиота дигестивног тракта животиња (укључујући и опортунистичке зоонотске патогене) суб-инхибиторним концентрацијама антибиотика, представља притисак на селекцију и ширење сојева бактерија са механизмима резистенције на антибиотике. На људе се ове бактерије могу пренети директним контактом са фармским животињама или на посредан начин, преко ланца исхране. Иако је у земљама Европске уније употреба антибиотика за промоцију раста животиња забрањена 2006. године, у многим државама, укључујући највеће произвођаче и потрошаче антибиотика у свету, ова пракса се задржала до данас. Губитак ефикасности антибиотика који су тренутно на располагању за лечење бактеријских инфекција код људи је растући проблем, због чега је неприхватљиво да употреба антибиотика у сточарској производњи није под глобалном контролом. Клиничка пракса у хуманој медицини оставља дискутабилан простор за редукцију примене антибиотика, али је нетерапеутска употреба у сточарству област у оквиру које се може значајно допринети продужавању века употребљивости појединих класа антибиотика и очувању здравља будућих генерација.

Кључне речи: *антибиотици, додаци храни, резистенција бактерија*

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