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Review scientific paper

THE IMPORTANCE OF ANTIMICROBIAL RESISTANCE FOR HUMAN HEALTH AND THE ROLE OF DOCTORS OF VETERINARY MEDICINE IN THE SPREAD AND PREVENTION

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Abstract
Antimicrobial drugs are very important in the treatment of many infectious diseases in humans and animals. This article deals with the importance of antimicrobial resistance, as it is one of the most significant problems of modern medicine, but also with the role of doctors of veterinary medicine in this issue. Due to the frequent and irrational use of antimicrobial drugs, doctors of veterinary medicine have an undoubted contribution to the current (it can be said) high prevalence of bacterial resistance around the world.
Therefore, numerous organizations, both in human and veterinary medicine in the world today, are trying to create national programs and strategies to fight against the development of antimicrobial resistance. The fight against resistance is long-lasting and requires the coordination and global participation of all parties - from doctors and veterinarians to legislators and politicians - under the umbrella of the "One Health" principle.
Key words: antimicrobial resistance, AMR, antimicrobial agents

INTRODUCTION

The development of resistance to antimicrobial drugs or antimicrobial resistance (AMR) is one of the biggest and most significant problems of modern medicine. The growing development of resistance to numerous pathogens of infectious diseases leads to a significant threat to public health in many countries around the world and a large number of human sectors. This change in bacterial cells disturbs the effective prevention and treatment of infections caused by these pathogens. As a consequence, the infection persists in humans and animals, causing a serious threat to their health and life, and allows the further spread of resistant microorganisms. Without effective antimicrobial agents to prevent and treat infections, medical procedures such as transplantation of organs, chemotherapy, diabetes treatment, and major surgeries (e.g., cesarean section or hip replacement) could become very risky (Prestinaci et al., 2015). Antimicrobial resistance in human medicine increases the cost of health care due to longer patient hospital stays and increased need for more intensive care since patients with infections caused by drug-resistant bacteria are at increased risk of poor clinical outcomes and death. Also, antimicrobial resistance may lead to the ineffectiveness of sustainable development and may make its outcome questionable.

AMR is a complex and multidimensional problem. Resistance to highly prevalent bacteria has reached alarming levels in many parts of the world, indicating that a large number of available treatments for common infections are becoming ineffective in some regions. Strengthening global surveillance of AMR is a crucial issue and basis for creating global strategies, monitoring the effectiveness of public health interventions, and discovering new trends in resistance (WHO, 2014). The mechanisms of the development of resistance in bacteria that cause various diseases (the spectrum of diseases) in humans and animals are constantly changing over time. Collateral effects of the use of sub-inhibitory concentrations of antibiotics indicate that the risk of developing AMR should not be exclusively associated with the therapeutic use of antibiotics, but AMR should be perceived as a problem caused by numerous factors. There is a large gap in knowledge related to the actual presence of AMR problems as well as a lack of information necessary to conduct public health emergency actions. The World Health Organization (WHO), together with partners from many sectors, has developed a global action plan to mitigate AMR.

Occurrence and spread of antimicrobial resistance

Antimicrobial resistance develops naturally over time, usually through genetic changes (Aminov and Mackie, 2007; Tenover, 2006). However, the abuse and overuse of antimicrobials accelerate this process. In many cases, antibiotics are used irrationally and often unnecessarily in humans and animals whose products are used for human consumption. Examples of abuse in humans most often include their use to treat viral infections such as colds and flu. In animals, antibiotics have been used or are still used as growth promoters or as a part of routine prophylactic measures for certain diseases in healthy animals without an appropriate indication which further contributes to the development and spread of AMR on farms.

Current status and monitoring of antimicrobial resistance

Antimicrobials (including antibiotics, antivirals, and antifungals) are critical drugs that are used to fight against diseases in humans, terrestrial and aquatic animals, and plants, but their effects begin to be questionable. AMR pathogens are present in humans, animals, food, and the environment (water, soil, and air). They can spread between humans and animals, through the food of animal origin, and from person to person. Poor and inadequate sanitation and inappropriate food-handling encourage the spread of antimicrobial resistance. In its reports, the WHO records very high rates of development of resistance in bacteria that cause hospital-acquired infections (e.g. urinary tract infections, pneumonia) in all WHO member countries. It was also noted that there are significant shortcomings in adequate surveillance measures, as well as a lack of standards for methodology, data exchange, and coordination of sectors dealing with AMR issues (WHO, 2014). Currently, there is no global consensus on a methodology for collecting data to monitor AMR. Routine surveillance in most countries is often based on samples taken from patients with severe infections - especially hospital-acquired infections, and those in whom first-line antimicrobial treatment has failed. Nevertheless, it is extremely important to get a broad picture of the international scope of the AMR problem. The WHO is collecting the latest surveillance information for a selected set of nine combinations of bacteria and antibacterial drugs of high health importance from 129 Member States. Many data sets were based on a small number of tested isolates of each bacterium (<30), which contributes to the uncertainty of data accuracy; this reflects the lack of national structures that could provide an overview of the situation as well as the limited capacity to exchange information on time. The unrepresentativeness of surveillance data is a limitation for interpreting and comparing results. Among the regions of the WHO, the most numerous data at the state level were obtained from the countries of Europe and America, where there is long-term regional supervision and cooperation.

According to a 2019 CDC report (CDC, 2020) that estimates the level of the AMR threat in the United States, more than 2,8 million infections with various antibiotic-resistant pathogens occur in this country each year. More than 35,000 cases end in death. In 2017, more than 223,900 cases i.e. infections caused by *Clostridioides difficile* were reported, with 12,800 deaths. The CDC also published a list of the most dangerous AMR pathogens in the United States in this report, which confirms that the threat of AMR is constantly present in the United States.

Bacteria and fungi on the list of dangerous, resistant pathogens in the 2019 CDC report (CDC, 2020)
Urgent threats:

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae
- Drug-resistant *Neisseria gonorrhoeae*

Serious threats:

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida spp.*
- ESBL-producing Enterobacteriaceae
- Vancomycin-resistant *Enterococci* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*

- Drug-resistant *Salmonella serotype Typhi*
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

Concerning threats:
- Erythromicin-Resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

Watch list:
- Azole- resistant *Aspergillus fumigatus*
- Drug-resistant *Mycoplasma genitalium*
- Drug-resistant *Bordetella pertussis*

In some member countries of the Organization for Economic Cooperation and Development (OECD), about 35% of common human infections are already resistant to currently available drugs. Some low- and middle-income countries have an AMR development rate of as high as 80 to 90% for some combinations of antibiotics and bacteria (OECD, 2018). One-third of countries that sent to WHO their data related to antimicrobial resistance in the year 2017, reported a wide degree of AMR on common pathogens (WHO, 2018). AMR on the second and third line of antibiotics - the last line of defense against some common diseases - is projected to be almost doubled between the years 2005 and 2030 (OECD, 2018). At the same time, millions of lives are lost each year due to lack of access to existing antimicrobials: inadequate access to antibiotics kills nearly 6 million people annually, including one million children who die from sepsis and pneumonia which can be prevented (Laxminarayan et al., 2016; Rochford et al., 2018; Daulaire et al., 2015).

AMR surveillance

Surveillance of certain diseases, such as tuberculosis, malaria, and AIDS to detect resistance, determine disease burden, and monitor public health interventions is well established by the WHO. The WHO established approximately 480,000 new cases of tuberculosis in 2014, caused by bacteria resistance to the two most powerful anti-tuberculosis drugs (MDR-TB). Focal points of resistance to artemisinin, by *P. falciparum malaria* as malaria causative agent, have been identified in several countries. Further spread or occurrence in other regions, of artemisinin-resistant strains may disturb recent improvements in malaria control. In 2010, about 7% of people in developing countries, who started antiretroviral therapy, had drug-resistant HIV. In developed countries, this percentage was 10-20%. Some countries have recently reported levels above 15% among people who had just starting HIV treatment and up to 40% among people already starting treatment, which requires urgent attention. Using experiences from these programs, the

WHO can also make plans for surveillance in the control of AMR developed in other specific pathogens (WHO, 2014).

Inadequate access to clean water, sanitation, and hygiene in health facilities, farms, schools, and households; poor disease prevention; lack of access to quality antimicrobials, vaccines, and diagnostics; poor health, food and food production, food safety, and waste management increase the incidence of infectious diseases in animals and humans and contribute to the emergence and spread of drug-resistant pathogens.

Antibiotic resistance is present in each country. The resistance of *Klebsiella pneumoniae* - a common intestinal bacterium that can cause life-threatening infections to the drugs used to treat it (antibiotics of the carbapenem group) has spread to all regions of the world. In some countries, due to resistance, carbapenems are not effective in more than half of the people treated for the infection caused by this bacterium (WHO, 2018).

The high proportions of resistance to third-generation cephalosporins and fluoroquinolones reported for *E. coli* mean that carbapenems should be used as a last option to treat severe infections caused by this bacterium (WHO, 2014).

Failure to treat gonorrhea with third-generation cephalosporin antibiotics due to AMR has been confirmed in at least 10 countries (Australia, Austria, Canada, France, Japan, Norway, Slovenia, South Africa, Sweden, the United Kingdom, and Northern Ireland) (WHO, 2018). Resistance to first-line drugs for the treatment of infections caused by the bacteria *Staphlylococcus aureus*, a common cause of severe infections in healthcare facilities, is widespread. It is estimated that 64% more people with MRSA (methicillin-resistant Staphylococcus aureus) will die compared to people with a non-resistant form of infection. Colistin is used to treat infections caused by bacteria of the family Enterobacteriaceae, which are resistant to carbapenems. However, resistance to colistin has recently been discovered in several countries and regions, making infections caused by such bacteria incurable diseases.

Drug-resistant diseases already cause at least 700,000 deaths a year globally, including 230,000 deaths from multidrug-resistant tuberculosis. These numbers could, globally, rise to 10 million deaths annually until the year 2050 under the worst-case scenario and if nothing is done. It is estimated that approximately 2,4 million people could die in high-income countries between years 2015 and 2050 without continuous efforts to suppress antimicrobial resistance (WHO*,* 2019).

Data on resistance to antibacterial drugs commonly used to treat infections caused by seven bacteria of international importance, which cause some of the most common infections in hospitals or are transmitted through the food chain, are presented in the following table (WHO, 2014):

Bacterial names/ resistance	Examples of typical diseases	Number of WHO member states that provided data (N=194)	Number of WHO regions where resistance is present in 50% of cases or more, according to national reports
Escherichia coli/ -the third-generation cephalosporin - fluoroquinolones	Urinary tract infections, bacteriemia	86 92	5/6 5/6
Klebsiella pneumoniae/ - the third-generation cephalosporin -3. carbapenems	Pneumonia, bacteriemia, urinary tract infections	87 71	6/6 2/6
Staphylococcus aureus/ methicillin “MRSA”	Wound infections, bacteriemia	85	5/6
Streptococcus pneumoniae/ penicilin	Pneumonia, meningitis, otitis	67	6/6
Non-typhoidal *Salmonella*/ fluoroquinolones	Alimentarna diarrhea, bacteriemia	68	3/6
Shigella species/ - fluoroquinolones	Diarrhea (“bacillary dysentery”)	35	2/6
Neisseria gonorrhoea/ the third-generation cephalosporin	Gonorrhea	42	3/6

Economic consequences of AMR

The economic damage from antimicrobial resistance arises as a result of a dramatic increase in health care expenditures; this affects the production of food for humans and animals, trade, and increasing poverty and inequality (WHO, 2019).

National AMR action plans are in the focus of a multisectoral "One health" approach. However, for successful implementation of the plan, barriers in funding and capacity that exist in many countries need to be urgently resolved. A long-lasting “One health” approach has to be included, to unite all stakeholders around a shared vision and goals (McEwen and Collignon, 2018).

Use of antimicrobials in animals

Responsible use of antimicrobial drugs in animals, under appropriate supervision and global standards prescribed by the World Organization for Animal Health (OIE), ensures their effectiveness and reduces the risk of abuse as well as potential negative consequences, i.e. further spread of AMR.

Bacterial diseases are the main limitation for the most efficient production of food obtained from farm animals. They cause diseases and suffering, not only in food-producing animals, but also in other animals, and potentially humans. Many animal bacterial diseases are fatal, while others cause pain and workability reduction. In some situations, bacterial diseases can be controlled by keeping animals of a certain health condition, ensuring well-being, vaccination, and good hygiene. However, antimicrobial therapy remains vital for the treatment and, in some cases, for the prevention of bacterial diseases in farm animals. In some production systems, the spread of bacterial diseases can be accelerated due to the proximity of animals. Appropriate use of antimicrobials will be effective in treating sick animals as well as in the rapid recovery of others and may improve the welfare of treated animals and reduce the spread of infection to other animals or, in the case of zoonotic disease, to humans.

The biggest issue is how to effectively use antimicrobial drugs, with minimum risk of resistance. The short generation time and the ability to exchange genetic material led to the development of resistance to many antimicrobial drugs in a large number of animal bacteria (causes of infections in animals) (Linton, 1977). Nevertheless, some drugs have retained excellent activity against certain target organisms, such as penicillin against *Streptococcus agalactia* despite widespread use over 40 years (Wagner and Erskine, 2013). Non-zoonotic animal bacteria can still pose a danger for transmission through food because there is a risk of transferring their genetic material that encodes resistance to pathogenic human bacteria. There is a risk to humans when the same antimicrobial drug is used in animals and humans or when the used drug is cross-resistant to a drug used in human medicine, although this risk has not yet been adequately quantified (McKellar, 1998).

AMR in animals

The appropriate pharmacokinetic-pharmacodynamic relationships of antimicrobial drugs used in animals should always be taken into account. Bacteria usually develop resistance to some antimicrobial drugs by chromosomal mutation, rather than by accumulating genetic material from other bacteria. Zoonotic bacteria present the greatest potential danger to human health when these drugs are used in animals. Therefore, it is very important to develop the best and most effective dosing strategies for antimicrobial drugs to remove zoonotic organisms from animals. The minimum inhibitory concentrations required for the target pathogen may differ significantly from those in commensal organisms. In this way, the coded genetic material for AMR in commensal organisms can be transmitted to humans and then to human pathogens. Nevertheless, even for these antimicrobial drugs, optimal dosing strategies will expose commensal bacteria to minimal selective pressure (Soulsby, 2007).

The risk of AMR transmission from animals to humans could be significantly reduced if bacterial transmission could be minimized. This implies the application of strict hygiene protocols in markets, slaughterhouses, and food processing plants. Pasteurization has very effectively limited transmission in the dairy industry, and some measures could do the same with other foods of animal origin. Consumer attitudes towards food are always important, so good hygiene in the kitchen and adequate heat treatment of food significantly reduces the risk of AMR pathogen transmission (McKellar, 1998).

Antimicrobial drugs are used in veterinary medicine in therapeutic doses, but in some countries also prophylactically, as well as to improve or stimulate growth. Prophylactic antimicrobials should be used only when the spread of the disease cannot be limited by better hygiene, vaccination, management changes and when the development of the disease in animals, that are in contact with infected subjects, is almost unavoidable without antimicrobial intervention.

Prophylactic use of antimicrobials is more common in veterinary than human medicine and reflects livestock systems in which animals are kept nearby. In 1997, 48% of total antibiotic sales in Europe were for veterinary use. However, there are significant differences between classes of antibiotics in terms of either the amount administered or purpose of use, for example as for growth promoters or therapeutics (Laval, 2000).

In the Republic of Serbia, the use of antimicrobial drugs for growth stimulation, as well as for prophylactic purposes is prohibited in animals whose products are used for human consumption.

It is clear that antimicrobial resistance in many animal pathogens would not develop if antimicrobial drugs were not used. However, experts believe that banning their use would be detrimental to the livestock industry, since it would lead to an increased number of bacterial and zoonotic diseases, and would have a catastrophic effect on animal welfare. However, best practice guidelines for the use of antimicrobials need to be carefully developed to ensure that the benefits to animals and society outweigh the risks (McKellar, 1998).

Concerns about the transmission of multiple resistance through the food chain to human patients have provoked numerous discussions. The widespread use of antibiotics in humans and animals raises concerns related to the acquisition of resistance by commensal organisms in waste material from hospitals, farms, fisheries, and food processing plants. Criticism is mostly focused on the use of antibiotics in livestock, whose products are used for human consumption, although there is clear evidence that multidrug-resistant intestinal microorganisms rarely lead to infections in people resistant to antibiotics. Nevertheless, there is a general opinion that the use of antibiotics in animals, whose products are used for human consumption, is risky. Although concerns focus on bacteria of animal origin that cause disease in humans (zoonoses), there are cases where infections go the other way, such as the multi discrete Salmonella Newport which can cause severe cases of a disease in cattle and horses and is becoming more common in humans. Salmonella Newport easily transmits resistance, besides its pathology, to other organisms (Soulsby, 2007).

However, numerous studies support the concern that the use of antibiotics in animals whose products are used for human consumption (especially in non-therapeutic use) may affect human health on farms and more broadly, through the food chain (Fey et al., 2000; Levy et al., 1976a).

The direct spread of bacteria from animals to humans has been documented in cases where the same species of tetracycline-resistant *E. coli* strains were found in the intestinal flora of farmers caring for chickens eating tetracycline-containing foods (Levy et al., 1976b). Other studies have consistently shown a higher prevalence of resistant bacteria in the gut among farmworkers than among the general public or among farmworkers who do not use antibiotics (Aubry-Damon et al., 2004).

A ban on the use of antibiotics for non-therapeutic purposes is thought to not only help limit additional harm but also opens up opportunities for better preservation of future antimicrobials in an era when their effectiveness is severely compromised and when only a few new are in preparations (Marshall and Levy, 2011).

On the other hand, antimicrobial resistance to some antimicrobial drugs (tetracycline, erythromycin, and ampicillin) has been found in some animal pathogens without the use of antibiotics (Schroeder et al., 2003; Jackson et al., 2004). Also, some experts believe that although the use of antibiotics in animals whose products are used for human consumption contributes to an increase in the occurrence of resistant microorganisms, the advantages of using antibiotics far outweigh the disadvantages (Oliver Murinda and Jayarao, 2011).

It is very difficult to make a clear connection between human health problems in people that work on the farms and animals treated with antibiotics mixed into food either in a therapeutic or preventive dose. There are cases of salmonellosis of animal origin in humans, but there is no evidence of an association with the prophylactic use of antibiotics in foods (Feeds, 1980). It is generally considered better to use antimicrobial drugs in therapeutic than in prophylactic doses when the drug is given to diseased animals over a long period of time (Hardy, 2002).

The biggest concerns in the animal health and agriculture sectors are the mass treatment of animals whose products are used for human consumption with antimicrobials that are crucial for humans, such as third-generation cephalosporins and fluoroquinolones, and the long-term use of medically important antimicrobial drugs such as colistin, in the diet, or tetracyclines and macrolides, as growth promoters. In the human sector, it is necessary to prevent infections, reduce the prescribing of antimicrobial drugs, and improve sanitary protection and control (McEwen and Collignon, 2018).

For a long time, the AMR in human medicine was mainly viewed through the agricultural sector that was marked as the main culprit, i.e. as the source of the development of resistance. Until recently, the use of antibiotics in livestock was considered the main source or root of the development of resistant bacteria dangerous to human health (Wise et al., 1998). In Europe, from the mid-1990s to the mid-2000s, there was an opinion that the use of antibiotics in agriculture, especially as a growth promoter, posed a high risk for the development of resistance (Fortané, 2019). Some of the most commonly used growth promoters, tylosin, and spiramycin, show cross-resistance to the macrolide erythromycin, which is an essential drug in human medicine (Pedersen, 1999). In the year 2006, this led to a ban on the use of growth promoters in the European Union (Regulation, 2003).

Today, the situation is much better when it comes to the use of antimicrobials in animals. The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) collects information on how antimicrobial veterinary medicines are used across the European Union (EU). In the 25 countries that provided data on sales of these drugs between 2011 and 2017, a total sales decline (mg/PCU) for 32.5% (ESVAC, 2019).

The importance of doctors of veterinary medicine in the fight against AMR

Given that some groups of antimicrobials of the class used in veterinary medicine are the same as those used in human medicine, concerns have increased, as such use in animals can undoubtedly contribute to the development of resistance in human pathogens, especially those transmitted by food and cause common foodborne illnesses, such as salmonellosis and campylobacteriosis. Doctors of veterinary medicine, as health workers who deal with farm animals and pets, are in close contact with both human and animal health, which puts them in a unique position to fight against the development of antibiotic resistance.

Another difficulty in managing the development of drug resistance is the fact that, usually, there is no alternative treatment for bacterial diseases. This in many cases prevents a simple solution that could be reducing the number of antibiotics, since in that case sick animals and people would be left without treatment. This also puts medical workers in a difficult position since they must, in order to reduce drug resistance, weigh the risk of the disease on the one hand and use of drugs on the other. To make this successful, it is necessary to support the efforts of doctors of veterinary medicine who, with their scientific training, technical knowledge, and professional expertise, can carefully choose the an adequate approach based on scientifically validated methods. In the first place, that means supporting doctors of veterinary medicine to prevent the disease not only in animals but also indirectly in humans.

Some diseases are zoonoses that can be transmitted between animals and humans, so preventing these diseases in pets and livestock automatically reduces the chance of animals and humans become infected with a disease that requires treatment with antibiotics. Recognizing the concept of "One Health" - in which human, animal, and environmental health are strongly connected – doctors of veterinary medicine are working hard to reduce the spread of the disease in order to reduce the need for antibiotics. This includes the full and proper use of vaccination, as well as good hygiene, nutrition, and well-being management. Such a preventive approach contributed to a reduction in sales of antimicrobial drugs for animals by a third in Europe between years 2011 and 2017. In July 2018, the European Medicines Agency (EMA) initiated a project to stratify data on the sale of veterinary antimicrobial drugs by animal species. This allows an approximate estimate of the antimicrobials used for different species, by assigning proportions of total sales to each species in which a veterinary antimicrobial is used. Sales of polymyxin declined by 66%, and sales of third- and fourth-generation cephalosporins decreased by more than 20%. These classes include colistin and other antibiotics used to treat serious infections in humans caused by bacteria resistant to most antimicrobial drugs. However, the situation across Europe remains full of contrast. A significant decline in some countries indicates that in other countries there is also the potential to reduce the use of antimicrobial drugs (ESVAC, 2019).

However, since we can not eradicate all bacterial diseases, there will always be a need for antibiotics to treat sick animals unless sufficiently effective alternatives are found, which have no or have less negative consequences.

It is necessary to develop and follow best practice guidelines for the use of antimicrobials to ensure that they are used as little as possible, but as much as necessary. Veterinarians must be equipped to be able to determine the adequate treatment for controlling the threat of disease in an animal or herd, and thus to be able to reduce both the disease spreading and developing drug resistance.

Animal protection organizations, including the European Platform for the Responsible Use of Medicinal Products for Animals (EPRUMA), have conducted campaigns to raise awareness of this issue and encourage the responsible use of these important medicines.

However, we can do more to ensure consistency in the guidelines for the responsible use obtained by all relevant organizations, from national authorities to the European Medicines Agency (EMA) and the World Organization for Animal Health (OIE). By developing common and consistent approaches, doctors of veterinary medicine can be better supported to use antibiotics responsibly.

Finally, regulators should resist the temptation to implement open bans of critical antimicrobial drugs (CIAs) use in animals. While this move could protect those drugs for future generations, comprehensive restrictions would tie the hands of veterinarians and make it impossible to treat sick animals, posing a risk not only to other animals but also to humans. Untreated cattle face unnecessary suffering and even death, which would mean that the ban on the use of antibiotics provokes a directly opposite goal from the one that was intended. Instead, we should focus on establishing access to a full range of preventive and therapeutic tools, as well as adequate training for all veterinarians.

Doctors of veterinary medicine can be the main link that unites doctors, drug manufacturers, legislators, and industry to ensure that we fight against the development of drug resistance on all fronts. In a relatively short time, doctors of veterinary medicine have significantly reduced the use of antimicrobial drugs through education, vaccination, increased biosecurity measures and hygiene, and improved livestock farming.

CONCLUSIONS

The challenges of antimicrobial resistance are certainly complex and multidimensional but can be overcome. Antimicrobial agents are key agents against disease in humans and animals. But the growing level of resistance to these agents poses a danger to human and animal health. At the same time, there is a lack of scientific innovation which led to market failure, a small number of new antimicrobial drugs, vaccines, diagnostic preparations, and alternatives to antimicrobials for human and animal use, which are currently in various stages of research and development. Given that antibiotic resistance could be responsible for high mortality (up to 10 million a year by 2050), if nothing is done about the current situation, it is natural to look for a more simple and immediate solution. However, the fight against AMR is long-lasting and requires the coordination and global participation of all parties - from doctors and veterinarians to legislators and politicians.

Strengthening the prevention and control of infections in health facilities, on farms, in schools, households, and farms using available tools, sanitation, and hygiene, are key factors that lead to minimizing the transmission of disease and the occurrence and transmission of antimicrobial resistance in humans and animals. Although the use of antibiotics as growth promoters is banned in Europe, it is still allowed in many parts of the world. The use of antimicrobial drugs as growth promoters should be stopped immediately and it should be on the list of WHO's highest priority (critically important antimicrobial agents in human medicine).

Strong political leadership, quality information, coordination, and responsibility are needed at all levels to enable a sustained response to AMR. All stakeholders - including governments, civil society, and the private sector - need to be engaged and have to work together for a shared vision and goals. It is clear that strengthening the regulatory framework, professional education, and supervision of antimicrobials by prescribing and raising awareness among all participants in this action are also important steps to ensure responsible use of antimicrobials and minimize the occurrence of resistant microorganisms in humans and animals. Additional efforts and investments are needed to improve innovations in antimicrobials, diagnostics, vaccines, effective antimicrobial alternatives, and alternative practices. In many regions around the world, people still do not have access to quality antimicrobials, which needs to be solved to ensure a quality global response to AMR.

Although agriculture and veterinary medicine have been blamed for the emergence and spread of AMR, this livestock sector has responded to criticism by establishing responsible use of medicines in agriculture (EPRUMA), as a consortium of veterinarians, farmers, and pharmaceutical organizations. In addition to collecting and analyzing data related to the sale and use of antimicrobials, they provide guidelines and advice on the use of antimicrobial drugs. This is a welcome move by veterinarians who show, by their actions, that they are ready to be at the center of the fight against resistance to drugs since the veterinary sector often deals with the common health issues of animals and humans.

Coordination and cooperation at the global level are needed because if investments and actions are further delayed, it is clear that uncontrolled antimicrobial resistance could have a far greater catastrophic impact in the future. For this reason, the WHO response is also very important in helping countries to develop their national action plans and strengthen their health and surveillance systems so that they can prevent and manage antimicrobial resistance. WHO is working closely with the Food and Agriculture Organization of the United Nations (FAO) and the World Organization for Animal Health (OIE) on the One Health approach to promoting best practices to avoid the emergence and spread of antibiotic resistance, including optimal use of antibiotics in both humans and animals. This cooperation is key to an adequate global response to AMR.

REFERENCES

Aminov R. I., Roderick I. M. (2007): Evolution and Ecology of Antibiotic Resistance Genes. FEMS Microbiology Letters, 271(2):147-61.

Aubry-Damon H., Grenet K., Sall-Ndiaye P., Che D., Cordeiro E., Bougnoux M. E., Rigaud E., Le Strat Y., Lemanissier V., Armand-Lefèvre L., Delzescaux D., Desenclos J. C., Liénard M., Andremont A. (2004): Antimicrobial Resistance in Commensal Flora of Pig Farmers. Emerging Infectious Diseases, 10(5):873-79.

CDC. (2020): Antibiotic-Resistant Germs: New Threats. Centers for Disease Control and Prevention.

Daulaire N., Bang A., Tomson G., Kalyango J. N., Cars O. (2015): Universal access to effective antibiotics is essential for tackling antibiotic resistance. J Law Med Ethics., 43:17-21.

ESVAC (2019): Sales of Veterinary Antimicrobial Agents in 30 European Countries in 2017. European Surveillance of Veterinary Antimicrobial Consumption. Available online at: https://www.ema.europa.eu/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2017_en.pdf (accessed March 15, 2020).

Fey P. D., Safranek T. J., Rupp M. E., Dunne E. F., Ribot E., Iwen P. C., Bradford P. A., Angulo F. J., Hinrichs S. H. (2000): Ceftriaxone-Resistant Salmonella Infection Acquired by a Child from Cattle. The New England Journal of Medicine, 34 (17):1242-49.

Fortané N. (2019): Veterinarian “Responsibility”: Conflicts of Definition and Appropriation Surrounding the Public Problem of Antimicrobial Resistance in France’. Palgrave Communications, 5(1):1-12.

Hardy B. (2002): The Issue of Antibiotic Use in the Livestock Industry: What Have We Learned? Animal Biotechnology, 13(1):129-47.

Jackson C. R., Fedorka-Cray P. J., Barrett J. B., Ladely S. R. (2004): Effects of Tylosin Use on Erythromycin Resistance in Enterococci Isolated from Swine. Applied and Environmental Microbiology, 70(7):4205-10.

Laval A. (2000): Veterinary use of antibiotics and resistance in man: what relation? Pathologie-Biologie, 48(10):940-44.

Laxminarayan R. et al. (2016): Access to effective antimicrobials: A worldwide challenge. Lancet. 2016; 387:168-75

Levy S. B., FitzGerald G. B., Macone A. B. (1976a): Spread of Antibiotic-Resistant Plasmids from Chicken to Chicken and from Chicken to Man. Nature, 260(5546):40-42.

Levy S. B., FitzGerald G. B., Macone A. B. (1976b): Changes in Intestinal Flora of Farm Personnel after Introduction of a Tetracycline-Supplemented Feed on a Farm’. The New England Journal of Medicine, 295(11):583-88.

Linton A. H. (1977): Antibiotic Resistance: The Present Situation Reviewed. The Veterinary Record, 100(17):354-60.

Marshall B. M., Levy S. B. (2011): Food Animals and Antimicrobials: Impacts on Human Health’. Clinical Microbiology Reviews, 24(4):718-33.

McEwen S. A., Collignon P. J. (2018): Antimicrobial Resistance: A One Health Perspective. Microbiology Spectrum, 6(2): 521-547.

McKellar Q. A. (1998): Antimicrobial Resistance: A Veterinary Perspective. BMJ: British Medical Journal, 317(7159):610-11.

Merlin C.(2020): Reducing the Consumption of Antibiotics: Would That Be Enough to Slow Down the Dissemination of Resistances in the Downstream Environment? Frontiers in Microbiology, 11:33.

OECD. (2018): Stemming the superbug tide: Just a few dollars more. Organization for Economic Cooperation and Development.

Oliver S. P., Murinda S. E., Jayarao B. M. (2011): Impact of Antibiotic Use in Adult Dairy Cows on Antimicrobial Resistance of Veterinary and Human Pathogens: A Comprehensive Review. Foodborne Pathogens and Disease, 8(3):337-55.

Pedersen K B. (1999): Some Growth Promoters in Animals Do Confer Antimicrobial Resistance in Humans. BMJ: British Medical Journal, 318(7190):1076.

Prestinaci F., Pezzotti P., Pantosti A. (2015): Antimicrobial Resistance: A Global Multifaceted Phenomenon. Pathogens and Global Health, 109(7):309-8.

Regulation. (2003): Regulation on additives for use in animal nutrition 1831/2003. Official Journal of the European Union, L 268:29-43.

Rochford C., Sridhar D., Woods N., Saleh Z., Hartenstein L., Ahlawat H., Whiting E., Dybul M., Cars O., Goosby E., Cassels A., Velasquez G., Hoffman S., Baris E., Wadsworth J., Gyansa-Lutterodt M., Davies S. (2018): Global governance of antimicrobial resistance. Lancet, 391(10134):1976-1978.

Schroeder C. M., White D. G., Ge B., Zhang Y., McDermott P. F., Ayers S., Zhao S., Meng J. (2003): Isolation of Antimicrobial-Resistant Escherichia Coli from Retail Meats Purchased in Greater Washington, DC, USA. International Journal of Food Microbiology, 85(1-2):197-202.

Shryock T. R., Richwine A. (2010): The Interface between Veterinary and Human Antibiotic Use. Annals of the New York Academy of Sciences, 1213:92-105.

Soulsby L. (2007): Antimicrobials and Animal Health: A Fascinating Nexus. The Journal of Antimicrobial Chemotherapy, 60(1):i77-78.

Tenover F. C. (2006): Mechanisms of Antimicrobial Resistance in Bacteria. American Journal of Infection Control, 34(5 Suppl 1):S3-10;S64-73.

Wagner S., Erskine R. (2013): Antimicrobial Drug Use in Mastitis. In Antimicrobial Therapy in Veterinary Medicine. John Wiley & Sons, Ltd, 519-28.

WHO. (2014): Antimicrobial Resistance: Global Report on Surveillance. World Health Organization.

WHO. (2018): Global Antimicrobial Resistance Surveillance System (GLASS) Report: Early Implementation 2016-17. World Health Organization.

WHO. (2019): No time to wait: Securing the future from drug-resistant infections report to the secretary-general of the united nations. World Health Organization, Interagency Coordination Group on Antimicrobial Resistance.

Wise R., Hart T., Cars O., Streulens M., Helmuth R., Huovinen P., Sprenger M. (1998): Antimicrobial Resistance. BMJ: British Medical Journal, 317(7159):609-10.

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