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Original Contribution

RULES FOR ENHANCED CONTROL OF ANTIMICROBIAL RESISTANCE AS PART OF THE ONE HEALTH CONCEPT

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ABSTRACT

This work includes an overview of legislative changes in the use of veterinary medicinal products. These developments are a result of global initiatives of control over antimicrobial resistance (AMR). The main focus of the research is the list of antibiotics intended only for human use by the World Health Organization (WHO). In synchrony with the intention of the European Commission to familiarize young people, this report may contribute to a better understanding of the One Health concept and the awareness of the threat of AMR. Public documents of the WHO and the United Nations, as well as documents of harmonized European legislation and national regulatory framework were analysed with methods of documentary analysis, content analysis, complex analysis and synthesis. Databases for monitoring the use of antimicrobials have been analysed, the impact of risk factors for AMR has been compared, and conclusions for adequate future actions to control AMR have been drawn.

Keywords: antimicrobial, AMR, One Health, MIA List, veterinary practice

INTRODUCTION

Antimicrobial resistance (AMR) is the reason for the revision of the standards and recommendations of the World Organization for Animal Health (WOAH) for the use of antimicrobial agents (AMBs) in animals in 2024.

A new approach for categorizing antibiotics has been adopted, reflected in the "WHO List of Medically Important Antimicrobials" (WHO MIA List) (1) published by the World Health Organization (WHO) and the "WOAH List of Antimicrobial Agents of Veterinary Importance" (WOAH AAVI List) (2) published by the World Organization of Animal Health (WOAH). Both documents categorize antimicrobial agents into classes and subclasses, however in the meantime, only antibiotics are included. Both organizations state the need for the lists to be revised and supplemented for other antimicrobial agents.

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The WHO MIA List 2024 is the sixth edition of the document, but for the first time, it includes antibiotics approved only for use in humans. The WOAH AAVI Lis was established in 2007 and updated periodically until 2024 (2). Although these organizations' documents are not legally binding, they contain harmonized guidelines aimed at introducing skills and habits for the prudent use of AMBs in the context of the One Health concept – the unified protection of common animal, human, and environmental health in all of its aspects.

The two lists are in line with the intensified action taken to limit antimicrobial resistance as a result of over 20 years of efforts by the so-called Quadri-Coalition for One Health, which includes: the Food and Agriculture Organization of the United Nations (FAO); the United Nations Environment Programme (UNEP); the World Health Organization (WHO); and the World Organisation for Animal Health (WOAH) (3).

Recognizing the fundamental link between the environment and human and animal health, the European Commission is not only actively promoting and developing the idea, but is also a leading power on the implementation of the One

Health concept and the understanding of the potential threat to humanity from AMR. In this regard, the principal initiative belongs to the Netherlands, as it was the first to take national measures to reduce the use of AMR with positive results (3, 4).

The EU has successfully adapted the basic principles of the prudent use of antimicrobials to its legislative acts, and has adopted the lists of the two health organizations, creating up-to-date global instruments for the control of AMR. In addition to legislative initiatives and measures for enhanced control, as a key means of sustainably building skills and habits for the prudent use of antimicrobials, the European Commission calls for the familiarization of young people with the One Health concept and the potential danger of antimicrobial resistance (5). This calling is taken as the basis for the argumentation of the present paper.

MATERIAL AND METHODS

The goal of the research is to contribute not only to the promotion of international and European policies on the containment and control of antimicrobial resistance, but also to the adoption of their ground principles in a practical and applied aspect, particularly, from the point of view of veterinary science and practice. The focus is placed on enhanced measures against antimicrobial resistance implemented by the unique WHO MIA-list and WOAH AAVI List and the amendments introduced in the EU legislative acts.

For the study, an overview analysis of the introduced amendments to the EU rules for the use of veterinary medicinal products depending on global initiatives, and international efforts to control antimicrobial resistance in chronological order was carried out. Risk factors for resistance in microorganisms and the role of veterinary medicine among them were visualized. Key legislative initiatives of the EU for the control of AMR were noted. The basic principles of a recommendatory or normative nature in antimicrobial use in veterinary medicine were systematized. Databases for monitoring antimicrobial use (national and European systems for pharmacovigilance and ANIMUSE) were briefly reviewed.

Primary information from public sources was used: documents of Quadri-Coalition for One Health, European and national regulatory documents, scientific publications from PubMed, Oxford Academic, Europe PMC, and national sources. The documentary method and evaluating research methods (methods of comparison and analogy; content analysis; complex analysis, and synthesis) for systematizing and analyzing the data were used. Conclusions have been drawn on the established global measures for the control of AMR, positive trends in coordinated actions to limit the problem have been noted, and possible difficulties in the fight against resistance arising from modern reality have been identified.

RESULTS AND DISCUSSION

1. Key points and background of antimicrobial resistance problem

Penicillin was the first antibiotic in the world, discovered by the Scottish scientist Alexander Fleming in 1928. The purification and first clinical use of Penicillin took over a decade. Its production began in 1943. In the next 40 years, there was a boom in the discovery and use of antibiotics, which became the leading weapon of medicine (6,7). However, antibiotic production is an expensive and complicated process. According to data from the European Court of Auditors it would take nearly one billion euros and about ten years for a new drug to reach the market, as the process includes long-term research and testing, with no guarantee of success (8). Thus, because of many reasons, mainly financial and technological, after 1984 no newly discovered classes of antibiotics have been registered **(Figure 1).**

At the same time, data on the emergence of antibiotic-resistant bacteria is accumulating, and so-called infections associated with medical care are appearing. It has been established that the use of antibiotics, especially their unreasonable use, directly influences and provokes the development of resistance in microorganisms (7, 9).

Data on penicillin-resistant bacteria were reported in the 1970s associated with the introduction of broad-spectrum penicillins (Ampicillin; Amoxicillin). In connection with these phenomena, in 1969 John E. McGowan and Dale N. Gerding introduced the term “antimicrobial stewardship” arguing for the need to manage antibiotic use. They discuss that there is an association between the use of antimicrobial agents and the development of resistance, and that it is likely causal. Their method is based on precise epidemiological

research and is a large-scale study of antibiotic use, molecular typing, and analysis of resistance mechanisms (9, 10).

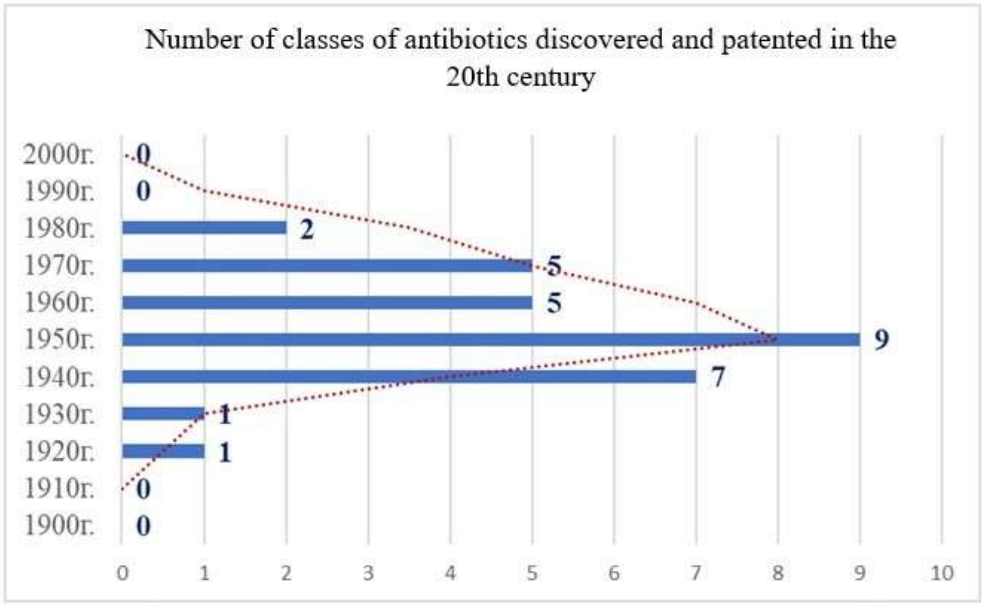

Figure 1. Trends in antibiotic classes discovery in the 20th century. By data from ECA, 2019 in: Special Report: measures to address antimicrobial resistance (8)

Today, antibiotic resistance is associated with the possibility of microorganisms that are developing mechanisms to overcome the effects of antibiotics. The broader concept is antimicrobial resistance (AMR). AMR refers to the established resistance of microorganisms to various drugs - antiviral, antifungal, antiprotozoal, antibacterial, antiparasitic or "the ability of microorganisms to survive or multiply in the presence of an antimicrobial agent at a concentration that is normally sufficient to inhibit or kill microorganisms of the same species" (Regulation (EU) 2019/6, Article 4, Para 11) (11). There is also evidence of observed resistance of microorganisms to disinfectants (12, 13), although this group of medicinal products is absent from the official modern concept of AMR control.

Gradually, in the conditions of lack of new antibiotics and increasing resistance worldwide, the understanding that AMR represents a serious threat to humanity with its potential to create superbugs (resistant to several antimicrobial agents), to aggravate the clinical course of diseases, to cause the appearance of incurable diseases and human death, is established. The need for strict antibiotic policy, enhanced measures, and unified coordinated efforts of governments and international organizations worldwide to control AMR is realized. Europe, where the global One Health movement also emerged, has contributed greatly to this understanding. The concept of One Health appeared first in 1950s documents and reports, related to veterinary medicine. Scientific publications including the term have been found since 1990 however since 2012, its use has increased nearly 80 times (4). One Health concept's crucial role in raising public awareness and engaging governments, politicians, NGOs, and all people in actions to limit AMR is undeniable (3).

In 2019 the WHO declared AMR one of the top ten global public health threats endangering humanity (14). The same year, the EU adopted Regulation (EU) 2019/6 on veterinary medicinal products. In 2022 Commission and EU countries also established antimicrobial resistance as one of the greatest risks to human health and as one of the top 3 health threats of top priority, alongside pathogens with high pandemic potential and CBRN (chemical, biological, radiological, and nuclear) threats. The data collected showed that AMR causes the death of around 700,000 people per year. It is estimated that in the absence of measures to control and limit AMR, by 2050 it would cause greater financial damage to healthcare and cause more human deaths than cancer (15).

2. Key legislative initiatives to address the problem of antimicrobial resistance in the European Union

The analysis of public sources shows a targeted EU policy towards AMR, reflected in successive legislative initiatives for over 20 years **(Figure 2).**

Directly linked to AMR is the restriction imposed by Regulation (EC) No 1831/2003 on the use of antibiotics in animal feed (other than coccidiostats and histomonostats) as feed additives with a grace period until the full implementation of the ban on 01.01.2006 **(Figure 2).** The justification for this action indicates the recognized need to review all rules on feed additives to take into account the need to ensure a higher level of protection of animal and human health, as well as the environment (16).

Figure 2. Significant stages of introduction of measures to control antimicrobial resistance in the European Union.

In the meantime, Directive 2003/99/EC was introduced establishing Community rules for the monitoring of infectious agents and the exchange of information on them. The monitoring measures include the collection of data on the extent of their levels of threat to public health. It covers zoonoses, infectious agents, the associated antimicrobial resistance; epidemiological investigation of food-borne outbreaks (Article 1, Para 2), indicator organisms and their capacity to create a reservoir of resistance genes, including pathogenic bacteria, and the exchange of information relating to the monitored sites (17). In 2013, the European Parliament argued in favour of the need to extend the legal framework of the network for the epidemiological surveillance and control of communicable diseases in the Community, with a focus on the importance of cross-border threats to health, antimicrobial resistance, and nosocomial infections (Decision No 1082/2013/EU, Article 2, Para 1a, ii) (18). Detailed rules are laid down for the monitoring and reporting of AMR, established for pathogens of infectious diseases of the digestive system: Salmonella spp., C. jejuni, C. coli, E. coli., E. faecalis and E. faecium (Decision No 2013/652/EU, Article 1, Para 1), as well as for Salmonella spp. and E. coli producing extended-spectrum β-lactamases (ESBL); AmpC β-lactamases (AmpC); carbapenemases (Decision No 2013/652/EU, Article 1, Para 2) (19).

In 2015 efforts to control AMR worldwide led to the adoption of the "Global Action Plan on Antimicrobial Resistance" – GAP by WHO, WOAH, and FAO (20). The plan was fully supported by the political leaders of the UN member states in 2016 when they committed to implementing GAP at global, regional, and national levels with the Declaration on AMR (21). In this regard, the EC introduced in 2018 and 2019 a single regulatory framework for antimicrobial use in veterinary medicine, reconsidered the treatment and prevention of animal health, and took enhanced measures to control AMR in the Community. Particularly important for the control of AMR in the EU is 2022, when the new rules on the use of veterinary medicinal products began to be fully implemented.

In 2018 the European Union took action to introduce uniform Community rules on the production, placing on the market, and use of medicated feed, which apply in full from 28 January 2022 (Regulation (EU) 2019/4, Article 26) (22). The rules are based on the principle that animal treatment with medicines (in particular antimicrobials) should not be used as a substitute for good husbandry, biosecurity, and management practices. They introduce rules for the supply of medicated feed only against a valid prescription issued by a veterinarian (or, exceptionally, by another qualified person) based on an examination or other appropriate assessment of the health status of the animals subject to treatment. In 2019 Regulation (EU) 2019/6 on veterinary medicinal products was adopted with a similar deadline for application – 28 January 2022 (Article 160) (11).

In 2024, a list of specific rules for the use of certain antimicrobials was established with Regulation (EU) 2024/1973, which is expected to be in force from 8 August 2026 (23). This is a list concerning derogations from Regulation (EU) 2019/6 for non-productive (Article 112) and productive (Article 113) animals (11)

3. National legislation regarding antimicrobial resistance

With the application of Regulation (EU) 2019/6 in the beginning of 2022, the EU Member States are obliged to synchronize their national legislation properly. In this regard, in March 2022, Bulgaria completely revised Chapter XI of the Veterinary Medical Activity Act - Veterinary Medicinal Products (24), adapting it to the new Community rules for the production, trade, and use of veterinary medicinal products. Uniform definitions are introduced for key terms related to AMR, such as antimicrobial agent, resistance, antibiotic, metaphylaxis, prophylaxis, etc. Special conditions of restrictions on the use of antimicrobial agents and antiparasitic veterinary medicinal products are defined in order to limit the risk of antimicrobial resistance development.

Thus, national legislation in veterinary medicinal products, including antimicrobials, fully reflects current international trends and European policies. The goals of WHO and WOAH to build habits and skills for the responsible use of antimicrobials in both animals and humans are reflected. The WHO definitions have been adopted, according to which the group of antimicrobials includes antibiotics, antivirals, antiprotozoals, antifungals, or "any substance with a direct effect on microorganisms, used to treat infections or infectious diseases" (11). The call for increased caution in the use of antiparasitic drugs is recognized, due to the ability of certain parasites to develop resistance to them (1, 2).

4. Groups of factors for antimicrobial resistance, indicated by WHO and WOAH, and the relationship of veterinary medicine to them

Metadata from publications by WHO and WOAH in the years preceding the preservation of antibiotics for use only in humans identify four main groups of factors for the development of AMR in microorganisms:

- unreasonable use of antimicrobials;
- violations of hygiene standards;
- non-compliance with current rules;
- environmental causes **(Figure 3).**

Participation of veterinary medicine activities and their contribution to the development of AMR has been recognized in each of them (1, 2, 4).

The global instruments for the control of AMR have immediate significance for veterinary medical activity, especially in controlling the health of productive animals. This imposes the need for a veterinary practice to rethink the methodology for selecting appropriate veterinary drugs for the treatment, prophylaxis, and animal health protection.

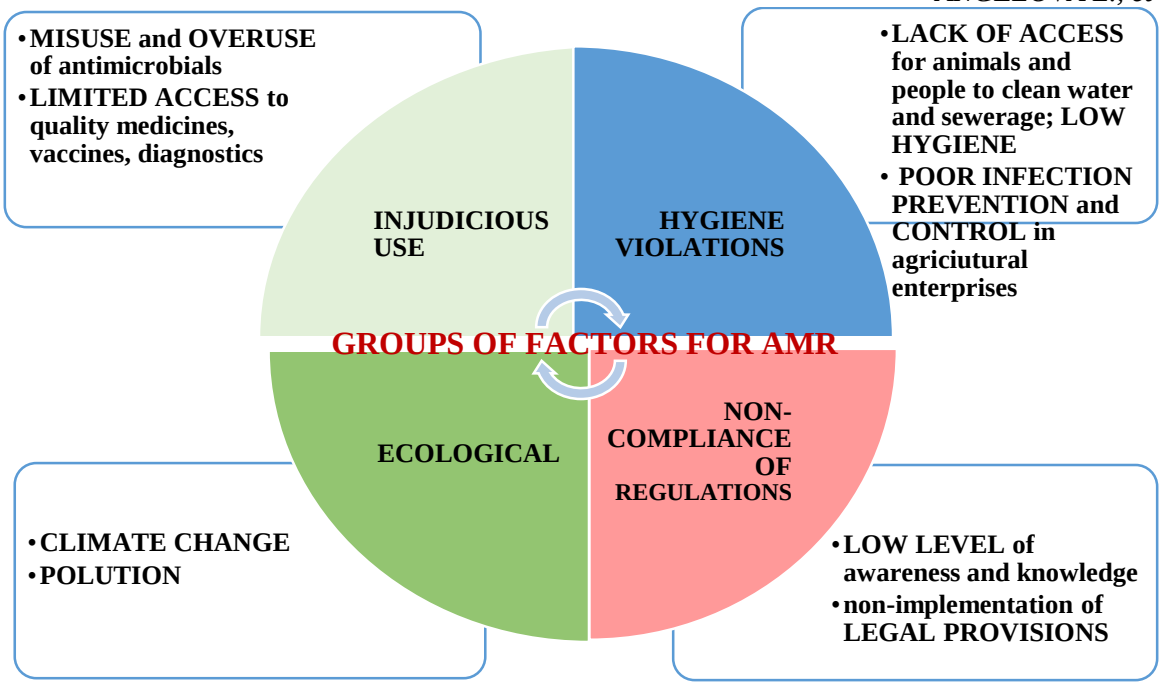

Figure 3. Groups of factors for the development of AMR in microorganisms.

5. Current global tools for AMR control relevant to veterinary medicine

5.1. World Health Organization List of Medically Important Antimicrobials (MIA List)

The list was first published in 2005 as the "Critically Important Antimicrobials List" (CIA). The CIA categorizes antimicrobial classes based on their importance to human medicine and the contribution of inhumane use to the risk of AMR transmission to humans (25). For the categorization in the MIA List, issued in 2024, WHO introduces additional assessment criteria, the most important of which is the risk of developing AMR to the respective antibiotic (1). The MIA List contains only antibiotics, and it is planned to be similarly supplemented for all other antimicrobials – other antibacterials, antivirals, antiprotozoals, and antifungals. The current scale of prioritizing antibiotics in the MIA List introduces (for the first time) some antibiotic classes and subclasses reserved only for humans. In summary, the list divides antibiotics into three main groups: approved for use only in humans; approved for use in both humans and animals; approved for use only in animals **(Figure 4).**

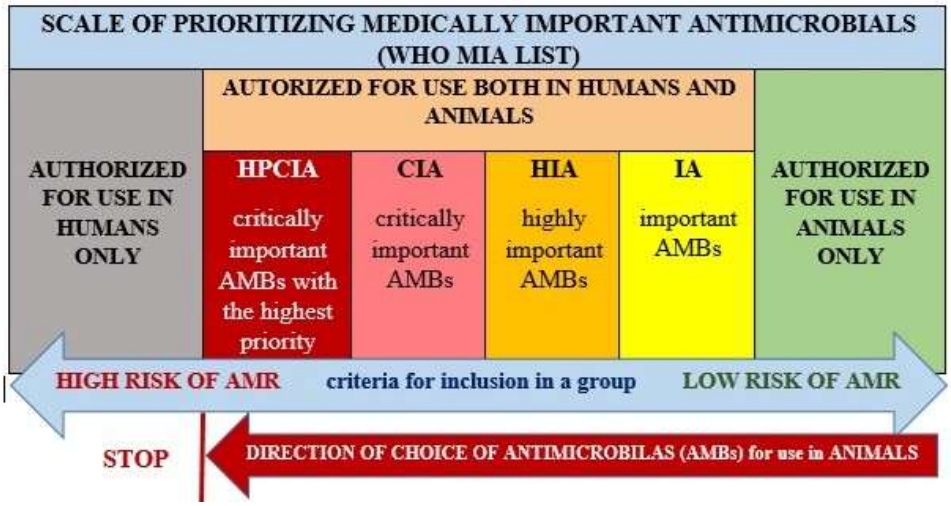

Figure 4. Groups of antimicrobial agents, according to the categorization of the WHO MIA List and recommended direction of choice of antibiotics for use in animals (adapted **Figure 1.** Prioritization of antimicrobial classes in the WHO MIA List, p.4) (1)

Antimicrobials (AMBs) approved for use in both animals and humans are divided into four sub-categories: critically important with the highest priority (HPCIA), critically important (CIA), highly important (HIA), and important (IA). Antimicrobial classes used in both humans and animals are the focus of the MIA List in order to reduce the risk of AMR to human health.

Particularly important for veterinary practice is the recommended approach when choosing a suitable antimicrobial for use in animals, which directs the search for an applicable product from left to right or from green to grey zone **(Figure 4).** It is necessary to search for an applicable product, firstly in a group authorized for use only in animals. This group includes antibiotics for which the development of AMR has not been registered. The search maintains the direction, following a review of the group authorized for use in both humans and animals. Here, a suitable product is first searched for in subgroup IA, then in HIA, CIA, and finally HPCIA.

The antibiotics in the leftmost group - approved for use only in humans **(Figure 4)** remain unavailable for animal use. The group is listed in **Table 1** of the MIA List and includes over 20 subclasses of antibiotics, such as: 3rd, 4th, 5th generation carbapenems; cephalosporins; drugs used only for the treatment of tuberculosis or other mycobacterial diseases, etc. Structured, as this, WHO MIA List aims to ensure that antimicrobial classes not approved for use in food-producing animals will not be used in animals in the future. Additionally, the measure is adopted that newly discovered classes of antibiotics for human treatment will be automatically added to this group, without the need to revise the list.

5.2. World Organization of Animal Health List of Antimicrobial Agents of Veterinary Importance

In 2024 the AAVI List of WOAH was updated and synchronized with the MIA List of WHO. AAVI List contains antimicrobial agents for use in productive animals - birds, bees, Equidae, rats, ruminants, pigs, camels, and fish. It does not include antimicrobial classes and subclasses used only in human medicine. The list does not include antimicrobial agents used only as growth promoters. This list currently focuses mainly on antibiotics with idea to be supplemented for other antimicrobial agents.

In practice, both the WHO and WOAH lists were prepared following the recommendations of expert seminars organized and held in 2003 (Oslo, Norway) and 2004 (Geneva, Switzerland) with the participation of representatives of FAO, WHO, and WOAH (1, 2). In connection to the commitments made in 2005, the Director General of WOAH surveyed in order to identify veterinary important antimicrobials, using a pre-prepared questionnaire. Two main criteria have been adopted for the preparation of the WOAH list (2):

1) identification of the antibiotic as important for veterinary medicine by over 50% of the respondents included in the survey;
2) availability of alternative methods of treatment of a serious disease in animals.

The WOAH list divides veterinary important antibiotics into three main groups, according to the extent to which they meet the two adopted categorization criteria **(Figure 5).**

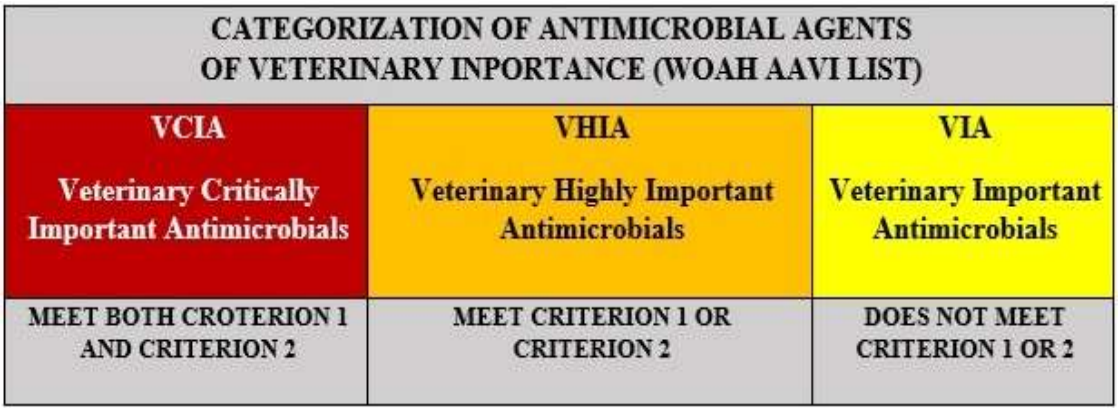

Figure 5. Groups of Veterinary Important Antimicrobials for use in productive animals on the WOAH list.

The first group, veterinary critically important antimicrobial agents (VCIA) includes antibiotics that meet both criteria simultaneously. They are important for the treatment of serious diseases in productive animals AND there are no alternatives for therapy.

The second group, highly important veterinary antimicrobial agents (VHIA) includes antibiotics that meet one of the two criteria. They are important for the treatment of serious diseases in productive animals OR there are no alternatives for therapy.

The third group, veterinary important antimicrobial agents (VIA) includes antimicrobials that are not included in any of the other two groups and are not an alternative for the treatment of serious diseases in productive animals.

5.3. Basic principles of the use of antimicrobials in productive animals, adopted by the EU with Regulation (EU) 2019/6

The basic principles for the use of antimicrobial agents in prophylaxis, mass treatment (metaphylaxis), and therapy of productive animals introduced by Regulation (EU) 2019/6, complementing and expanding the global tools for AMR control are significant for veterinary practice **(Figure 6).** The preamble to Regulation (EU) 2019/6 – recital 44, sets out the guiding rules for the antimicrobials use applicable to veterinary practice. These rules are further developed in the main text of the document, in particular in Article 107.

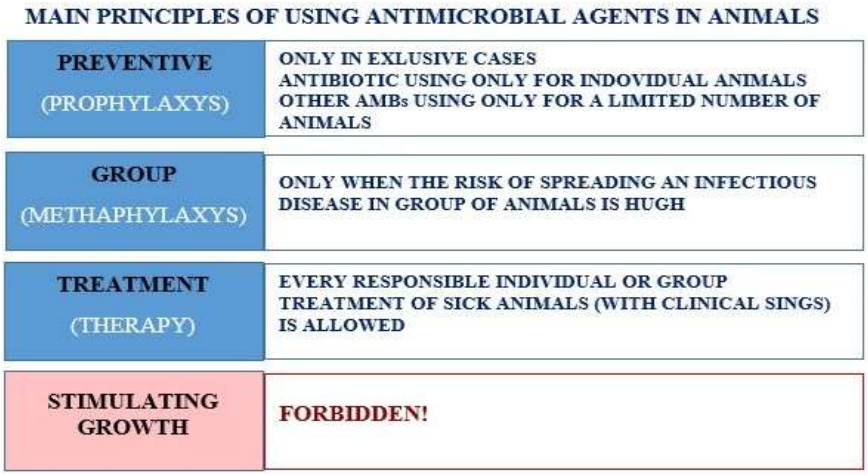

Figure 6. Basic principles for the use of antimicrobials in productive animals, according to Regulation (EU) 2019/6.

No restrictions are introduced solely for responsible individual or group therapy of animals with clinical signs of infectious disease, as long as the treatment follows the lists and recommendations of WHO and WOAH.

The use of antimicrobials to promote growth in productive animals remains prohibited.

Prophylactic treatment (administration of a medicinal product to an animal or group of animals before the appearance of clinical signs of a disease, to prevent the appearance of a disease or infection - Article 4, Para 16) is allowed only in exceptional cases when the risk of infection is very high or the consequences will be severe. Prophylactic use of antibiotics is permissible only for individual animals, and other antimicrobials may be applied only to a limited number of animals.

Metaphylaxis with antimicrobials is permissible only when the risk of spreading an infection or an infectious disease in a group of animals is high and when there are no suitable alternatives. Some other guiding principles for the use of antimicrobials for veterinary purposes, set out in Regulation (EU) 2019/6, are:

• AMBs shall be used under the marketing authorization while restricting the use of certain new or critically important antimicrobials for humans in the veterinary sector (preamble, recitals 41 and 42). Marketing authorization for an antimicrobial veterinary medicinal product shall be refused if the antimicrobial is reserved for human treatment.

• Veterinary prescriptions shall be based on strict rules for their issuance and on clinical examination or other proper assessment by a veterinarian (Article 105) except for a

prescription issued by a professional other than a veterinarian, but under identical rules.
• The prescription for an antimicrobial is valid for only 5 days after its issuance and should comply with an accepted model for its issuance (preamble, recital 83).
• The veterinarian must be able to justify the prescription of antimicrobial, especially in case of prescribing for preventive and group use (preamble, recitals 47 and 48).
• Obligation for Member States to collect data on the sale and use of antimicrobials is established (Section 2, Article 57).
• A veterinarian, under his direct responsibility and to avoid unacceptable suffering for the animal, may use medicinal products outside the terms of their marketing authorizations (Article 112) but under special conditions and special withdrawal periods referred to in Article 115. For this purpose, the methodology shown in **Figure 7** for selecting an appropriate AMB is applied.

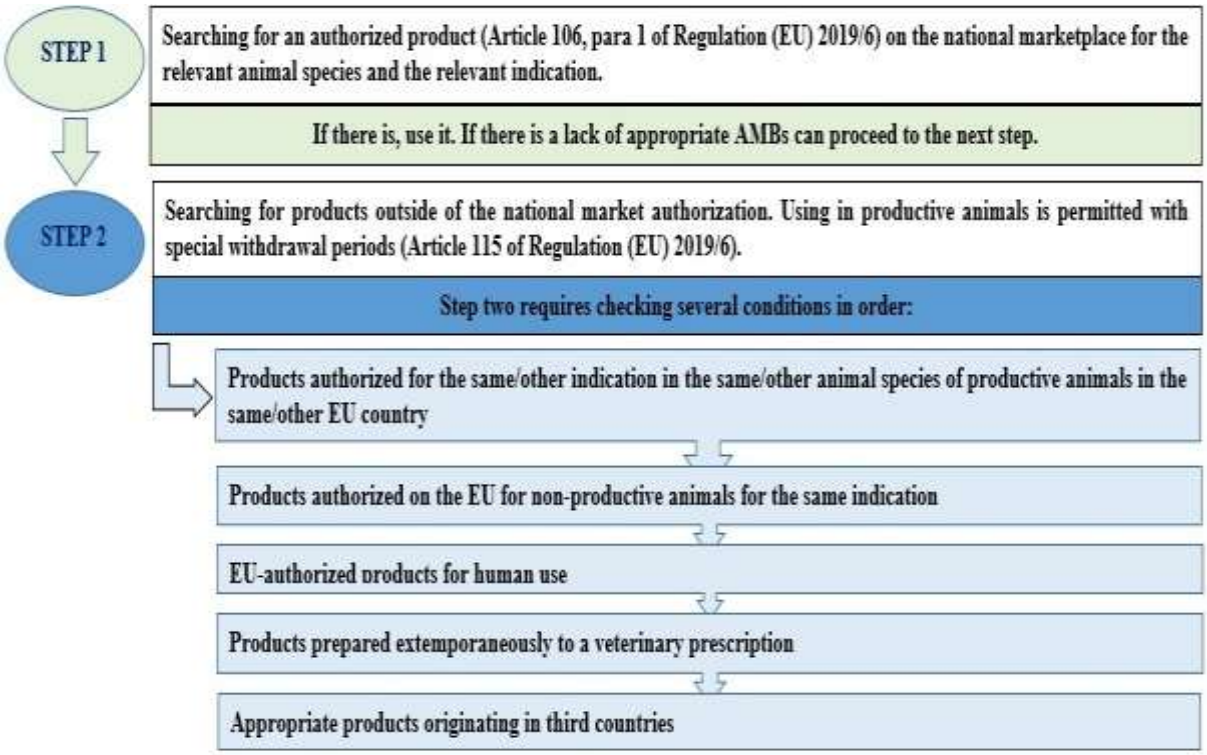

Figure 7. The principle of searching for a suitable antimicrobial agent for productive animals according to Regulation (EU) 2019/6.

When selecting an antimicrobial agent suitable for the productive animal, the veterinarian must first search among the AMBs authorized for marketing by Article 106, Para 1 on the national market. If a suitable agent is available, it shall be applied.

If no suitable AMB is available, it shall be applied among the AMBs authorized for marketing in another EU Member State for productive animals. Thirdly, an agent may be sought among the AMBs authorized for use on the national and/or European market for use in non-productive animals, but with the same indications. If no suitable antimicrobial is found, it is permissible for an animal to be treated with a product authorized for human use, as long as it does not fall into the group of AMBs reserved only for human use.
If all the alternatives listed above have been exhausted, extemporaneous preparations prepared according to a prescription prescribed by a registered veterinarian should be considered.

Finally, to avoid unnecessary pain and suffering of the animal and in the absence of an appropriate remedy from any of the listed groups, the veterinarian, on his responsibility, may proceed within the use of an AMB registered on the market in a third country.

In every case, if AMBs outside of their marketing authorization are applied to productive animals, it is necessary to comply with special withdrawal periods (by Article 115

of Regulation (EU) 2019/6). In short, for meat, milk, and eggs, the withdrawal period specified by the antimicrobial manufacturer in days, multiplied by a coefficient of 1.5 is applied. The same coefficient needs to be applied to the described withdrawal period for aquatic animals bred for the production of meat for human consumption, expressed in degree days. For bees, the withdrawal period is determined by the veterinarian based on an individual assessment carried out separately for each hive.

5.4. Databases for monitoring antimicrobial resistance

Monitoring of AMR in the EU is ensured by the currently operating national pharmacovigilance systems and the European Pharmacovigilance System. The information that the national competent authorities will process now covers not only monitoring of treatment response but also data on the quantities and reasons for AMR use (26, 27).

The World Organization for Animal Health has been collecting data on the quantities and reasons for antimicrobial use in animals since 2015. This information is a key asset for reducing the overuse and misuse of medicines and limiting the spread of antimicrobial resistance, now more widely available through ANIMUSE.

ANIMUSE is an interactive and automated online platform, a global database that allows countries to report, access, and analyze data on antimicrobials intended for use in animals. It also can be used to provide the aforementioned data to various stakeholders. It includes tools for easier reporting, error detection, and data visualization. (28)

CONCLUSION

The analysis carried out allows us to draw several conclusions:

1. The One Health concept is of key importance for the establishing of the rules for AMR control, the terminology of which originates from discussions on veterinary topics.
2. There are enhanced measures to control and limit antimicrobial resistance worldwide, established both in the recommendations of the leading international organizations WHO, WOAH, FAO, and UN, and included in legislative initiatives and regulatory documents of the European Union.
3. The danger of AMR as a potential cause of many human deaths is recognized at the highest level, with noticeably stricter rules being introduced after the adoption of the WHO Global Plan in 2015.
4. If the first necessary condition for controlling the AMR problem is the undertaking of joint and coordinated actions by all of humanity, then the main elements for this are already in place - unified rules and functioning information products for monitoring and using AMR.

It can be summarized that there are adequate and powerful tools for controlling and limiting AMR. However, significant financial resources will inevitably be needed to ensure the global actions taken in this direction. These funds could only be provided with the combined efforts and will of all governments and supra-governmental organizations. A positive factor concerning the control of AMR in the EU is the Community's firm policy on environmental protection, combating pollution, and the ambition for a carbon-neutral Europe by 2050.

At the same time, we could not help but worry that the unstable political situation in the world today is indeed a negative factor for the control of AMR. The allocation of huge financial resources for armaments and the prioritization of the EU's defense will inevitably weaken the Community's positions in the fight against antimicrobial resistance.

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