



# The Problem of Antibiotic Resistance Control: A Possible Alternative to Antimicrobials in Veterinary Medicine

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## Mini Review

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## Abstract

**Aim of Study:** The study included prospects for using autogenous immunobiological drugs as an alternative to antimicrobials.

**Materials and Methods:** For the analysis databases of WHO–World Health Organization, WOHA–World Organization for Animal Health, FAO–Food and Agricultural Organization, CDC–Center for Control and of disease prevention in the USA, ECDC–European Center for Disease Control and Prevention, EFSA–European Food Safety Authority, as well as informational Internet resources of scientific journals, normative legal acts of Ukraine.

**The Results:** According to the results of the conducted analysis, the global spread of microorganisms resistant to the action of antimicrobial drugs was established, which jeopardizes the possibility of effective treatment of infectious diseases. In Ukraine, as in other developed countries of the world, strict regulation of the circulation of antimicrobials has been adopted at the legislative level, which inevitably leads to the limitation of their use. International experience shows that restrictions on the use of antimicrobial agents should be compensated by measures aimed at increasing the level of biosafety. The use of autogenous immunobiological drugs for the specific prevention of infectious diseases of bacterial etiology can be a reasonable alternative to antibiotics in veterinary medicine.

**Conclusions:** The introduction of new rules for the circulation of veterinary antimicrobial drugs will significantly affect the level of use of antimicrobial drugs. A reasonable alternative to antimicrobial agents is the use of autogenous immunobiological agents.

**Keywords:** Resistance to Antimicrobial Agents; Microorganisms; Autogenous Vaccines

## Mini Review

The World Health Organization [1] states that the resistance of microorganisms to antimicrobial preparations is a serious threat that can significantly reduce the global level of health care and the achievement of sustainable development goals, increase the gap of inequality within and

between countries - that is, significantly affect for global well-being. Microorganisms that develop antimicrobial resistance are sometimes called “superbacteria”.

Antibiotic resistance is a phenomenon of microorganism resistance to the influence of one or more antibacterial drugs. Resistance of microorganisms to antibiotics can be natural or

acquired. Natural resistance is characterized by the absence in microorganisms of an enzyme or a structural molecule on which the antibiotic acts, or the inaccessibility of the enzyme system or structural molecule of microorganisms to the antibiotic as a result of the initially low permeability of the cell wall of the microorganism to the antibiotic or the inactivation of the antibiotic by specific enzymes of the microorganism. Acquired resistance is understood as the property of individual strains of bacteria to maintain viability at such concentrations of antibiotics that suppress the main part of the microbial population. The possibility of microorganisms acquiring resistance to the main groups of antibacterial drugs is related to the ability of bacteria to acquire new genetic information. A key factor in the spread of resistance is the ability of bacteria to transmit this information using plasmids, conjugation, and transduction [2].

According to the literature data [3-5] in the European Union alone, antibiotic-resistant microorganisms are responsible for 25,000 deaths per year. The authors calculated possible economic losses caused by the spread of antimicrobial-resistant microorganisms and substantiated economic losses at the level of 1.1-3.8% of global GDP by 2050, which could lead to 10 million deaths [6,7].

The purpose of this study is to analyse the danger of antimicrobial-resistant microorganisms' spread for public health and the potential of using autogenous immunobiological agents in veterinary medicine as an alternative to antibiotic therapy.

## Materials and Methods

The analysis of regulatory and legislative documents of Ukraine, the United Nations (namely: World Health Organization - WHO, World Organization for Animal Health - WOAH, Food and Agricultural Organization - FAO), Center for Disease Control and Prevention in USA - CDC, European Union (European Center for Disease Control and Prevention - EuroCDC, European Food Safety Authority - EFSA, European Committee for Antimicrobial Susceptibility Testing - EUCAST). In order to study the specified issues, the Internet information resources of the specified international organizations and special literature, etc., were developed.

## Research Results and their Discussion

The spread of resistance signs concerning antimicrobial preparations in a wide range of microorganisms (both among the populations of pathogenic bacteria and among commensals) is the global problem that nullifies scientific achievements in the field of the use of antibiotics as a means of treating infections in humans and animals, which poses a

threat not only to health and the quality of human life, but negatively affects the health, well-being and productivity of farming animals.

Authors confirmed that human infections caused by antimicrobial-resistant pathogens can be linked to the uncontrolled use of antimicrobials in production animals [8,9]. That is, the excessive and incorrect use of antibacterial agents in veterinary medicine is a legitimate concern of both specialists and society as a whole [10].

Under the auspices of the UN, namely WHO, WOAH and FAO, the Global Plan of Action against Antimicrobial Resistance (adopted by the World Health Assembly in May 2015) [11] was developed, the main goal of which is to maintain the effectiveness of antimicrobials. The main objectives of the plan includes (<https://www.who.int/publications/i/item/9789241509763>) the following: to improve awareness and understanding of antimicrobial resistance through effective communication, education and training; to strengthen the base of knowledge and evidence through observation and research; to reduce the incidence of infectious diseases by carrying out effective sanitary and hygienic measures; to optimize the use of antimicrobial agents to ensure the health of people and animals; to develop an economic rationale for sustainable investment, ..., and increase investment in the development of new drugs, diagnostic tools, vaccines, etc.

As a result of Global Action Plan introduction in the EU countries, the functioning of the monitoring system for the spread of antibiotic-resistant bacterial populations among farm animals and products was started. Given that the excessive use of antimicrobials contributes to the emergence of antibiotic-resistant clones of microorganisms, the use of antibiotics in animal husbandry is under scrutiny in EU countries [12,13].

The EFSA report for 2017-2018 revealed several positive trends regarding the spread of antibiotic resistance in indicator species of microorganisms, namely a decrease in the prevalence of *Escherichia coli* AmpC (producing extended-spectrum beta-lactamases), in some countries an increase of almost 25% in the circulation of susceptible to all E. coli antibiotics tested, no carbapenemase-positive *Escherichia* isolates from poultry were detected [14]. That is, the implemented measures showed a certain effectiveness.

The potential for the spread of "incurable" diseases of bacterial aetiology, which are caused by microorganisms resistant to antimicrobial drugs, nowadays has signs of a global threat and leads to a significant increase in health care costs. Although resistance to antimicrobial agents is a natural phenomenon, the negative trends in the development and

spread of this phenomenon are induced by anthropogenic factors. At the same time, it is necessary to take into account that the excessive use of antibacterial agents in veterinary medicine/animal husbandry is one of the conditions for the formation and further spread of resistant pathogens through food chains.

WHO identified the main modern anthropogenic factors contributing to the spread of the phenomenon of resistance to antibacterial agents among synanthropic microorganisms: irrational/excessive use of antimicrobial agents for humans, animals and plants; limited availability of vaccines, diagnostic tools and appropriate therapy; lack of access to clean water, proper level of sanitation and hygiene; inadequate levels of compliance with infection prevention and infection control requirements; transmission of resistant pathogens along the food chain; improper waste disposal systems.

Among the specified anthropogenic factors, the following are directly within the sphere of responsibility of the field of veterinary medicine: a) irrational and excessive use of antimicrobials for the needs of veterinary medicine/animal husbandry, which ensures the spread and transmission of resistant pathogens along the food chain; b) inadequate level of prevention of infections among productive animals due to violation of their welfare conditions; c) limited access to appropriate means of specific prevention and therapy due to the unavailability of proper timely diagnostics.

So, it turns out that the key factor in reducing the risks of the formation and spread of antibiotic-resistant zoonotic pathogens is the rational use of antimicrobial drugs in veterinary medicine, and in particular, not using them for the purpose of disease prevention.

For this purpose, in the field of veterinary medicine, as indicated by Magnusson U, et al. [15], it is necessary to ensure: availability of veterinary services for consumers/farmers; restrictions on the circulation of antibiotics in veterinary medicine and animal husbandry (prescription antibiotics); making it impossible to obtain additional profits from the sale or prescription of antibiotics; increasing the awareness of veterinarians regarding the benefits of preventive measures (animal welfare, effective bioprotection, specific prevention of infectious diseases/vaccination); awareness raising among the farmers about the importance of preventive measures over treatment in animal husbandry.

In Ukraine, strict regulations on the circulation of antimicrobials have been adopted at the legislative level and, accordingly, the problem of excessive and irrational use of antimicrobials in veterinary medicine/animal husbandry will be resolved in the near future, which will ensure a

reduction in the risks of the spread of antibiotic-resistant clones of bacteria through food chains.

Formally, an unsolved problem, among those mentioned, in terms of curbing the spread of resistance to antimicrobial substances, remains the inaccessibility to timely proper diagnosis of the causative agents of infectious diseases of animals (both instrumental and financial) and, accordingly, the unavailability/absence of means of specific prevention and therapy.

It should be noted that in Ukraine, according to the List of veterinary immunobiological preparations, 544 different commercial vaccines are registered. The producers of these vaccines are both foreign biotechnological corporations (mainly) and domestic producers. However, licensed veterinary vaccines do not fully ensure the prevention of infectious diseases of bacterial aetiology, which is indirectly evidenced by the high specific weight (36%) of antimicrobial agents among the medicinal chemotherapeutic agents registered in Ukraine - which amounts to about 1,300 drugs (according to the Register of the State Consumer Protection Service regarding veterinary drugs, feed additives, premixes and ready feeds).

International experience demonstrates the possibility to compensate for the absence or inadequate effectiveness of commercial vaccines, among other methods/means, due to the use of autogenous immunobiological preparations (vaccines, sera/globulins, etc.).

Autogenous immunobiological veterinary medicine is a means of specific prevention, made from an isolate of a microorganism isolated from a sick animal, and intended for this animal or for a herd of animals that came into contact with this sick animal within the same farm.

Autogenous vaccines are in demand by practicing veterinarians and animal owners and are quite widely used in the EU, USA, Canada, Australia. In these countries a significant segment of the veterinary market is occupied by autogenous vaccines and serums, which are an important and well-established tool of veterinary medicine to fill the gaps left by licensed vaccines and serums for all categories of animals. Such products' application prevents a number of infectious, including rare diseases, agricultural, zoo, exotic and companion animals, providing elements of their well-being.

It is important that unlike traditional vaccines, which are regulated to be used for the specific prevention of infectious diseases, the advantage of autogenous vaccines is the possibility of their use for the treatment of persistent

infections [2,16]. Autogenous vaccines and serums implementation within the limits of scientifically based preventive measures can be of key importance for reducing the level of use of antimicrobial substances and at the same time for breaking the food chain of the spread of resistant clones of microorganisms and antibiotic residues and, accordingly, protecting the environment [17].

It is necessary to note increased attention to autogenous vaccines in aquaculture. The rapid development of aquaculture, the global production of which has increased over the last 10 years by almost 37%, exceeding 90 million tons in 2021, the huge species diversity (over 500) of cultivated species [18], the intensification of production, which contributes to the increase in the frequency of outbreaks of infectious diseases and, accordingly, the growth of economic costs, taking into account the global crisis of antibiotic resistance and the limitation of the possibility of using antimicrobial agents in aquaculture as well, determined the question of the wider introduction of autogenous vaccines in the industry [19,20].

The authors believe that the relatively simple and significantly less expensive technology of safe and effective autogenous vaccines has significant untapped potential in aquaculture [21], and the joint efforts of regulatory authorities, producers and veterinary services on risk analysis, surveillance, compliance with the principles of biosecurity and identification of target pathogens according to recommendations [22], will contribute not only to sustainable production in the industry, but also to curbing the spread of antimicrobial resistance.

Autogenous vaccines are produced and used in the leading economically developed countries of the world. For example, the biotechnology company "Hygieia Biological Laboratories" (Woodland, California, USA) specializes, in particular, in the research, development and production of innovative autogenous veterinary vaccines, which are produced according to the rules of 9CFR. In particular, autogenous vaccines are produced for poultry, cattle, small ruminants, as well as for aquaculture. Including autogenous bacterial vaccines from *Streptococcus* (in particular *Streptococcus uberis*), *Salmonella*, *Mycoplasma*, *Haemophilus*, *Staphylococcus*, *Clostridium*, *Moraxella*, *Escherichia coli*, *Corynebacterium*, *Pasteurella* and *Erysipelothrix* antigens; autogenous viral vaccines are made from antigens of paramyxovirus, infectious bronchitis virus, avian influenza virus (low pathogenic), adenovirus, infectious bursal disease virus, and avian reovirus. "Ceva Biovac" - a division of the transnational corporation Ceva Santé Animale (5th place in the global market of animal health care in the world <https://www.ceva-biovac-campus.com/en>) - specializes in development, production and support during use autogenous vaccines.

The circulation of autogenous immunobiological agents in different countries has peculiarities: in the USA [23], the United Kingdom [24], Australia (APVMA, <https://apvma.gov.au/node/1108#Introduction>), France [25].

The circulation of autogenous vaccines and serums in the EU countries, is also not subject to agreed regulation; regulation varies from virtually no regulatory measures in some countries to quite complex and demanding regulation in others. That is, autogenous products were not covered by Directive 2001/82/EC, and therefore the production and use of autogenous products is regulated with certain features in each EU country. However, the introduction of standardized requirements and instructions regarding the rules for the production and use of autogenous agents is the basis for the development of harmonized international requirements at the national level regarding the safety and quality standards of such specific agents in European countries [26].

The interests of manufacturers of special (autogenous) vaccines and sera for animals in the EU are represented by the Association of European Manufacturers of Autogenous Vaccines and Sera (EMAV), which currently unites 9 manufacturers of autogenous vaccines and sera for animals from 11 EU member states and of the United Kingdom. It should be emphasized that in the EU, autogenous veterinary drugs are usually used in the absence of registered vaccines for farm animals, or when their preventive effectiveness is inadequate. Given that the use of this group of immunobiological agents carries certain risks, there is an objective need to harmonize the requirements for the circulation of autogenous vaccines in national legislation.

Regulation 2019/6 of the European Parliament and the Council of the EU of December 11, 2018 on veterinary medicinal products and repealing Directive 2001/82/EC entered into force in the countries of the European Union, which, in particular, outlined the general conditions for the standardization of the production and use of autogenous vaccines [27,28]. This document (paragraph 70) states that good manufacturing practice (GMP) must be followed for the manufacture of autogenous immunobiological agents, but that GMP guidelines should be developed specifically for these products, as such products are manufactured in original ways that are different from the products manufactured by industrial/traditional technologies [29-33]. At this time, on the proposal of the Association of European Manufacturers of Autogenous Vaccines and Serums (EMAV), common positions are agreed on the future special GMP guidelines for autogenous vaccines. In Ukraine, the production of autogenous vaccines to order is offered by the BioTestLab company (<https://www.biotechlab.ua/ua/products/vaccines-autologous/>) as well as, traditionally, by research institutes of the National Academy of Agrarian Sciences.



In our country, the current Law of Ukraine “On Veterinary Medicine” declares the possibility of production and use of autogenous vaccines, but at this time the requirements for production have not yet been developed [34]. The law provides that “...the use of autogenous immunobiological veterinary medicinal products is allowed only with a veterinary prescription in exceptional cases, if there are no registered immunobiological veterinary medicinal products...”. Article 3 of the “Law...” states that “...Production and circulation of autogenous immunobiological veterinary medicinal products, ..., are regulated in accordance with the requirements approved by the central executive body, which ensures the formation and implementation of state policy in the field of veterinary medicine.” That is, the development of the specified regulatory documents is entrusted to specialists of the State Production and Consumer Service, subordinate research institutions and stakeholders in the form of public associations. Taking into account the international experience, we believe that it is time to develop and introduce a national guideline for GMP of autogenous immunobiological medicinal products in Ukraine [35].

What is the effectiveness of autogenous vaccines, is there a prospect of their use as an alternative to antibiotics? The use of an autogenous vaccine in commercial farms made it possible to reduce the incidence of clinical mastitis in cows by 60.0%, the manifestations of subclinical mastitis decreased by 27.8%, the level of manifestations of postpartum endometritis decreased by 37.5%, the level of disorders of the digestive tract in new-born calves - decreased by 31.3%, respectively. That is, the use of autogenous immunobiological drugs can be considered a justified measure within the framework of the implementation of a systemic fight against the spread of antibiotic resistance among populations of zoonotic pathogenic microorganisms.

## Conclusion

The introduction of new rules regarding the circulation of veterinary antimicrobials and medicated feeds will significantly affect the level of use of antimicrobials in Ukraine in the near future. A reasonable alternative to antimicrobial agents is the use of autogenous immunobiological agents.

### • Conflict of Interests

All authors: Vygovska L., Ushkalov V., Chechet, O., Gerilovych A., Romanko M-declare no conflict of interest regarding the materials presented in this article.

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### • Statement of Ethical Approval

Hereby, I consciously assure V. O. Ushkalov that the following has been completed for the manuscript «The problem of antibiotic resistance control: a possible alternative to antimicrobials in veterinary medicine»:

- This material is the authors' own original work that has not been previously published elsewhere.
- The document is not currently under consideration for publication elsewhere.
- The article reflects the authors' own research.
- All used sources are properly disclosed (correct citation).

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