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Spread of antibiotic-resistant microorganisms and mechanisms of their transmission from animal to human

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Abstract. Antimicrobials are essential for the treatment and prevention of infectious diseases in both humans and animals. However, the emergence and spread of antibiotic-resistant microorganisms has become a global problem of the World Health Organisation. Transmission of antibiotic-resistant macroorganisms from animals to humans is conducted directly or indirectly through the environment. This spread affects the epidemiology of resistant bacterial infections in humans. Thus, the purpose of the study was to establish and analyse the methods of distribution and mechanisms of transmission of antimicrobial-resistant microorganisms from animal to human, analyse the experience of different countries in solving problems of antibiotic resistance. Through methods of analysis and systematisation of scientific research of researchers from different countries of the world, it was established that antimicrobial agents have been used in agriculture as feed additives and maintain the health and productivity of animals since the middle of the 20^{th} century. Animal products at all stages of food processing also often contain large amounts of antibiotic-resistant microorganisms. A substantial relationship was established between drugs used in humane and veterinary medicine. It is noted that difficult socio-economic conditions, limited laboratory facilities, and lack of regulatory authorities in developing countries also create favourable conditions for the spread of antibiotic-resistant pathogens. As a result, the treatment of many infectious diseases of people is substantially complicated or becomes impossible. The application of antibiotics should be accompanied by constant and enhanced monitoring of their spread in the animal–human–environment chain, a rational prescription in humane, veterinary medicine, and the food industry to minimise the risks of unjustified use of them

Keywords: bacteria; antimicrobials; antibiotic resistance; medicine; animal husbandry; mobile genetic elements; multi-resistance

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INTRODUCTION

Although antimicrobial agents have the ability to inhibit the growth or kill microorganisms, their excessive use has led to a substantial increase in the rate of elimination and release into the environment, and therefore an increase in the resistance of bacterial strains to drugs. In recent years, substantial progress has been made in the field of medicine and pharmacy in the development of a wide range of antibiotics, but the issue of antibiotic resistance is still not fully understood, since antimicrobials are widely used not only for the treatment of bacterial infections in humans and animals but also for non-medical purposes.

Antibiotics, or antibacterial agents, are drugs that can kill or inhibit the growth of bacteria that cause infections in humans, animals, and plants [1]. According to T.T.H. Van *et al.* [2], a substantial advance in medical science is the discovery of antimicrobials since the mid-20th century and the creation of more than 100 such compounds over the past 60 years. As S. Reardon [3] claims, the use of antibiotics in animal husbandry, despite various measures to limit their use, will increase between 2020 and 2030.

Antibiotic resistance is the ability of microorganisms to survive and multiply not only within a single species but also within bacterial genera, despite the presence of antibiotics [1, 4]. As C. Morel [1] notes, bacteria adapt quickly to environmental changes. The emergence of pathogen resistance to antibiotics is an adaptive property. Some bacteria have a natural resistance to certain antibiotics. However, when bacteria that are normally antibiotic-sensitive become resistant due to genetic changes, i.e. acquired resistance is formed, this becomes a serious problem for both public health and animal health. In a study by N.A. Lerminiaux & A.D.S. Cameron [4] it was indicated that horizontal gene transfer contributes to the rapid spread of resistance. According to the authors, plasmid conjugation, bacteriophage transduction, and natural transformation of extracellular deoxyribonucleic acid (DNA) allow genetic material to migrate between bacterial strains and species. Thus, horizontal gene transfer is important in the development of infectious diseases. In addition, the antibiotic resistance gene can be a causative agent of infections, transmitting resistance to several unrelated pathogenic microorganisms.

After a detailed examination of the molecular mechanisms responsible for both innate and acquired antimicrobial resistance, E. Palma *et al.* [5] reviewed the contribution of veterinary medicine to the overall problem of antibiotic resistance formation. Researchers describe the main sources of antibiotic reactions available in veterinary medicine, drawing attention to the indissoluble crosstalk that exists between different ecosystems and sectors, and future prospects for preventing the spread and/or development of bacterial resistance to antibiotics.

According to many researchers, resistant bacteria reduce the effectiveness of antibiotics in the treatment of animals and humans. Infectious diseases caused by such pathogens are difficult, and sometimes even impossible to treat. In such a situation, recovery often depends only on the state of the body's immune system. In addition, this trend in animal husbandry leads to substantial economic costs [1, 6]. I.I. Fohel *et al.* [7] emphasise that resistant microorganisms pose a danger not only to adults but also to children. This trend requires a special approach to prescribing antibiotics to children. Treatment of childhood infections caused by antibiotic-resistant microorganisms is more difficult to treat and requires special methods and approaches, so the choice of antibiotic drugs is limited.

Ukrainian researchers S. Tymoshchuk & L. Symochko [8] note that resistant pathogenic and opportunistic bacteria that can directly or indirectly infect humans can transfer the determinants of resistance to the human body in various ways, namely: directly through contact with animals and indirectly through the food chain, water, air, and soil fertilised with manure, or wastewater. Ultimately, in the soil (water)–microorganisms–plants chain, the soil (water) microbiota is an inseparable component. In particular, researchers in the microbiome of the water ecosystem of the Uzhgorod district detected, even after treatment in sewage treatment plants, antibiotic-resistant *Klebsiella pneumoniae* and *Enterococcus faecium*.

N.O. Vrynchanu & T.A. Bukhtiarova [9] note that the pronounced antimicrobial activity of agents of various pharmacological groups contributes to the activation of antibiotic resistance mechanisms in bacteria, which is the basis for resolving the question of the feasibility of their further use in clinical practice. L. Serwecińska [10] states that the antibiotic resistance of microorganisms has reached a critical level on a global scale. Therefore, the examination of antibiotic resistance issues is an important and urgent problem in relation to preserving human and animal health, which is caused by the transfer of bacterial resistance from animals to humans through the animal–human–environment relationship.

The purpose of the study was to summarise data on the formation of antibiotic resistance in bacteria and how they are transmitted between humans and animals, and potential solutions to this global problem.

SPREAD OF MICROORGANISMS IN THE ENVIRONMENT

There are many relationships between animals, humans, and the environment that contribute to the migration of not only bacteria, but also their mobile genetic elements. In the context of investigating microbial resistance to antibiotics, this interaction between ecological niches is particularly important [11, 12].

Since the middle of the 20th century, antimicrobial agents have been massively used for the treatment and Prevention of animal diseases. This contributed to an increase in meat production and a reduction in its prime cost, which in turn ensured an intensive increase in livestock production from year to year. However, the massive and sometimes uncontrolled use of antibiotics in animal husbandry has become one of the reasons for the ineffective treatment of infectious diseases in humans [11, 13]. Given the constant emergence of new antimicrobial-resistant pathogenic bacteria in animals, researchers point to the need to strengthen monitoring of the spread of resistant strains of microorganisms in the animal–human–environment chain [5, 14, 15].

Specialists in the medical industry are mainly engaged in investigating the mechanisms of the development of resistance of pathogenic strains of microorganisms to antibiotics in humans. However, in all living habitats, the total number of bacterial species is extremely large. As noted in the study by G. Chala *et al.* [16] and V. Oswaldi *et al.* [17], most of the bacteria that live in the human body are part of its normal microbiome. Only a small part of them, for example, *Mycobacterium tuberculosis* or *Staphylococcus pneumoniae*, *Salmonella typhi*, are obligate human pathogens. The vast majority of microorganisms are conditionally pathogenic. They lead to the development of opportunistic infections in humans only under certain circumstances, such as: *Listeria* spp. and *Campylobacter* spp. they enter the human body with food or water and can cause diseases mainly in children, pregnant women, the elderly, or people with weakened immune systems.

According to researchers, some types of microbes accidentally enter the human body and then are eliminated. Such microorganisms, as a rule, do not lead to the emergence and development of the disease. However, many pathogenic bacterial species and assumably many commensals are found not only in humans but also in the body of livestock and wild animals, causing anthoropozoonotic infections. Thus, representatives of the Enterobacteriaceae family: *Escherichia coli*, *Klebsiella* spp., and *Salmonella* spp. (which often cause urinary tract and circulatory system infections in humans) are established in the intestines and in animal meat [18-20].

After performing a sensitivity analysis of *Escherichia coli* to antibiotics in poultry excrement in Sierra Leone, A.H.D. Mansaray *et al.* [21] established that the prevalence of multi-resistant strains among these bacteria was 95.6%. Therewith, a high index of multiple antibiotic resistance was observed – from 0.5-0.7, with an optimal <0.2. The authors note that the data obtained indicate a high pre-effect of antibiotics in these birds and such high levels of resistance to *Escherichia coli* isolated from poultry excrement can pose a serious threat to human health.

C. Chen & F. Wu [19] conducted a systematic review and meta-analysis of the characteristics of colonisation and infection of animals, livestock workers, and veterinarians with methicillin-resistant *Staphylococcus aureus* (LA-MRSA). They confirm that *Staphylococcus aureus* is the most common cause of skin infections and the second most common cause of blood infections in humans, and is also established on the skin and in animal meat. These microorganisms easily migrate between pets and humans and spread in public places and healthcare facilities. They are responsible for the spread of antibiotic-resistant infections, leading to deaths worldwide.

H.C. Lepper *et al.* [22] note that micro-organisms are repositories of genetic information that encodes bacterial resistance to antibiotics, spreading not only within one species but often between others, including intergenerational transmission. Authors argue that the environmental potential for spreading antibiotic-resistant microorganisms has recently been increasingly recognised, for example, as a result of their abundance in wastewater discharged into natural reservoirs and soils. Researchers developed a compartment model of resistance transmission between bacteria, humans, animals, and the environment to examine the importance of the environment for the long-term dynamics of the spread of resistant bacteria and the cause of infections in humans, which is shown in Figure 1.

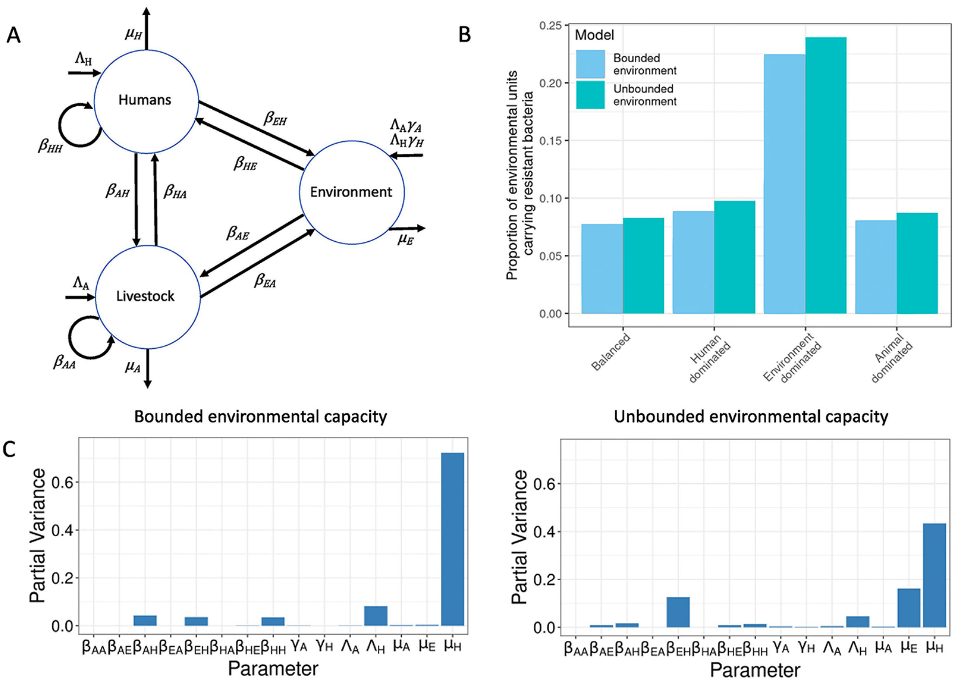

Figure 1. Model of environmental impact on human resistance levels and the role of measures aimed at reducing antibiotic consumption by animals

Notes: A – flowchart indicating the model structure. B – RE value in all transmission methods and both model structures. C – Fourier amplitude sensitivity test (FAST), which indicates how much the change in RH is explained by each parameter of the model. On the left is the FAST for the model version where RE is limited to 1. On the right is the FAST for the version of the model in which RE was unlimited

Source: [22]

According to J. Kim & J. Ahn [11], antibiotic-resistant bacteria can get directly or indirectly from animals to humans through contaminated food, water, or organic waste used as fertiliser. In addition, waste from hospitals, farms, and homes containing antibiotic-resistant microbiota is often disposed of openly without proper monitoring and treatment, leading to the spread of antibiotic resistance genes in the environment. Researchers note that animal food products at all stages of food processing contain a large number of antibiotic-resistant microorganisms.

APPLICATION OF ANTIMICROBIAL AGENTS IN ANIMAL HUSBANDRY AND FISHING INDUSTRY

According to the results of research by a number of researchers, antimicrobial agents are widely used to treat animals. Most often, antibiotics are used to treat respiratory and intestinal infections during the period of intensive growth of broiler chickens, pigs, and calves. The issue of using antibiotics in dairy cattle breeding for the treatment of sick dairy cows is relevant. A substantial part of antibiotics is used to prevent diseases of animals that come into contact with sick individuals [1, 14]. This practice provides certain economic benefits to animal producers and consumers in general [2].

In the paper by F. Ma *et al.* [14], it is reported that in the United States of America and other developed countries of the world, antimicrobials, as growth stimulants for animals, have been intensively used since the middle 20th century. Thus, in the 50s, researchers first reported that the addition of antibiotics (sulfasuxidin, streptotricin, and streptomycin) to the feed for chickens and pigs had a positive effect on increasing their productivity. Since then, the use of antibiotics has become an integral part of modern animal husbandry.

A group of researchers note that to stimulate the growth of animals, antimicrobial agents are added to the feed in doses ranging from subtherapeutic to therapeutic concentrations. Thus, an increase in meat production is ensured and it is possible to prevent the occurrence of local outbreaks of infectious diseases and their spread on a global scale [12]. However, according to F. Ma *et al.* [14], in many countries in Europe and the USA, the amount of antibiotics added to animal feed substantially exceeds the need for their use. In addition, a large number of antimicrobials are common in the treatment of humans and animals, including the latest classes of drugs such as third- and fourth-generation cephalosporins, fluoroquinolones, glycopeptides, and streptogramins.

Along with the positive effect of using antibiotics, in the early 50s of the 20th century, there were reports of their negative impact. Thus, in 1951, after streptomycin was used in turkey feed, the first cases of resistance of the bird body to this antibiotic were registered. Over time, the resistance of domestic animals to tetracycline, sulfonamides, penicillin, and other beta-lactams increased [23-25]. Based on the study, researchers established that with the daily care of infected animals, farm workers, slaughterhouses, and veterinary doctors are easily infected with antibiotic-resistant bacteria. They reported that back in 1957, researchers established that a week after feeding chickens a dietary supplement with tetracycline, microorganisms resistant to this drug were established in the gut microbiome of birds, and five to six months after the experiment was completed, more than 80% of bacteria resistant to this drug were established in 31.3% of their faecal samples. Other researchers selected 36 strains between 2004 and 2007 *E. Soli,* resistant to apramycin. They were randomly selected from biological material from pigs, chickens, and humans on six farms in areas of northeastern China. As a result, apramycin resistance genes of aminoglycoside acetyltransferase (AAC) (3)-IV type from humans and animals were established to have 99.3% homology [14].

The production of antibiotics continues to increase, and their total annual consumption in the world has increased from 100 000 to 200 000 tonnes [26]. In the European Union countries, the mass of antimicrobials used in animal husbandry in 2018 was 8 927 tonnes. In the United States, subtherapeutic doses of antimicrobials added to animal food in the same year reached approximately 14 600 tonnes. China, the world's largest producer and consumer of antibiotics, used 29 774.09 tonnes of antimicrobial agents for livestock needs in 2018, and 53.20% of total consumption was used to stimulate animal growth [14].

According to the WHO (World Health Organisation), as of 2019, the average annual global use of antimicrobials per volume of animal products is estimated at 45 mg/kg for cattle, 148 mg/kg for chickens, and 172 mg/kg for pigs. Based on this baseline, global antimicrobial consumption is projected to increase by 67% by 2030 [27].

R. Mulchandani *et al.* [28] analysed the use of antimicrobials in animal husbandry in 42 countries in different parts of the world in 2020. Researchers note that this year the use of antimicrobials worldwide was estimated at 99 502 tonnes. Antimicrobial use prevailed in Asia (67%), while it was at <1% in Africa. According to researchers' forecasts, the use of antibiotics will increase by 8.0% (to 107 472 tonnes) by 2030 [28]. The results of the study and forecasting of results are presented graphically (Fig. 2).

Along with the development of animal husbandry, the fishing industry is developing intensively. According to the Food and Agriculture Organisation of the United Nations (FAO) [29], global fish production in 2018 reached approximately 179 million tonnes. Of the total volume, 156 million tonnes were used for human consumption, which is equivalent to the estimated annual supply of 20.5 kg per capita. The remaining 22 million tonnes were intended for non-food purposes, and mainly for the production of fish meal and fish oil. Aquaculture support accounts for 46 per cent of total production and 52 per cent of fish for human consumption. And in 2020, as the FAO notes, the total production of fish and aquaculture products reached a record 214 million tonnes, including 178 million tonnes of aquatic animals and 36 million tonnes of algae. These results were achieved mainly due to the growth of aquaculture, especially in Asia. The amount intended for human consumption (excluding algae) was 20.2 kg per capita, more than double the average of 9.9 kg per capita in the 1960s [30].

However, as noted by F. Ma *et al.* [14], increased fish population density, poor sanitation, and the inability to separate healthy fish from infected ones contribute to the rapid spread of infections. The high population density in coastal areas and environmental pollution are well-known immunosuppressive factors that contribute to the high vulnerability of fish to protozoal infectious agents. Thus, at the beginning of the 21st century in China, more than 200 bacterial infections were detected among commercial fish species, which accounted for about 15-20% of losses from their total annual catch.

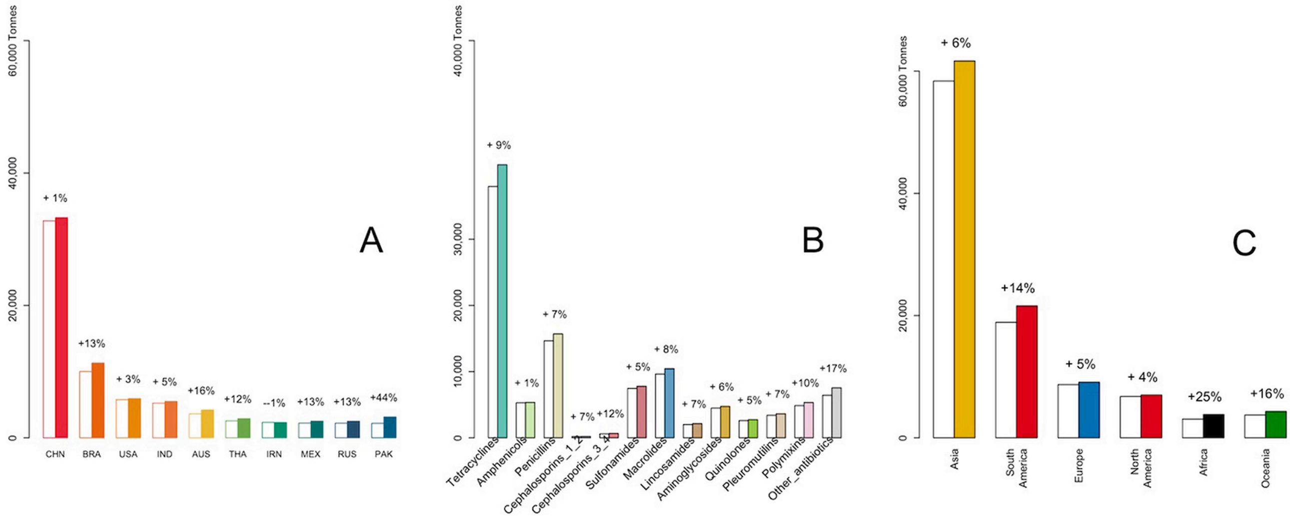

Figure 2. Antimicrobial consumption in Veterinary Medicine in 2020 (white columns) and their projected consumption in 2030 (colored columns)

Notes: A – by country (Top 10 consumers (CHN, China; BRA, Brazil; IND, India; USA, USA; Aus, Australia; IRN, Iran; Tha, Thailand; PAK, Pakistan; JPN, Japan; MEX, Mexico.)). B – by antimicrobial class, C – by continent

Source: [28]

Due to the erroneous belief that the use of a large number of antimicrobials in fish farming will ensure a large industrial production of fish products, various types of antibiotics continue to be widely used. In particular, in the paper by S. Chowdhury *et al.* [31], it is indicated that fish and other aquaculture products often contain various antimicrobial substances in concentrations that exceed the permissible norm. AMong these, oxytetracycline, ciprofloxacin, and amoxicillin are the most common. Researchers report that most antibiotics are used for both therapeutic and preventive purposes.

Residues of veterinary antimicrobials can be established in the waste products of fattening livestock, pigs, and chickens. Their high concentration in the urine and faeces of animals is very dangerous, because, in the urine and faeces, antimicrobial residues enter the water systems, pollute them, and enter the body of fish. The high concentration of antibiotics in animal droppings is also a cause for concern due to the fact that it is often used to feed water bodies to stimulate fish growth. Thus, the consumption of fish containing antibiotics becomes risky for human health [14].

WAYS TO TRANSMIT ANTIBIOTIC-RESISTANT MICROORGANISMS FROM ANIMALS TO HUMANS

There is a substantial relationship between drugs that are necessary for human use and those that are currently used in animal husbandry. World Health Organization (WHO) [27] classifies fluoroquinolones, third- and fourth-generation cephalosporins, macrolides, glycopeptides, and polymyxins as "top priority critical" antibiotics for human treatment. C. Morel [1] noted in a paper that macrolides and fluoroquinolones are most commonly used to treat diseases of the human body, and tetracyclines and sulfonamides are the most common drugs in animal husbandry. The use of antibiotics in animal husbandry continues to stimulate animal growth and critical top-priority antimicrobials needed for human treatment. According to the results of the researcher's study, Table 1 shows a list of classes of antimicrobial agents licensed for veterinary use in the European Union countries and their main indications for use.

Table 1. List of the main classes of antimicrobial agents licensed for use in veterinary medicine in the European Union

Class of antibiotics	Veterinary use (types)	Main indications	Risk to human health	Against what microorganisms are used	Probability of transmission of antibiotic-resistant microorganisms
Aminoglycosides (gentamicin, neomycin, etc.)	cattle, sheep, goats, horses, dogs, and cats	• Septicemia • Digestive, respiratory, and urinary infections	Requires additional research	Enterobacteriaceae *Enterococcus* spp.	High
Cephalosporins (3rd and 4th generation)	Cattle, pigs, horses, dogs and cats	• Septicemia • Respiratory infections • Mastitis	High	Enterobacteriaceae	High

Table 1. Continued

Class of antibiotics	Veterinary use (types)	Main indications	Risk to human health	Against what microorganisms are used	Probability of transmission of antibiotic-resistant microorganisms
Fluoroquinolones	Cattle, pigs, chickens, turkeys, rabbits, dogs, and cats	• Septicemia • Infections (e.g. colibacteriosis)	High	*Campylobacter* spp. Enterobacteriaceae	High
Macrolides (including ketolides)	Cattle, sheep, pigs, and poultry	• Infections caused by mycoplasmas (pigs and poultry) • Hemorrhagic digestive disease and proliferative enteropathies associated with *Lawsonia intracellularis* (pigs) • Respiratory infections (cattle and sheep) • Liver abscess (cattle)	Low and short-lived	*Campylobacter* spp. *Salmonella* spp.	High
Penicillins (naturally sensitive to lactamases)	Cattle, sheep, poultry, turkeys, horses, dogs, and cats	• Septicemia • Respiratory infections • Mastitis	Low or short-lived	Non-specific	High
Penicillins (broad spectrum beta-lactam sensitivity) Aminopenicillin	Cattle, sheep, pigs, poultry and dogs	• Pasteurellosis and colibacteriosis (poultry) • Streptococcal infections (pigs) • Respiratory infections (cattle and pigs)	Further risk analysis is needed	Enterobacteriaceae *Enterococcus* spp.	High
Penicillins (narrow spectrum of beta-lactam resistance)	Cattle and sheep	• Metrit • Mastitis	Low or short-lived	Non-specific	High
Penicillins (protected by broad-spectrum beta-lactamase) – co-amoxiclav	Cattle, pigs, dogs, and cats	• Respiratory infections • Metrit • Mastitis • Colibacteriosis (cattle and pigs)	Further risk analysis is needed	Enterobacteriaceae *Enterococcus* spp.	High
Polymyxins (including colistin or polymyxin E)	Cattle, sheep, pigs, and poultry	• Septicemia • Colibacteriosis • Urinary infections • Infections caused by Gram-negative bacteria	Currently evaluated	Enterobacteriaceae	Low
Rifamycin (rifampicin)	Cattle	• Metrit • Mastitis	Low or short-lived	Non-specific	High
Tetracyclines	Cattle, sheep, goats, pigs, horses, and poultry	• Respiratory diseases • Bacterial enteritis • Urinary system infections • Metrit • Mastitis • Chlamydia • Actinomycosis • Escherichiosis • Resistant strain *Staphylococcus aureus*	Low or short-lived	*Drucella* spp.	High

Source: adapted according to [1]

According to researchers, residues of veterinary antimicrobials such as ciprofloxacin, enrofloxacin, oxytetracycline, and chlortetracycline can be detected in the waste products of fattening livestock, pigs, and chickens [14, 32].

Based on the analysis, a schematic representation of possible methods of spreading antibiotics is proposed, which is shown in Figure 3. Excessive and irrational use of various antimicrobials has led to a rapid increase in bacterial resistance to several types of antibiotics simultaneously, that is, to the formation of multi-resistance. A bacterial cell can become resistant to multiple, unrelated groups of antimicrobials, even with a single mutation. The main mechanisms of bacterial resistance formation are based on a decrease in the permeability of the bacterial cell membrane to antibiotic molecules and the absence of specific molecules or inactivation of antimicrobial compounds. In addition, the genetically determined resistance created by these bacteria is effectively transmitted during clonal reproduction and/or to other bacteria through mobile genetic elements such as plasmids, transposons, and integrons [5, 11, 33]. C. Morel [1] and E. Palma *et al.* [5] focus on the fact that multi-resistance of microorganisms leads to a violation of the health status of animals and humans and reduces the effectiveness of treatment of patients according to the protocol.

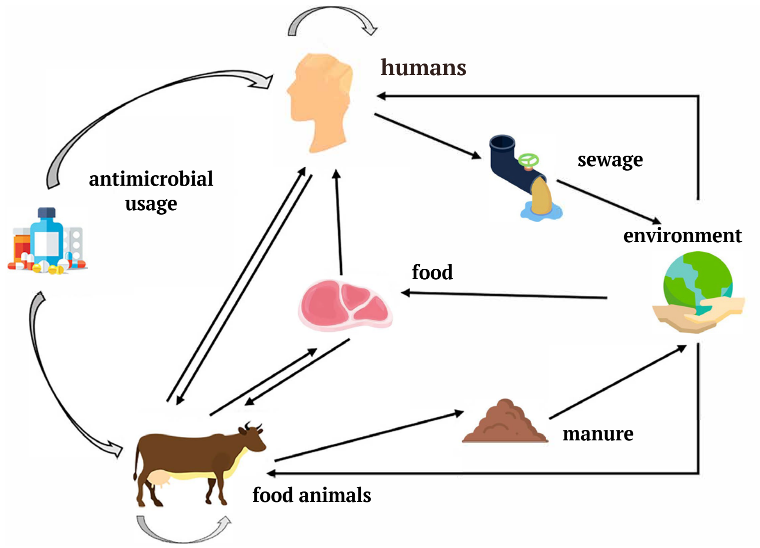

Figure 3. Potential pathways of antibiotic distribution and transmission between animals, the environment, and humans
Source: compiled by the authors

Many researchers have concluded that antibiotic resistance in the modern world is becoming one of the main problems in the field of health, animal husbandry, and food industry [32, 34]. According to the study by X.C. Monger *et al*. [32], in 2019, there were almost 5 million deaths worldwide related to antibiotic resistance of pathogenic bacteria. The authors identified six leading monoresistant and polyresistant pathogens (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii,* and *Pseudomonas aeruginosa*), which caused fatal consequences.

Researchers often attribute the increase in the prevalence of antibiotic-resistant microorganisms and, accordingly, their resistance genes to selective pressure on the use of antibiotics in both clinical and agricultural settings. Independent use of medications also strongly affects their distribution. People are at risk of contact with new resistant infectious agents or their genetic determinants through livestock products and water. One of the main factors for increasing the number of resistant microorganisms transmitted in each medium is the intensive and irrational use of antibiotics in it [13, 35].

K. Iskandar *et al.* [35] draw attention to the main mechanisms by which antibiotic-resistant animal microorganisms can pose a threat to human health. Infection can occur through: water or food that has been contaminated with antibiotic-resistant bacteria and is not properly cooked; improper hand hygiene after caring for dirty animals; interaction with contaminated surfaces. After that, the transmission of infectious agents to other people continues, and some infected people develop diseases. This variant of spread is a violation of the species barrier by a microorganism, which can be either directly pathogenic to humans or a commensal with the ability to cause opportunistic infections. Microbial resistance genes that occur when animals are infected become pathogenic to humans due to their horizontal transfer.

The spread of antibiotic-resistant microorganisms can also be affected by human activity. Thus, a study by E. Rousham *et al.* [36], which was conducted in Canada on clinical strains *Salmonella* of human and strains *E. coli* and *Salmonella* of chickens showed that stopping injections of ceftiofur, which belongs to the third generation of cephalosporins, substantially reduced the resistance of microorganisms in the examined birds and strains of these pathogens in the people who cared for them. Other researchers analysed the papers confirming the increased prevalence of resistant gut bacteria among farm workers compared to the population or farm workers who do not use antibiotics in animal feed.

Socioeconomic conditions can also affect the transmission of resistant microorganisms through human–animal communication. Inadequate sanitation in low-and middle-income countries, where people live in close proximity to animals, is considered to create ideal conditions for the interspecific spread of antibiotic-resistant pathogens. In addition, patients with antibiotic-resistant infections may not be able to provide or afford effective second-and third-line antibiotic treatment. The situation in these regions is complicated by pollution of available water sources, civil conflicts, and an increase in the number of people with weakened immune systems [13, 35]. As noted by A.H.D. Mansaray *et al.* [21], limited laboratory capacity and lack of regulatory authorities in these countries are serious problems in monitoring the impact of antibiotic use in animal husbandry, investigating the mechanisms of formation of antibiotic resistance of microorganisms, how they enter and affect the human body.

POTENTIAL SOLUTIONS TO THE PROBLEM OF ANTIBIOTIC RESISTANCE

Researchers argue that to reduce the migration of antibiotic-resistant microorganisms between animals and humans, the use of antibiotics in animal husbandry should be limited by including possible alternative substances, including probiotics, prebiotics, and various plant extracts for the treatment and prevention of diseases [36].

Understanding and knowledge of the dynamics of bacterial spread, horizontal transfer of antibiotic resistance genes between them, regardless of whether they belong to the same bacterial species or not, the use of antimicrobial drugs and the mechanisms of resistance formation in the host body and the environment, is the basis for a possible solution to the problem of increasing antibiotic resistance [1, 37]. In a study conducted by B.A. Wee *et al.* [38], the possibility of using phylogenetic analysis of bacterial genome sequences together with epidemiological data is indicated. This approach allows visualising characteristics such as the profile of antibiotic-resistant microorganisms and the host species for more information.

According to researchers, state governments, in cooperation with health authorities, should conduct scrupulous and versatile monitoring of antibiotic consumption in animal husbandry. In addition, the government and the public health sector should provide research and analysis services for data obtained from observational studies to track antibiotics and their residue levels in most environmental samples [36, 39].

According to L. Munkholm & O. Rubin [40], in 2013, The WHO Strategic Technical Advisory Group on Antimicrobial Resistance recommended the development of a global action plan for antimicrobial resistance. This recommendation was adopted in 2014 as a resolution of the World Health Assembly (WHA), and WHO began developing a global plan of action together with the FAO and the World Organisation for Animal Health (WOAH). The plan was approved by 194 WHO member states, which were called upon to develop and implement national action plans on antibiotic resistance. As a result, in a relatively short period of time, this tripartite committee was able to create the basis for a global antimicrobial resistance management regime. More than 120 member states, through self-reporting, have developed national action plans and established a monitoring regime. The authors recommend global governance initiatives based on individual responsibilities, some of which should be legally binding to strengthen the coherence of national antimicrobial resistance policies. They also note that regional governance agencies (such as WHO regional offices) should act as intermediaries between global and local requirements to strengthen the global governance regime.

Based on the fact that the problem of antibiotic resistance has acquired a global scale, in 2019 the Cabinet of Ministers of Ukraine approved the "National Action Plan to combat antimicrobial resistance" [9, 41], which includes a number of measures aimed at ensuring the rational use of antimicrobial drugs in the healthcare, veterinary medicine, and food industry. It is proposed to limit the use of antimicrobial drugs as growth stimulants in animal husbandry, poultry, and crop production. Doctors and veterinarians should follow clear instructions to minimise the risks of unjustified use of antimicrobials.

As a result of the analysis of scientific papers, it was established that antimicrobial resistance in the modern world is a global WHO problem. The accumulated results of studies show that improper and excessive use of antibiotics in animal husbandry is one of the main factors of acquired resistance to these drugs in humans. There is an urgent need to reduce the overall use of antibiotics in agriculture and aquaculture around the world. The experience of various developed countries shows that reducing their use will not have a substantial negative impact on the health or productivity of animals, and, in some cases, will benefit the health of people, animals, and the preservation of the environment. A number of effective measures aimed at reducing antibiotic resistance have been documented in different countries of the world.

CONCLUSIONS

There are many connections between animals, humans, and the environment that promote migration not only of bacteria but also of their mobile genetic elements. Antibiotic-resistant bacteria can enter the human body from the environment, namely: from water bodies, soil, air, contaminated vegetables and fruits, etc. Many pathogens present in the normal microbiome of agricultural, domestic and wild animals, and fish enter humans, causing complex anthropozoonotic infections.

Some critical classes of antibiotics used in medicine continue to be used to treat and stimulate growth in livestock. This misuse and overuse is one of the main factors of acquired antimicrobial resistance in animals and humans.

The global emergence and spread of antibiotic-resistant bacteria in the environment requires the promotion of a coordinated interstate and regional approach to reduce risks to human and animal health. The use of antibiotics should be accompanied by constant and enhanced monitoring of their spread and rational use in humane, veterinary medicine, and the food industry. Doctors and veterinarians should follow the procedure for using antimicrobials to minimise the risks of unjustified use. Active education is also an important aspect, especially in developing countries.

The use of various measures to prevent the spread of animal and human diseases without the use of antibiotics is an important factor in reducing the spread of antibiotic-resistant microorganisms. This can be facilitated by ensuring greater access to veterinary services for farmers. It is extremely important that antibiotics are sold only by prescription. Veterinarians should have a high level of professional knowledge in the fields of preventive medicine, effective biosecurity, and vaccinology.

In the future, it is necessary to improve understanding of the factors that contribute to the emergence, spread and permanent presence of antibiotic-resistant microorganisms in the biosphere, and monitor the rational use of antibiotics and alternative medications for the treatment and prevention of animal and human infections.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Поширення антибіотикорезистентних мікроорганізмів та механізми їх передачі від тварини до людини

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Анотація. Антимікробні засоби мають важливе значення для лікування та профілактики інфекційних захворювань як людей, так і тварин. Однак, поява та поширення мікроорганізмів, резистентних до антибіотиків, стала глобальною проблемою Всесвітньої організації охорони здоров'я. Передача антибіотикорезистентних макроорганізмів від тварин до людини здійснюється прямо чи опосередковано через навколишнє середовище. Таке їх поширення впливає на епідеміологію резистентних бактеріальних інфекцій у людей. Отже, мета дослідження полягала в тому, щоб за даними наукової літератури встановити та проаналізувати способи поширення та механізми передачі стійких до антимікробних засобів мікроорганізмів від тварини до людини, з'ясувати досвід різних країн щодо вирішення проблем антибіотикорезистентності. За допомогою методів аналізу та систематизації наукових досліджень вчених різних країн світу з'ясовано, що антимікробні засоби ще із середини XX сторіччя часто використовують в сільському господарстві як добавки в кормах, так і для підтримки здоров'я та покращення продуктивності тварин. Продукти харчування тваринного походження на всіх стадіях харчової обробки також часто містять велику кількість стійких до антибіотиків мікроорганізмів. Виявлено значну спорідненість між лікарськими засобами, які використовуються в гуманній медицині та у ветеринарії. Зазначено, що складні соціально-економічні умови, обмежені лабораторні потужності та відсутність контролюючих органів в країнах, що розвиваються, також створюють сприятливі умови для поширення антибіотикорезистентних збудників. Внаслідок чого значно ускладнюється або стає неможливим лікування багатьох інфекційних захворювань людей. Застосування антибіотиків повинно супроводжуватися постійним і посиленим контролем за їх розповсюдженням у ланцюгу «тварина–людина–навколишнє середовище», раціональним призначенням у гуманній, ветеринарній медицині та харчовій промисловості для того, щоб мінімізувати ризики невиправданого їх використання

Ключові слова: бактерії; антимікробні засоби; стійкість до антибіотиків; медицина; тваринництво; мобільні генетичні елементи; мультирезистентність