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ANTIMICROBIAL RESISTANCE: CHALLENGES IN WARTIME — UKRAINIAN PERSPECTIVE

The excessive and uncontrolled use of antibiotics in healthcare and agriculture has become the main cause of antibiotic resistance and the spread of antibiotic-resistant microorganisms in the environment. Every year, antibiotic resistance continues to grow worldwide, posing a significant challenge for humanity. The World Health Organization recognizes antibiotic resistance as one of the top 10 global threats to public health, jeopardizing the achievement of the United Nations Sustainable Development Goal. The consequences of antimicrobial resistance extend beyond the effective treatment of infections; it is a public health issue with global consequences. Socioeconomic losses and environmental threats are closely linked to this problem. Moreover, antibiotic resistance has long-term and unpredictable consequences related to wars and military conflicts. The impact of the war and a clear understanding of the global scope of antibiotic resistance as a result of hostilities can be seen through the outcome of Russia's invasion of Ukraine on February 24, 2022. This military conflict not only highlighted the importance of preserving human life and promoting peaceful development at both national and global levels but also revealed potential risks for various global environmental issues, particularly the increasing spread of antibiotic resistance. The disruption caused by the war has transformed the issue of antibiotic resistance in Ukraine from a national concern to a powerful factor that affects the global scale of this problem, transcending

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borders. During the war, resources and priorities have shifted toward military needs, relegating human health and environmental protection to secondary importance. Migration and loss of highly qualified medical specialists and biologists, deterioration of the environmental situation, sanitary, hygienic conditions, lack of food resources and medicines, and other factors directly and indirectly contribute to the emergence and spread of antibiotic resistance globally. This review demonstrates the relevance of the issue of antibiotic resistance, the main mechanisms of the development and spread of antibiotic resistance, the global scale and consequences of antibiotic resistance due to the war in Ukraine and aims to provide an overview of international initiatives to reduce antibiotic resistance, in particular the «One Health» concept and strategies, which are currently being implemented. Solving the issue of antibiotic resistance globally and at the level of the country affected by war requires a comprehensive approach, which includes mandatory systematic surveillance of antibiotic resistance, control of the use of antimicrobial drugs, informing all segments of society about the use of antimicrobial drugs and the consequences of antibiotic resistance, the introduction of educational programs to prevent an improper use of antibiotics, environmentally safe methods of waste disposal in medical, food, and other enterprises that produce or use antibiotics, safe disposal of antibiotics, etc.

Keywords: antibiotic resistance, «One Health» concept, biosafety, ecological risks, human health, war.

Antimicrobial resistance is one of the key issues worldwide, which has reached threatening socio-economic dimensions. At the same time, this issue has long been understood and considered in terms of human health protection, devoting a significant amount of scientific research. The World Health Organization (WHO) has recognized the issue of antimicrobial resistance as one of the 10 global threats to public health facing humanity, and the need to take urgent measures to mitigate its consequences (World Health Organization, 2019). Antibiotic resistance is defined as the ability of bacteria to resist the action of an antibiotic to which they were previously susceptible, allowing bacteria to survive and reproduce (Zaman et al., 2017; Uddin et al., 2021). That is, the formation of resistance is a normal evolutionary process for organisms, but this process is accelerated due to the selective pressure of various factors, in particular, the inappropriate or excessive use of antimicrobial drugs (World Health Organization, 2018).

Bacterial resistance to antibiotics can be intrinsic or acquired. Intrinsic resistance is characterized by the lack in bacteria of an enzyme or a structural molecule that are antibiotic targets, or the inaccessibility of the enzyme system or structural molecules of bacteria to the antibiotic as a result of the initially low permeability of the bacterial cell wall to the antibiotic or antibiotic degradation by specific bacterial enzymes. Ac-

quired resistance is understood as the property of individual bacterial strains to maintain viability at such concentrations of antibiotics that suppress the main part of the microbial population. Currently, the following mechanisms of acquired bacterial resistance are known: target modification, antibiotic degradation, active expulsion of the antibiotic from the bacterial cell (efflux), violation of the outer membrane permeability, and the formation of a metabolic shunt. Acquired resistance in bacteria can be provided by one of the above mechanisms, as well as their combinations (Bassetti et al., 2015; Peterson & Kaur, 2018).

The emergence of antibiotic resistance in all cases is determined genetically due to the acquisition of new genetic information or a change in gene expression levels. Many publications testify to the hidden danger of antibiotics to the environment and human health (Spellberg & Gilbert, 2014; von Wintersdorff et al., 2016; Molnar, 2019; Yao & Zhang, 2019; Symochko et al., 2019a; Symochko et al., 2019b; Uddin et al., 2021; World Health Organization, 2020; Agyeman et al., 2022; Nwobodo et al., 2022).

Microorganisms can transmit information about resistance to antibiotics through horizontal gene transfer during direct contact of one bacterium with another. Therefore, antibiotic resistance is an inevitable phenomenon because microorganisms develop genetic mutations to mitigate

the lethal effects of antibiotics (Subramaniam & Girish, 2020). For example, bacteria tend to develop and use resistance strategies as long as antibacterial drugs are used against them (i.e., there is selective pressure in their environment) (Uddin et al., 2021). However, the rate at which resistance of microorganisms, in particular bacteria to antibacterial drugs, is formed and spread is impressive. Medicines that were effective a few years ago are now losing their positions, and their use is forced to be limited. This poses a real threat to the prevention and treatment of bacterial infections and creates a significant medical and economic burden on healthcare systems and society (World Bank, 2012; Golkar et al., 2014; Smith et al., 2019). Current estimates from experts suggest that antibiotic resistance could reduce global GDP by more than 3.5% annually by 2050.

The greatest burden of antibiotic resistance is associated with *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, which the WHO has identified as priority pathogens (World Health Organization, 2017a).

In the United States, *S. aureus* (MRSA) alone leads to more deaths every year than HIV/AIDS, Parkinson's disease, emphysema, and homicide combined. Gram-negative pathogens are of particular concern because they become resistant to almost all available types of antibiotics, creating situations of the pre-antibiotic era. The most serious gram-negative infections occur in healthcare settings and are most commonly caused by *Enterobacteriaceae* (mainly *K. pneumoniae*), *P. aeruginosa*, and *Acinetobacter* multidrug-resistant Gram-negative pathogens are also becoming increasingly prevalent. These include *E. coli* and *Neisseria gonorrhoeae*, which produce extended-spectrum beta-lactamases (Golkar et al., 2014; Rossolini, et al., 2014).

Research results and discussion. Antibiotic resistance as a socioeconomic problem. Back in 2014, the WHO stated that the antibiotic re-

sistance crisis is becoming dire (Michael et al., 2014), and most public health organizations described the rapid emergence of resistant bacteria as a «crisis» or «nightmare scenario», which can have «catastrophic consequences» (Viswanathan, 2014). This jeopardizes the achievement of the United Nations' Sustainable Development Goals (SDGs), particularly Goal 3 «Ensure healthy lives and promote well-being for all at all ages» and indirectly affects other SDGs.

The global burden of bacterial resistance to antimicrobial drugs was estimated at 4.95 million deaths in 2019 (Antimicrobial Resistance Collaborators, 2022). However, the authors note insufficient data on the spread of bacterial infections and antibiotic resistance in resource-limited conditions. Although the presented figures are impressive, they do not sufficiently reflect the real situation in countries that are engulfed in military conflicts and wars.

In the European Union (EU), about 33,000 antibiotic-resistance-related deaths were confirmed, which is equivalent to nearly EUR 1.5 billion annually in healthcare costs (European Centers for Disease Control and Prevention, 2019). Seven leading pathogens were responsible for about 457,000 deaths associated with resistance in 53 countries of this region; these pathogens were, in order of descending mortality, *E. coli*, *S. aureus*, *K. pneumoniae*, *P. aeruginosa*, *Enterococcus faecium*, *S. pneumoniae*, and *A. baumannii* (European Antimicrobial Resistance Collaborators, 2022).

In the USA, more than 2.8 million cases of antibiotic resistance are recorded annually, including more than 35 thousand deaths (Centers For Disease Control Prevention, 2019; University of Oxford, 2021). In China, the total socioeconomic costs associated with antibiotic resistance in inpatients were estimated at \$77 billion, equivalent to 0.37% of China's GDP in 2017 and placing a significant burden on patient health and the healthcare system (Zhen et al., 2021).

Overall, infections caused by antibiotic-resistant bacteria are confirmed to have caused more

than 1.2 million deaths worldwide in 2019 (Murray et al., 2022), and by 2050, one death associated with antimicrobial resistance is projected to occur every three seconds. In the future (by 2050), 10 million lives annually and \$100 trillion of economic output may be at risk (O'Neill, 2016; Woolhouse et al., 2016; Subramaniam & Girish, 2020). Besides death and disability, the protracted course of diseases leads to an extension of hospitalization, requires more expensive treatment, and leads to an increase in financial costs for people who face this problem.

The WHO noted that modern antibiotics are losing their effectiveness because they were developed by modifying existing classes and have short cycles of action (World Health Organization, 2017b). The issue of antibiotic resistance, together with a shortage of innovative antibiotics, further exacerbates the situation on a global scale due to rapid spread through the food supply, urban population growth, and international travel (Holmes et al., 2016; Mangrio et al., 2021; Desai et al., 2022). The lack of development of new antibiotics limits the number of effective modern drugs against bacteria resistant to many antibiotics and contributes to the increase in the spread of antibiotic resistance (Quadri et al., 2015).

The main causes of the emergence of resistance to antimicrobial drugs are improper and excessive use of antimicrobial drugs, loss of sensitivity of patients and their self-treatment, lack of access of people and animals to clean water, sanitation and hygiene products, poor infection prevention and control in health facilities and agricultural enterprises, limited access to high-quality and affordable medicines, vaccines and diagnostic tools, low level of awareness and knowledge, lack of control over compliance with legislation, etc. (Nathan, 2004; Sreeja et al., 2017; Aslam et al., 2018; Mahmoud et al., 2018; Chokshi et al., 2019; Gilbert, 2020).

For the first time, the potential danger and risks to human health associated with the indiscriminate use of a large number of antibiotics with-

out complying with the norms were described by Swann back in the late 70s of the last century (Swann, 1969), and now official statistical data indicate an annual increase in cases of antibiotic resistance due to unjustified, excessive, and uncontrolled use of antibiotics in medicine, animal husbandry, and other branches of agriculture. There is a strong association between antimicrobial resistance and the overuse of antimicrobial drugs (Goossens et al., 2005; Malhotra-Kumar et al., 2007; Costelloe et al., 2010). Significant volumes of antibiotic consumption are also evidenced by the data of the US Expert Commission on Combating Antibiotic-Resistant Bacteria, according to which about 73 billion single doses of antibiotics or 300 thousand tons are used annually in the world. Another factor contributing to the emergence of antibiotic resistance is the increase in the availability of antimicrobial drugs in developing countries with imperfect control mechanisms.

In Ukraine, an increase in the total volume of all sales and purchases of antimicrobial drugs was also recorded by 40% in 2020 in comparison with 2018. In the pharmacy network, sales volumes of such drugs increased by 34% (Ministry of Health of Ukraine, 2022).

The situation in Ukraine is deepening due to the lack of state control and accounting of the consumption of antimicrobial drugs. Only from January 1, 2022, Ukraine introduced at the state level the administration and accounting of the use of antimicrobial drugs in health facilities, according to which 29 medicines will be subject to monitoring. These drugs are referred to as antibiotics of the surveillance group (drugs that are widely used to treat bacterial infections as first and second-line therapy) and antibiotics of the reserve group («last hope» drugs that are used to treat extremely severe bacterial infections when other antibiotics are ineffective) (Ministry of Health of Ukraine, 2022).

Resistant infections require more, sometimes stronger drugs, which can be expensive and have serious side effects. Pathogens against which antimicrobial drugs are ineffective and can lead to

the death of the patient are called «pandrug-resistant», partially effective — «multidrug-resistant». As an example, multidrug-resistant microorganisms are beta-lactamase- and carbapenemase-producing *Enterobacteriaceae* strains, methicillin- and vancomycin-resistant staphylococci, pandrug-resistant strains are *P. aeruginosa* and bacteria of the genus *Acinetobacter*.

Antibiotic resistance as an interdisciplinary field. Only during the last decade, antibiotic resistance began to be considered a complex problem that combines human health, animal health, and the environment (Aljeldah, 2022) and requires concerted action by many sectors on human, animal, and plant health, food and feed production, environmental protection, etc., since antimicrobial-resistant microorganisms are present in humans and animals, food, plants, and the environment (water, soil, and air). They can be transmitted from person to person or between humans and animals, including through food of animal origin. This was stated in the «One Health» concept, which focuses on the consequences, responses, and actions in the animal-human-ecosystem interface (Mackenzie & Jeggo, 2019). Especially, on emerging and endemic zoonoses, which have a much greater impact on diseases in developing countries, societal impact in resource-poor settings, and antimicrobial resistance, since resistance can occur in humans, animals, or the environment and can spread between countries.

The «One Health» concept recognizes that the health of people, animals, and ecosystems is interconnected. This involves applying a coordinated, collaborative, interdisciplinary, and cross-sectoral approach to eliminate potential or existing risks that arise in the link between animals, humans, and ecosystems. The world may return to the pre-antibiotic era without a synchronized and multisectoral «One Health» approach (Aslam et al., 2021; Uddin et al., 2021).

Subsequently, an international consensus was reached, and the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) was created

in 2009; the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) was launched in 2015; the Global Action Plan on Antimicrobial Resistance was adopted in 2015; the UN Interagency Coordination Group on Antimicrobial Resistance was established in 2016; the Global AMR R&D Hub was created and launched in 2018; the UN Interagency Coordination Group on Antimicrobial Resistance presented its report in April 2019, the Tripartite Secretariat of the FAO, WOAHA, and WHO was created; the Global Antibiotic Research and Development Partnership (GARDP) was initiated, and the Global Leaders Group on Antimicrobial Resistance was formed in 2020, which became a confirmation of a growing global problem that has no borders and threatens the existence of humanity. These policy decisions demonstrate the readiness of the world to take a broad, coordinated approach to address the underlying causes of antimicrobial resistance in many sectors of the economy and to develop national action plans on antimicrobial resistance in accordance with the Global Action Plan on Antimicrobial Resistance.

In the global context, the «One Health» concept integrates molecular and epidemiological aspects that contribute to the understanding of the evolution or genetic relationship of antibiotic resistance in pathogens/vectors, host (human/animal), and associated environment on a global scale. Socioeconomic factors such as world trade, conflicts, displacement, travel, and human and animal migration are important factors in the global spread of antibiotic resistance (McMichael, 2015; Hernando-Amado et al., 2019). At the local level, the concept defines geographically close ecosystems that play a crucial role in the emergence and spread of antibiotic resistance. Currently, the main attention is paid to antimicrobial residues in foods, which can accumulate due to the uncontrolled use of antibiotics in animal husbandry and agriculture. Food can be contaminated with antibiotic-resistant microorganisms throughout the entire food chain from the production of livestock

and crop products to consumption (Aslam et al., 2021; Buschhardt et al., 2021; United Nations Environment Programme, 2023).

To reduce the global risks associated with antimicrobial resistance, national and international organizations have begun to develop policies to control the use of antibiotics and fund research aimed at identifying the causes of resistance and solving the problems of environmental contamination with antimicrobial drugs and their residues. For example, the «Farm to Fork» Strategy, which involves taking measures to reduce the overall EU sales and use of antimicrobial drugs for animals and aquaculture by 50% by 2030, was adopted in the EU within the framework of the European Green Deal.

However, according to the UN report, only 29 out of 106 countries have national surveillance systems (United Nations, 2019). It is therefore important that each country involves stakeholders from different sectors such as government, industry, experts, practitioners, and international organizations to set an achievable and practical goal to reduce antibiotic consumption (O'Neill, 2016).

In Ukraine, the National Action Plan for Combating Antimicrobial Resistance (Government Portal of Ukraine, 2019) was developed and approved by the Decree of the Cabinet of Ministers of Ukraine No. 116 of March 6, 2019, which is aimed at ensuring the rational use of antimicrobial drugs in the fields of human health, veterinary medicine, and food industry following the best world and European practices; implementation of an effective system of epidemiological surveillance of antibiotic resistance, its integration into the Pan-European Network; minimization of the risks of the emergence and spread of intra-hospital strains of microorganisms that are resistant to antimicrobial drugs, bringing them into line with the EU requirements for laboratory diagnostics of infectious diseases and determining the sensitivity of microorganisms to antimicrobial drugs; conducting scientific research on issues of antibiotic resistance and implement-

ing the latest diagnostic methods in coordination with leading European and world centers.

Therefore, the key provisions of the «One Health» concept have been included in the Global and National Action Plans on Antimicrobial Resistance. However, it is recognized that more attention should be paid to the environmental aspects of the issue of antibiotic resistance, namely to deepen the understanding of the importance of the environment in the spread of antibiotic-resistant microorganisms and resistance genes within and between humans, plants, and animals. Environmental monitoring can provide important information to limit the spread of antibiotic resistance, including assessing antibiotic resistance genes circulating in humans, identifying key hotspots in the evolution and spread of resistance and informing about epidemiological models, human health risk assessment models, etc. (Liguori et al., 2022).

Coordinated efforts and interdisciplinary collaboration are needed to mitigate antibiotic resistance at the local, national, and international levels. Strong political commitment can play an important role in policy formulation, implementation, and regular educational updates based on scientific evidence to better regulate the use and sale of antibiotics, control the unethical promotion of antibiotics, and implement strategies to eliminate their overuse or inappropriate use (Murugaiyan et al., 2022).

Key factors in the dissemination of antibiotic resistance in the environment. With the spread and emergence of epizootics, zoonoses, and epidemics, the risks of pandemics became more and more critical not only for humans but also for animals. This situation was exacerbated by environmental pollution and the growth of unpredictable consequences of human-animal-ecosystem interaction, which influenced the evolution and emergence of new pathogens and the emergence of antibiotic resistance to existing dangerous biological agents. Recent studies revealed that pollution and other factors related to the industrialization during the last 150 years are the main cause

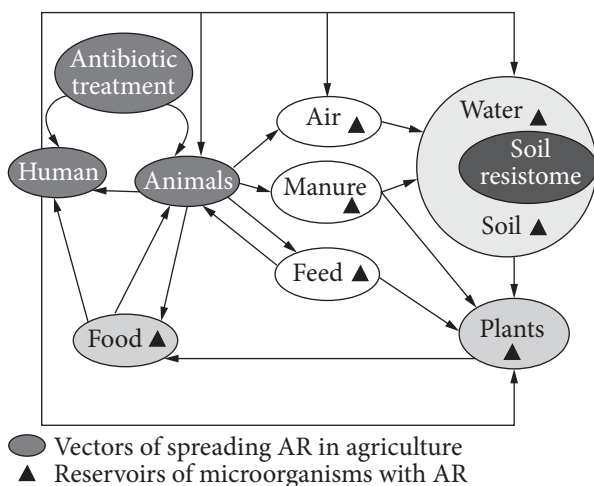


Fig. 1. Vectors of spreading antibiotic resistance in the environment. Source: generated by the authors

of the spread of antibiotic resistance (Baquero et al., 2019; Hernando-Amado et al., 2020).

Antimicrobial drugs used to treat people, as well as in livestock and crop production, enter the natural environment and water sources (including drinking water) with liquid and solid waste and domestic and sewage effluents (Munk, et al., 2022; Larsson et al., 2023).

Therefore, the surrounding natural environment is a reservoir of antimicrobial residues, resistant pathogenic microorganisms, and other molecules with antimicrobial properties, which increases the spread of resistance genes in microbial populations (Fig. 1). This can contribute to the more intensive emergence and spread of «superbugs» resistant to several types of antimicrobial drugs simultaneously, and pose a potential threat to other living organisms in ecosystems (United Nations Environment Programme, 2017).

Therefore, microorganisms resistant to antimicrobial drugs exist everywhere and can spread to new ecological niches, transferring resistance to other organisms (Davies & Davies, 2010; Gonzalez-Zorn & Escudero, 2012). Recognizing this, the Global Leaders Group on Antimicrobial Resistance, ahead of the session of the UN Environment Assembly in 2022, appealed to all

countries to reduce the number of antimicrobial drugs entering the environment through waste. To do this, in particular, it is necessary to develop and implement measures for safe waste disposal in the food industry, human and veterinary medicine, and production enterprises containing residues of such drugs.

Climate change, which affects ecosystems and biota, may also contribute to the spread of antimicrobial resistance (Global Leaders Group on Antimicrobial Resistance, 2021). Studies confirmed that rising global and local temperatures have led to an increase in antimicrobial resistance and rates of bacterial infection among humans, animals, and plants (McGough et al., 2020). It is proved that an increase in temperature by 10 °C causes an increase in antibiotic resistance by 2.2—4.2% in common pathogens of bacterial infections such as *E. coli*, *K. pneumoniae*, and *S. aureus*, and the relationship between temperature and antibiotic resistance is constant for most classes of antibiotics and pathogens and may increase over time (MacFadden et al., 2018).

The FAO states that the emergence of antibiotic resistance in the food chain is an issue that is related to the widespread use of antibiotics in aquaculture, livestock, and crop production (Food and Agriculture Organization of the United Nations, (2015).

Antibiotics have been used for decades not only for medical purposes but also as a preventive measure in various fields, including animal husbandry and other branches of agriculture (Gajdacs & Albericio, 2019). It is believed that treating livestock with antimicrobials improves the general health of animals by increasing their weight gain and producing a higher-quality product (Michael et al., 2014). At the same time, 60% of all human infectious microorganisms come from animals (Taylor et al., 2001).

However, there is a substantial evidence base, which suggests that the use and misuse of antibiotics in livestock production, either as growth promoters or as non-specific means of prevent-

ing and treating infections, has increased antibiotic consumption and resistance among bacteria in the animal habitat. This reservoir of resistance can be directly or indirectly transmitted to humans through food consumption and/or direct or indirect contact. Resistant bacteria can cause serious health consequences directly or through the transfer of antibiotic resistance traits to pathogens, causing diseases that are difficult to treat and therefore have higher rates of morbidity and mortality. In addition, the selection and spread of antibiotic-resistant strains can spread into the environment through livestock waste, reinforcing the resistance reservoir that exists in the environmental microbiome (Silbergeld et al., 2008; Economou & Gousia, 2015).

Antibiotic-resistant bacteria found in animals can be pathogenic to humans, spread easily through food chains, and spread widely in the ecosystem through livestock waste. In the human body, this can lead to the development of complex, incurable, and persistent infections (Sreeja, et al., 2017; Manyi-Loh et al., 2018). The transfer of resistant bacteria from farm animals to humans was initially observed 20 years ago when high rates of antibiotic resistance were identified in the gut microbiome of animals. Molecular techniques have since confirmed that resistant bacteria present in farm animals can reach consumers through meat products (Golkar et al., 2014; Depoorter et al., 2012; Bartlett et al., 2013).

Exposure to antibiotic resistance occurs through indirect routes, such as consuming contaminated food, and direct routes, such as contact with infected animals or their biological components (Golkar et al., 2014; Chang et al., 2014). This is attributed to a series of factors: the use of antibiotics in animal husbandry: The administration of antibiotics in animal farming kills or suppresses susceptible bacteria, creating an environment that promotes the growth of antibiotic-resistant bacteria.

Transmission through food: Resistant bacteria can be transmitted to humans through the con-

sumption of contaminated food (Symochko et al., 2021; Symochko et al., 2023).

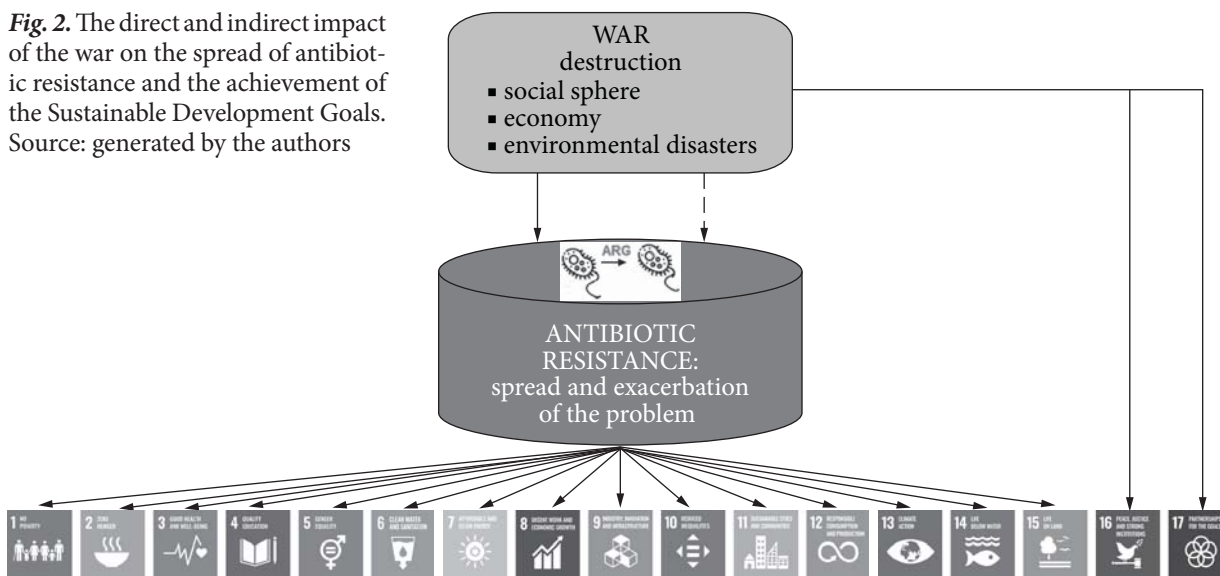
Risk of infection and health complications: These bacteria pose a high risk of causing infections in humans, leading to subsequent health complications. In animal husbandry, antibiotics are often used for preventive purposes, and it is predicted that by 2030 such use will have increased by almost 67% worldwide (Van Boeckel et al., 2015).

Antimicrobial-resistant bacteria and/or antimicrobial resistance genes (transfer in pathogenic bacteria) can contaminate food at any stage, from the field to retail and consumption. Therefore, it is important to control the use of antibiotics during food production, both for livestock and crop production, to reduce the risk of antibiotic resistance in humans (Samtiya et al., 2022).

Seafood raised in aquaculture systems and farms is considered a hotspot for antibiotic resistance due to greater genetic exchange that makes seafood more susceptible to acquiring resistance. Antibiotic resistance in foods derived from aquaculture may reduce antibacterial efficacy in humans. Aquaculture has also enabled the indirect transfer of resistance genes from the aquatic environment (bacteria) to human-associated pathogens (Watts et al., 2017; Tate et al., 2022). Several studies demonstrate that antibiotic-resistant microorganisms and antibiotic resistance genes found in humans are present in animals that have not come into contact with humans. This suggests the transmission of antibiotic resistance to humans through the consumption of contaminated food and food mishandling (Marshall & Levy, 2011).

Ways of spreading microorganisms and antibiotic resistance genes in the environment are currently being actively investigated. For example, it has been established that in animal husbandry, this can occur through contact with contaminated meat products, occupational contact (farmers, butchers, packers, etc.), and potential secondary spread to the wider community from those occupationally exposed, or spread through environmental routes including air, water or soil, in areas located near

Fig. 2. The direct and indirect impact of the war on the spread of antibiotic resistance and the achievement of the Sustainable Development Goals. Source: generated by the authors



livestock farms or farms where manure is used as a fertilizer (Graham et al., 2019). *S. aureus* can spread over long distances by the air through attachment to dust particles (Hartung et al., 1998).

Water, particularly drinking water, contaminated with animal or human feces containing antibiotic-resistant bacteria is considered a key source of the spread of antibiotic resistance, antibiotic residues, and extracellular mobile genetic elements associated with antibiotic-resistant organisms and a source of new antibiotic resistance genes (Larsson & Flach, 2022). Urban and livestock wastewater, circulating water, and effluents from antimicrobial drug manufacturing facilities are identified as hotspots for antibiotic-resistant bacteria and resistance genes that spread into the environment and require special monitoring (Rizzo et al., 2013; Burgmann et al., 2018; Symochko et al., 2019a; Symochko et al., 2023).

Contamination with antibiotics or their residues, which come from various sources, is an important factor in the formation of soil resistome — a collection of soil microorganisms with a high level of antibiotic resistance, which poses a potential threat to human health and makes it difficult to control environmental consequences in the future (Symochko et al., 2019b; Symochko et al., 2021).

Warfare and military conflicts as influencers of antibiotic resistance propagation and the attainment of the Sustainable Development Goals. Military conflicts and their consequences are among the powerful factors in the spread of antibiotic resistance on a global scale. This issue is relevant today in the world as a result of the war launched by the Russian Federation against Ukraine in 2014 and the large-scale armed invasion on February 24, 2022. The war is a rapidly growing humanitarian and refugee crisis, with geopolitical, economic, and environmental waves that are felt worldwide (World Health Organization, 2022a).

The issue of antibiotic resistance in the conditions of military conflicts is complex and covers the issues of normative and legislative regulation, state control over the use of antimicrobial drugs and antibiotic resistance surveillance systems, epidemiological surveillance, qualified personnel, etc. Each country has its specific conditions and requires appropriate approaches to solving the problem (Gelband & Laxminarayan, 2015; Bunduki et al., 2019). All this together has a direct and indirect impacts on the achievement of the SDGs.

Currently, in the conditions of war, Ukraine has to solve a number of important socio-economic and environmental tasks, primarily re-

lated to ensuring the safety of life and health of Ukrainians, food and energy security, etc., which affects the achievement of the SDGs (Pereira et al., 2022) and directly or indirectly affects the issue of antibiotic resistance (Fig. 2).

As a result of hostilities, there is not only the destruction of military facilities, military and civilian infrastructure, and residential areas but also death, various wounds, and injuries among military personnel and civilians. As a result of attacks, shelling, and bombing, the number of people injured and, as a result, disabled (including those with severe forms) is constantly increasing, both among civilians, including children, and military personnel. According to the data of the Office of the United Nations High Commissioner for Human Rights as of December 19, 2022, 6,826 civilians were killed and 10,769 injured during the war (including 428 killed and 790 injured children). The primary task remains the provision of timely and high-quality medical care, including antimicrobial therapy, in many cases to save the life of the injured, prevent serious consequences, and quickly restore combat and work capacity. There is an increasing need for the use of antibiotics to treat wounds, injuries, or acquired disabilities that require constant supportive therapy, and diseases during service in combat areas. At the same time, the global trend of increasing antibiotic resistance has negative consequences in the treatment of combat pathology (Stewart et al., 2020; Yaacoub et al., 2022). There are also indirect effects, due to the complete disruption of everyday social life, infrastructure, and deterioration of the environmental situation.

The war took a heavy toll on the healthcare system. As of the beginning of November 2022, the WHO confirmed 630 attacks on health facilities in Ukraine, as a result of which 1,157 objects were damaged and destroyed (National Institute for Strategic Studies, 2022a). According to the Minister of Health of Ukraine, as of February 2023, as a result of a full-scale invasion, 1,218 health care facilities were damaged, in particular,

540 hospitals were partially destroyed, and 173 were completely destroyed.

The destruction of the medical infrastructure, the impossibility of complying with the norms of prevention and treatment, the lack of medical personnel in some regions, and the disruption of logistical connections prevent the timely and complete provision of medical supplies to the people. Since the demand for medical services has changed significantly in different regions due to the migration of a large part of citizens within the country and beyond its borders, the disparities in resource provision in the healthcare sector have worsened (National Institute for Strategic Studies, 2022b; World Health Organization, 2022b). Health risks for the Ukrainians have increased due to less availability of drugs in the pharmacy network, reduced access to qualified medical care and medical services, and exacerbation of chronic diseases under the influence of post-traumatic stress disorder not only among military personnel but also among civilians who have suffered from hostilities. Due to the lack of qualified medical specialists, there is the uncontrolled use of antibiotics in the combat zone and self-treatment without the supervision of doctors, including a preventive purpose. Also, a question arises regarding the quality of these drugs, namely storage conditions and expiration dates. There is also no reliable information about the number of antimicrobial drugs imported by the invaders into the territory of Ukraine, their uncontrolled use and disposal, etc.

In Ukraine, there is a problem of low awareness of the dangers and potential threats of antibiotic resistance and issues related to the indications for antibiotic use, its actions, and the principles of rational antibiotic therapy among doctors and pharmacists, as well as ordinary citizens. Our survey on the understanding of antibiotic resistance-related risks showed that 93% of the ordinary Ukrainians have not heard of this problem at all, and 86% consider antibiotic treatment effective and prefer such drugs.

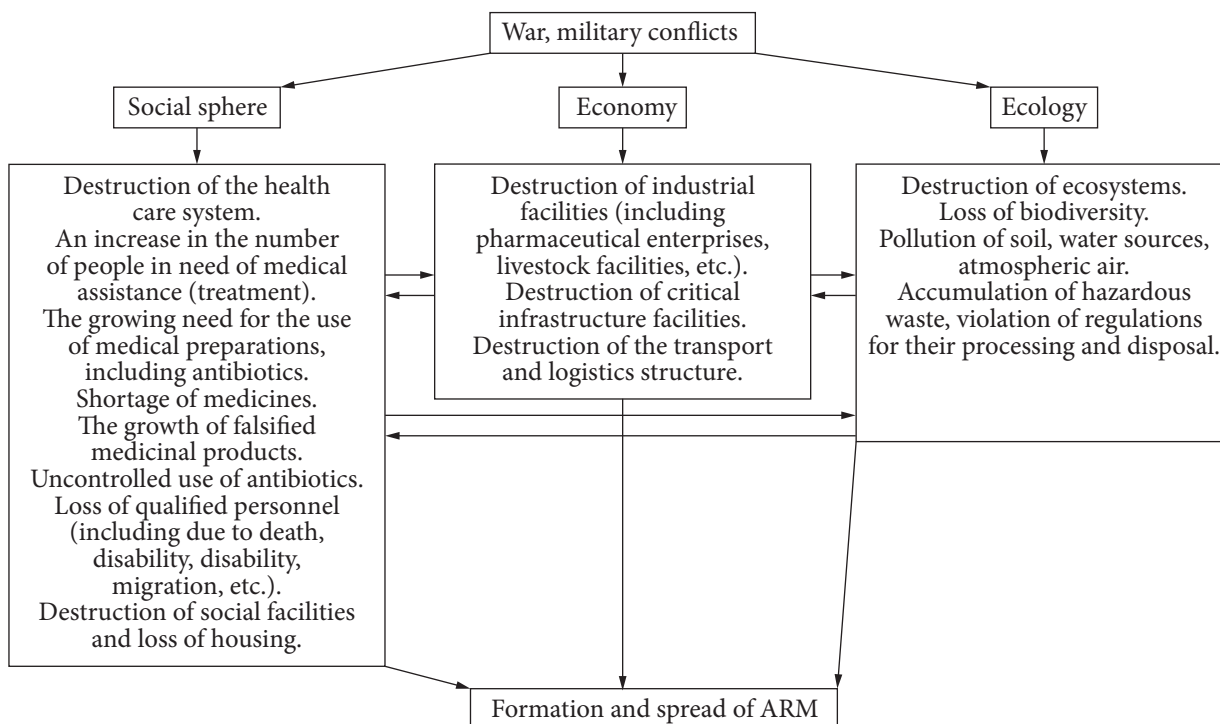


Fig. 3. Factors of AMR formation and spread in the world under conditions of military conflicts. Source: generated by the authors

Besides, in Ukraine, the issue of the rational use of antibiotics is even more urgent due to the free public access to antimicrobial drugs, not always optimal use in everyday practice, and self-treatment. Only in April 2022, restrictions on access to antibiotics were adopted at the state level (Ministry of Health of Ukraine, 2021), and the Medical Care Standard «Rational Use of Antibacterial and Antifungal Drugs for Therapeutic and Prophylactic Purposes» was approved in May 2022 (Ministry of Health of Ukraine, 2022).

With the beginning of the large-scale invasion of the Russian Federation's army, the logistics of medicines and medical devices became one of the most difficult problems. Especially in regions where active hostilities took place, due to the uncertainty of the situation regarding the temporary occupation of territories and risks on the roads. Due to the periodic complications of cargo traffic at checkpoints, the cargoes of several pharmaceutical companies are delayed while

crossing the border. In addition, the transportation of certain medicines, raw materials for their manufacture, and medical devices requires compliance with the appropriate storage conditions (National Institute for Strategic Studies, 2022b). As a result, the healthcare system of Ukraine has a shortage of quality pharmaceutical products, so the problem will have to be partially solved by the citizens themselves, which may negatively affect their standard of living and health and contribute to the formation of antibiotic resistance.

One of the ways to the spread of antibiotic resistance in the world is through the migration of people (Mangrio et al., 2021; Desai et al., 2022). Among migrants, infectious diseases aggravated by antibiotic resistance are of particular concern. Migrants, like all mobile populations, including tourists, are potentially exposed to multiple antibiotic-resistant strains but are at particular risk due to overcrowding and inadequate conditions in refugee camps and detention centers, extreme

psychological stress due to the conditions of instability they experience, and often lack of access to medical care for conditions that are otherwise easily treatable (de Smalen et al., 2017).

As of 28 March 2023, the United Nations High Commissioner for Refugees (UNHCR) has recorded 8.1 million refugees from Ukraine in Europe. A total of 5 million were registered for temporary protection or similar national protection schemes in Europe. For cross-border movements, 19.7 million crossings out of Ukraine and 11.2 million crossings into Ukraine were recorded. These figures do not reflect individuals. The International Organization for Migration (IOM) estimates that 5.4 million people are internally displaced across Ukraine as of 23 January 2023, a slight decrease from 5.9 million on 5 December 2022. The estimated number of people internally displaced within Ukraine has been steadily declining since August 2022 (World Health Organization, 2023).

Of course, the numbers given in official sources are impressive and not constant, since every day the number of killed military and civilian people, wounded and sick, and destroyed objects of the housing stock and critical infrastructure is constantly increasing.

The destruction of wastewater treatment infrastructure (domestic, industrial, agricultural, and medical facilities) during hostilities increases the risks of water contamination worldwide and the spread of AMR, thus further exacerbating the AMR problem at the global level (Fig. 3). The destruction of buildings, medical facilities, storage warehouses for medical supplies, industrial sites, including livestock enterprises, has resulted in the generation of a significant volume of waste containing hazardous substances. This, in turn, contributes to the proliferation of antibiotic resistance within the environment and the formation of a reservoir of resistance (Symochko et al., 2019b; Symochko et al., 2021).

According to the technical report on assessing the costs and risks of water pollution around the world, prepared for the World Economic Forum

(Vivid Economics, 2020), Ukraine was in the risk group even before the full-scale invasion and the start of active hostilities, according to experts.

Conclusions. The issue of antibiotic resistance, which poses a real threat to humanity, is globally recognized and currently, most countries worldwide are developing and implementing national strategies/action plans to combat antimicrobial resistance, which are based on the «One Health» Concept and are aimed at deepening the understanding of the importance of the environment in the spread of antibiotic-resistant microorganisms and resistance genes.

The issue of antibiotic resistance lies in the lack of geographical, sectoral, or environmental boundaries and particularly arises when the state of war or peace is not recognized. At the same time, in war conditions, the risks of the emergence and spread of antibiotic resistance globally are increasing and may have catastrophic consequences soon. Ukraine in the conditions of war with the destroyed health care system, the crisis state of the environment, broken epidemiological surveillance, a constantly growing number of wounded and killed, the loss of qualified doctors, biologists, and other specialists, a shortage of high-quality antimicrobial drugs, high migration of people to neighboring countries, etc., is a powerful factor in the emergence and spread of antibiotic resistance.

The war has resulted in the widespread displacement of people, worsening of serious diseases, the spread of previously uncommon illnesses, mental health issues, burnout and displacement of healthcare workers, destruction of infrastructure and supply chains, and a significant decline in people's and the state's incomes. Presently, it is crucial to devise effective measures to combat and prevent antibiotic resistance, considering all the risk factors associated with its emergence and spread during the conflict. Drawing upon global experience in addressing this issue within the framework of the «One Health» concept, it is important to raise awareness about the significance of tackling this escalating threat to humanity.

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АНТИМІКРОБНА РЕЗИСТЕНТНІСТЬ: ВИКЛИКИ У ВОЄННИЙ ЧАС — УКРАЇНСЬКИЙ ВЕКТОР

Необґрунтоване, надмірне та безконтрольне використання антибіотиків у сфері охорони здоров'я та різних галузей сільського господарства стало основною причиною формування антибіотикорезистентності (АР) та поширення стійких до антибіотиків мікроорганізмів у навколишньому середовищі. З кожним роком фіксують зростання АР у світі, що стало викликом для людства. ВООЗ визнає проблему АР однією з 10 глобальних загроз здоров'ю населення, що ставить під загрозу можливість досягнення Цілей Сталого Розвитку ООН. Проте наслідки резистентності до антимікробних препаратів є не лише загрозою ефективного та успішного лікування інфекцій, а й становить проблему громадської охорони здоров'я. Ця проблема має більш глобальні наслідки та тісно пов'язана з соціально-економічними збитками і екологічними загрозами. Водночас ця проблема поглиблюється і має непередбачувані пролонговані в часі наслідки, пов'язані з війнами і військовими конфліктами. Вплив війни та реальне розуміння масштабів проблеми АР на глобальному рівні внаслідок ведення бойових дій світ побачить за результатами нападу РФ на Україну 24 лютого 2022 р. Цей військовий конфлікт не лише окреслив зрозумілі для всіх важливі речі безпеки життя людини і мирного розвитку окремої країни та світу загалом, а й визначив потенційні ризики для низки глобальних екологічних проблем, зокрема зростання поширення АР. Внаслідок порушення нормального функціонування всіх сфер життя, питання АР в Україні перестає бути національним, а набуває ознак потужного чинника впливу на глобальні масштаби цієї проблеми, яка не має кордонів. В умовах війни більша частина ресурсів і пріоритетів зміщена на військові потреби, а питання охорони здоров'я людини, охорони довкілля набувають другорядного значення. Міграція і втрата висококваліфікованих фахівців-медиків, біологів, погіршення екологічної ситуації, санітарно-гігієнічних умов, брак продовольчих ресурсів і медикаментів та інші чинники прямо та опосередковано сприяють формуванню і поширенню АР на глобальному рівні. Цей огляд демонструє актуальність проблеми стійкості мікроорганізмів до антибіотиків, основні механізми розвитку та розповсюдження АР, глобальні масштаби і наслідки АР, пов'язані з війною в Україні, та має на меті дати уявлення про міжнародні ініціативи щодо зниження АР, зокрема Концепцію «Єдине здоров'я» та стратегії, які нині імплементуються. Вирішення проблеми АР на глобальному рівні та на рівні країни, охопленою війною, потребує комплексного підходу, що включає обов'язковий систематичний моніторинг стану стійкості мікроорганізмів до антибіотиків, контроль застосування антимікробних препаратів, інформування всіх верств населення щодо застосування антимікробних препаратів та наслідків АР, запровадження освітніх програм для запобігання неправильного використання антибіотиків, екологічно безпечні методи утилізації відходів підприємств медичної, харчової та ін. галузей, які виробляють або використовують антибіотики, тощо.

Ключові слова: антибіотикорезистентність, Концепція «Єдине Здоров'я», біобезпека, екологічні ризики, здоров'я людини, війна.