

The importance of antibiotics and the evolution of resistance to antimicrobial substances

Importanța antibioticelor și evoluția rezistenței de substanțele antimicrobiene

Adrian Rădulescu^{1,2}, Maria Crivineanu¹, Diana Mihaela Alexandru^{1,*}

1. University of Agronomic Sciences and Veterinary Medicine, Faculty of Veterinary Medicine, Bucharest, Romania

2. Vrancea Sanitary Veterinary and Food Safety Directorate, Vrancea, Romania

*Corresponding author: albu.dm@gmail.com

Keywords: antibiotic resistance, antibacterial substances, public health

Cuvinte cheie: antibioretistență, substanțe antibacteriene, sănătate publică

Abstract

By exploring the history of antibiotic discovery and how antimicrobial resistance has become a global problem, this study aims to provide a comprehensive perspective on the impact of these factors on public health. At the same time, we will analyze the strategies proposed to counter this worrying development and to ensure a future in which antibiotics remain effective tools in the treatment of bacterial infections. The purpose of this paper is to review proposed strategies for countering antimicrobial resistance, including the development of new antibiotics, improved prescribing practices, and public awareness of the responsible use of these drugs. In an era where treatment-resistant infections are becoming more common, it is crucial that we engage in concerted efforts to maintain the effectiveness of antibiotics and ensure the future health of the global population.

Rezumat

Prin explorarea istoriei descoperirii antibioticelor și a modului în care rezistența la antimicrobiene a devenit o problemă globală, această lucrare oferă o perspectivă comprehensivă asupra impactului acestor factori asupra sănătății publice. Totodată, se vor analiza strategiile propuse pentru a contracara această evoluție preocupantă și pentru a asigura un viitor în care antibioticele rămân instrumente eficiente în tratarea infecțiilor bacteriene. Scopul acestei lucrări este de a analiza strategiile propuse pentru contracararea rezistenței la antimicrobiene, inclusiv dezvoltarea de noi antibiotice, îmbunătățirea practicilor de prescriere și conștientizarea publicului cu privire la utilizarea responsabilă a acestor medicamente. Într-o eră în care infecțiile rezistente la tratament devin din ce în ce mai frecvente, este crucial să ne angajăm în eforturi concertate pentru a menține eficacitatea antibioticelor și a asigura sănătatea viitoare a populației globale.

Introduction

The discovery of antibiotics marked a crucial moment in the history of medicine, offering effective solutions for the treatment of bacterial infections.

At the center of this revolution stands the emblematic figure of Alexander Fleming, whose observations on the effects of penicillin opened new therapeutic horizons.

Over the decades, antibiotics such as streptomycin and tetracycline have become

essential tools in the treatment of infections, saving millions of lives.

However, the apparent success of antibiotics has been overshadowed by the emergence and spread of antimicrobial resistance, a phenomenon fueled by reckless practices such as the excessive and inappropriate use of these drugs.

The evolution of antibiotic discovery has been a complex and fascinating process, from Fleming's accidental discovery of penicillin in

1928 to the subsequent development of a wide range of broad-spectrum antibiotics.

These medications have had a significant impact on improving the survival rate of patients affected by bacterial infections, revolutionizing medical practice and reducing mortality associated with these diseases.

However, the success of antibiotics has come with unexpected challenges.

The intensive and often inappropriate use of these drugs has paved the way for the evolution of antimicrobial resistance.

Bacteria have developed defense mechanisms against the action of antibiotics, thus compromising the effectiveness of these treatments and posing a global threat to public health (13,17).

The phenomenon of antimicrobial resistance is fueled by several factors, including the pressure exerted by extensive use in medicine and agriculture, the lack of compliance with antibiotic administration rules, and even self-medication.

This vicious cycle has created a conducive environment for the natural selection of resistant bacterial strains, thereby accelerating their spread in communities and worldwide (16,18).

Faced with this growing threat, the medical community and researchers have sought innovative solutions to counteract antimicrobial resistance.

Their efforts have included the development of new classes of antibiotics, improving prescribing practices to reduce inappropriate use, and promoting public awareness of the importance of responsible antibiotic use.

History of antibiotics

The discovery of penicillin represented a crucial moment in the evolution of medicine, marking the significant contribution of British microbiologist Sir Alexander Fleming.

At a time when bacterial infections posed a major challenge in medical practice, Fleming's research had profound consequences for the treatment of these conditions. Alexander Fleming's observations on bacterial cultures,

especially those of the genus *Staphylococcus*, revealed that a fungus, later identified as *Penicillium notatum*, released a substance that inhibited bacterial growth (14).

The initial impact of the discovery of penicillin was profound, leading to a significant change in the paradigm of bacterial infection treatment.

The scientific and medical community quickly recognized the therapeutic potential of penicillin, paving the way for further research and the development of other classes of antibiotics.

Alexander Fleming's contribution to the discovery of penicillin was recognized with numerous awards and honors, consolidating his status as a pioneer in the field of medicine. His legacy remained fundamental to the progress of modern medicine, with penicillin continuing to be "one of the essential tools in the fight against bacterial infections" (11).

Penicillin was successfully used in the treatment of conditions such as pneumonia, septicemia, and endocarditis, significantly contributing to the reduction of mortality associated with these diseases.

The application of penicillin in surgery also had a major impact, allowing for more extensive surgical interventions and reducing the risk of postoperative complications caused by bacterial infections.

Over time, the use of penicillin expanded to other conditions, including sexually transmitted infections such as syphilis and gonorrhoea.

The positive impact of penicillin in treating these conditions was notable, substantially changing perspectives on the control and treatment of infectious diseases (8,14).

As penicillin solidified its place in the medical arsenal, its multiple applications and benefits became evident. Penicillin treatment quickly became a reference point in medicine, marking a significant transition from previous approaches with limited effectiveness.

The main contribution of penicillin manifested in the treatment of severe and often fatal bacterial infections, restoring hope for affected patients. In surgical interventions, the use of penicillin reduced the risk of postoperative infectious complications, thus

expanding the range of possible surgical procedures and improving patient prognosis (19).

However, as penicillin became increasingly prevalent in medical practice, challenges began to emerge.

The development of penicillin resistance in certain bacterial strains underscored the need for ongoing approaches in researching and developing new antibiotics to counteract bacterial evolution.

After the discovery of penicillin, the development of antibiotics saw a significant stage with the isolation and characterization of streptomycin.

This substance, initially identified in *Streptomyces* strains, represented a major advance in antimicrobial therapy (14).

Streptomycin, discovered in 1943 by Waksman and Schatz, marked a new era in the fight against infections.

This broad-spectrum antibiotic was initially successfully used in the treatment of tuberculosis, representing a significant progress compared to previous treatment options (23,24).

Through further development, streptomycin was identified as an example of a new class of antibiotics, aminoglycosides. This discovery stimulated research in the field, contributing to the identification and isolation of other classes of antibiotics with diverse chemical structures and specific mechanisms of action.

As new antibiotics were discovered and developed, it became evident that their diversity could cover a wide range of bacterial infections.

Tetracyclines, macrolides, and cephalosporins, among others, became essential components of the medical arsenal, offering alternatives and tailored solutions for various clinical contexts (23).

With progress in antibiotic development, a window of opportunities opened in the treatment of various bacterial conditions.

Tetracyclines were introduced into the medical arsenal with an extended spectrum of action, addressing various infections such as respiratory, urinary, and dermatological.

This diversity of medications allowed doctors to tailor treatments according to the specificity of each infection, contributing to the optimization of therapeutic outcomes.

Macrolides, such as erythromycin, were successfully used in the treatment of upper respiratory infections, while cephalosporins became essential in surgical interventions and the treatment of more severe bacterial infections (6,14).

However, the extensive and often uncontrolled use of antibiotics raised concerns about the emergence and spread of antimicrobial resistance. The phenomenon of antibiotic resistance became a global issue, significantly impacting the ability to treat bacterial infections and public health outcomes (7).

Addressing antibiotic resistance became a priority, and research focused on developing innovative strategies.

Efforts included identifying new classes of antibiotics, improving prescribing practices by adopting more precise protocols, and promoting awareness of the rational use of these medications among healthcare professionals and the general public (5).

The benefits of antimicrobial substances

The significant beneficial effects of antibiotics on the treatment of bacterial infections indeed mark remarkable progress in the field of medicine.

These effects have positively influenced the course of patients affected by various infections, bringing tangible benefits both at the individual and public health levels. Thus, antimicrobial pharmacological agents have contributed to:

- **Eradicating bacterial infections:** antibiotics have had a major impact on the treatment of bacterial infections, successfully destroying or inhibiting the growth of pathogenic bacteria. This direct effect on the causative agent of the infection allows for faster recovery and prevents the progression of the disease to more severe stages.

- **Reducing morbidity and mortality:** the use of antibiotics has led to a significant decrease in the morbidity and mortality rates associated with bacterial infections. Through early and effective interventions, antibiotics have saved lives and contributed to improving the quality of life for those affected.

- **Preventing postoperative complications:** in surgery, antibiotics are used to prevent postoperative infections. This has allowed for the expansion of surgical procedures, increased success rates of interventions, and reduced the risk of complications associated with infections.

- **Controlling sexually transmitted diseases:** Antibiotics have had a significant impact on controlling and treating sexually transmitted diseases, offering effective solutions in cases such as syphilis and gonorrhea (13).

- **Improving quality of life:** by rapidly and efficiently treating bacterial infections, antibiotics have contributed to reducing convalescence periods, facilitating the return to a normal and active life for patients.

However, it is essential to emphasize that responsible use of antibiotics is crucial to prevent the development of antimicrobial resistance and ensure their long-term effectiveness.

The considerable benefits of antibiotics are accompanied by responsibilities in the proper management of these medications to protect public health and maintain treatment efficacy in the future (1, 7, 20).

The evolution of antimicrobial resistance

The evolution of resistance in the context of extensive use has been determined by a series of interconnected factors, reflecting the complex relationship between microorganisms and their environment.

Globally, the widespread use of antibiotics in medicine and agriculture has significantly

contributed to the natural selection of resistant bacterial strains.

The frequent and uncontrolled administration of these medications has created a favorable environment for resistance development.

As antibiotics are used excessively or inappropriately, bacteria exhibiting resistance capabilities to them become predominantly selected, leading to an increase in the frequency of these strains in the community (3,10).

In the medical field, pressure on antibiotics through self-medication, inappropriate prescriptions, and their use in preventive treatments or clinically unjustified situations contribute to the emergence and spread of resistance.

Additionally, the increasing use of antibiotics in agricultural practices, both for treating animals and promoting their growth, has raised additional concerns in the evolution of antimicrobial resistance.

The process of transferring resistance genes between different environments, such as medical and agricultural, adds a level of complexity. Resistance genes can be transferred between various types of bacteria and between bacteria and other microorganisms, contributing to the rapid and global spread of resistance capabilities (17).

One of the significant challenges in the evolution of antimicrobial resistance is the phenomenon of "selective pressure."

The more frequently antibiotics are used, the greater the pressure exerted on bacteria to develop resistance.

This phenomenon is exacerbated by the inappropriate use of antibiotics, such as administering them at suboptimal doses or for viral conditions where they are ineffective (2,15).

Another important aspect of resistance evolution is the transfer of resistance genes between different bacterial species (Figure 1).

This ability to transfer genetic material between them allows bacteria to rapidly and efficiently acquire resistance characteristics to multiple antibiotics.

The transfer of resistance can occur not only between bacteria of the same type but also between bacteria of different species and even between bacteria and other microorganisms, such as plasmids or transposons (16).

Antimicrobial resistance is not limited to the medical field but has serious consequences for

animal health and ecosystems as well. The intensive use of antibiotics in agricultural practices can contribute to the emergence and spread of antimicrobial resistance among animals and the surrounding environment, potentially affecting human health indirectly through food chains or direct contact (1,5).

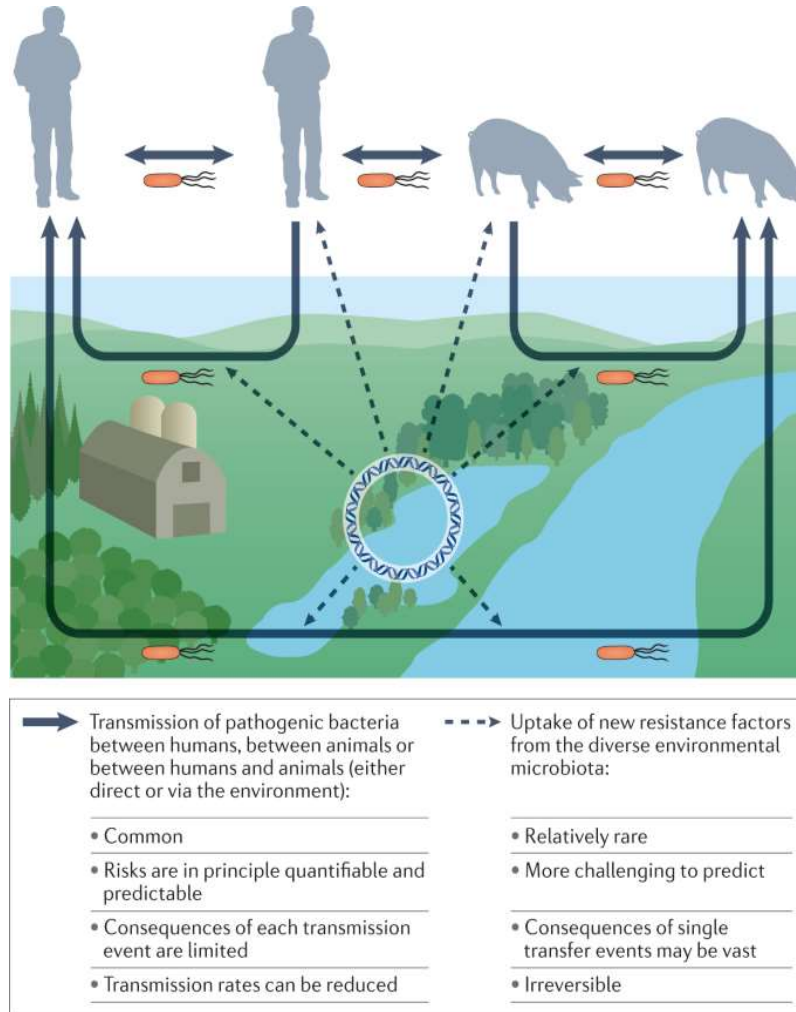


Figure 1. Routes of transmission of bacterial pathogens.

The dominant routes of transmission of (resistant) pathogens (arrows) are between humans and animals, and sometimes between animals and humans. These routes of transmission can be direct or indirect through the external environment, often through faecal contamination. (Source: Larsson D.G.J., Flach C.F., 2022)

The factors that contribute to the appearance of antibiotic resistance

The emergence of antimicrobial resistance is a complex and multifactorial phenomenon, influenced by a series of elements that interact synergistically. Understanding these contributing factors is essential for developing

effective strategies for prevention and control of resistance (26).

• **Excessive and Inappropriate use of antibiotics:** one of the most significant causes of antimicrobial resistance is the excessive and inappropriate use of antibiotics. This practice includes administering antibiotics in the

absence of a clear diagnosis, using them in suboptimal doses, and not adhering to the recommended treatment duration.

- **Self-medication and self-prescription:**

Self-treatment with antibiotics without the supervision of a medical professional and self-prescription of these medications contribute to the emergence of resistance. These practices can lead to the unjustified use of antibiotics and incorrect administration of these medications.

- **Inappropriate practices in agriculture:**

the use of antibiotics in agricultural practices, such as promoting animal growth or disease prevention, contributes to the development of antimicrobial resistance. The transfer of resistance genes between bacteria in the agricultural environment and those in the medical environment represents an additional threat (4).

- **Lack of monitoring and control:** in some regions, there is a lack of monitoring and control regarding the use of antibiotics and resistance to them. This can facilitate the uncontrolled increase of resistance in communities and healthcare institutions.

- **Transfer of resistance genes:** the ability of bacteria to transfer resistance genes between them is an important mechanism in the evolution of antimicrobial resistance. This phenomenon can occur not only between bacteria of the same type but also between different species and in various environments.

- **Use of antibiotics in food and aquaculture industries:** in addition to agricultural practices, the use of antibiotics in the food and aquaculture industries can contribute to the spread of antimicrobial resistance, with potential consequences for human health through the consumption of contaminated food.

Overall, combating antimicrobial resistance requires an integrated approach that addresses all these contributing factors.

This involves improving antibiotic use practices, public education, promoting research

for the development of new antibiotics, and strengthening global efforts to monitor and control resistance (25, 26).

The impact of antimicrobial resistance

The impact of antimicrobial resistance on public health is complex and manifests in various ways, with a global spread of resistant bacteria posing a series of threats to the effectiveness of medical treatments.

1. Global spread of resistant bacteria:

antimicrobial resistance knows no national borders and is a problem that affects the entire world. Resistant bacteria can travel widely, either through traveling individuals or through the export of food or other goods.

This contributes to the increasing prevalence of resistant bacteria worldwide, posing a cross-border threat to public health.

2. Spread of multidrug-resistant infections:

resistant bacteria can cause multidrug-resistant infections, meaning infections that no longer respond to multiple classes of antibiotics.

This makes treating these infections more difficult and sometimes impossible.

Multidrug-resistant infections are associated with higher rates of morbidity and mortality, higher treatment costs, and the need for more complex medical interventions.

3. Complication of treating common diseases:

antimicrobial resistance affects the treatment of common diseases such as respiratory, urinary, and skin infections.

What would have been treatable conditions with common antibiotics in the past can now become a significant challenge, with serious implications for population health (11).

4. Prolonged hospital stays:

patients infected with resistant bacteria often require longer hospital stays and more intensive treatments. This not only puts an additional burden on healthcare systems but also

increases the risk of transmitting resistant bacteria in the hospital environment.

5. Limitation of therapeutic options: as antimicrobial resistance spreads, available therapeutic options become limited.

This can lead to situations where doctors are forced to use stronger or more toxic antibiotics, with potential negative side effects.

6. Global health issues: Antimicrobial resistance poses a serious threat to global public health efforts, affecting the ability to manage pandemics, complex surgical interventions, and the treatment of chronic infectious diseases.

Overall, the global spread of resistant bacteria has significant consequences for public health, necessitating the need for global and collaborative strategies to combat antimicrobial resistance (12, 21).

Consequences of antimicrobial resistance

Antimicrobial resistance generates significant consequences for the treatment and management of infections, introducing substantial challenges and limitations in the medical approach to these conditions.

These consequences affect both the individual level, through the impact on patients, and the healthcare system as a whole (4).

1. Treatment failure: antibiotic-resistant bacteria can lead to the failure of standard treatment, as they no longer respond to common antibiotics.

This complicates the management of infections, allowing them to persist or worsen, putting patients at increased risk of complications and requiring more intensive medical interventions.

2. Increased morbidity and mortality: infections caused by bacteria resistant to treatment may be associated with higher rates of morbidity and mortality.

Difficulty in treating these infections increases the risk of complications and reduces

the effectiveness of treatment, thus contributing to the negative impact on the health status of patients.

3. Prolonged hospitalization: patients infected with antibiotic-resistant bacteria often require longer hospital stays and more complex treatments, contributing to the increased costs of the healthcare system and limiting the availability of hospital beds for other patients.

4. Use of stronger antibiotics: antibiotic resistance forces doctors to resort to the use of stronger antibiotics or combinations of antibiotics, with potential side effects and risks for patients. The choice of these options may be limited and may be associated with higher treatment costs.

5. Postoperative complications: in surgery, postoperative infections with antibiotic-resistant bacteria can lead to significant complications, including soft tissue infections, sepsis, and surgical failure. These complications can affect the recovery and long-term outcomes of patients.

6. Limitation of therapeutic options: as antimicrobial resistance spreads, available therapeutic options become limited, affecting the ability to treat infections effectively and properly manage associated diseases.

Challenges and opportunities in managing antimicrobial resistance

Managing antimicrobial resistance faces numerous challenges and, at the same time, offers opportunities for innovation and improvement in medical and public health practices (22).

Challenges:

- **Excessive and inappropriate use of antibiotics:** Inappropriate prescribing practices and excessive use of antibiotics in medical treatments or agricultural practices constitute a major challenge, generating selective pressure for the development of bacterial resistance.

- **Global transfer of resistant bacteria:** antimicrobial resistance knows no boundaries, and the global movement of people and goods can contribute to the rapid spread of resistant bacteria worldwide.
- **Lack of rapid and accurate diagnostics:** Limited availability of rapid and accurate diagnostics for identifying pathogens and their antibiotic resistance may delay the prescription of appropriate treatments and contribute to the inefficient use of antibiotics.
- **Pharmaceutical industry and the economic incentives:** The lack of sustainable economic models for the development of new antibiotics is a challenge. The pharmaceutical industry often faces economic uncertainties and profitability challenges compared to other types of medications.

Opportunities:

- **Development of new diagnostic technologies:** innovations in diagnostic technologies can improve the speed and accuracy of identifying bacteria and their sensitivity to antibiotics, allowing for the prescription of personalized treatments.
- **Global collaboration:** collaboration among countries, research institutions, the pharmaceutical industry, and international organizations provides opportunities for the exchange of knowledge, resources, and joint initiatives to combat antimicrobial resistance.
- **Education and public awareness:** continuous education and public awareness can contribute to changing behaviors regarding antibiotic use, thereby reducing pressure on resistance development.
- **Promotion of research and innovation:** Supporting research and innovation in the

development of new antibiotics, including providing financial incentives and encouraging collaboration across sectors, can be essential opportunities in combating antimicrobial resistance (22, 25).

Managing antimicrobial resistance involves addressing both challenges and opportunities with an integrated and collaborative framework to promote sustainable and effective medical practices globally (9,22).

Conclusions

The evolution of antibiotic discovery and antimicrobial resistance represents a complex process, influenced by significant scientific discoveries as well as medical and socioeconomic practices, with substantial implications for public health and the medical approach to bacterial infections.

Antimicrobial resistance is now a serious threat to public health, making it essential to recognize the shared responsibility in preventing resistance progression.

Promoting responsible use of antibiotics becomes crucial for maintaining the effectiveness of these medications and ensuring effective treatments in the future.

Implementing rational medical practices and appropriate usage protocols are important steps in addressing antimicrobial resistance and protecting public health.

Continuous education of healthcare professionals and the general public is essential in this regard.

Looking to the future, addressing antimicrobial resistance involves integrating efforts globally, including promoting responsible antibiotic prescribing practices, developing new antibiotics and innovative diagnostic technologies, and stimulating research to deeply understand resistance mechanisms and identify innovative therapeutic strategies.

Thus, in the context of medical evolution and antibiotic discovery, the future depends on the responsible use of these medications, promoting continuous research for the development of new antibiotics, and strengthening global collaboration.

References

1. **Abdelrazik E., El-Hadidi M.** (2023). Tracking Antibiotic Resistance from the Environment to Human Health. *Methods Mol Biol*, 2649:289-301. doi: 10.1007/978-1-0716-3072-3_15.
2. **Andersson, D.I., Hughes, D.** (2014). Microbiological effects of sublethal levels of antibiotics. *Nature Reviews Microbiology*, 12(7), 465-478.
3. **Baquero F.** (2021). Threats of antibiotic resistance: an obliged reappraisal. *Int Microbiol*, 24(4), 499-506. doi: 10.1007/s10123-021-00184-y.
4. **Bush, K., Courvalin, P., Dantas, G., Davies, J., Eisenstein, B., Huovinen, P., Paterson, D.L.** (2011). Tackling antibiotic resistance. *Nature Reviews Microbiology*, 9(12), 894-896.
5. **Carlet, J., Pulcini, C., Piddock, L.J., & members of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance** (2018). Antibiotic resistance: a geopolitical issue. *Clinical Microbiology and Infection*, 24(9), 808-810.
6. **Cocoş D.I., Folescu M., Orăşan-Alic S., Dumitrescu E., Cristina R.T.** (2023). Agenţii patogeni ESKAPE şi rezistenţa la antimicrobiene. *Veterinary Drug*, 17(2), 10-19.
7. **Cristina, R.T.** (2023). Despre: antibiorezistenţa în medicina Veterinară. *Veterinary Drug*, 17(2), 3-8.
8. **Davies, J., Davies, D.** (2010). Origins and Evolution of Antibiotic Resistance. *Microbiology and Molecular Biology Reviews*, 74(3), 417-433.
9. **Ding D., Wang B., Zhang X., Zhang J., Zhang H., Liu X., Gao Z., Yu Z.** (2023). The spread of antibiotic resistance to humans and potential protection strategies. *Ecotoxicol Environ Saf*, 1, 254:114734. doi: 10.1016/j.ecoenv.2023.114734.
10. **Doma O.A., Cristina R.T.** (2023). Data on the evolution of the resistance phenomenon to anti-infectives in 16 pig breeding units from Banat. *Veterinary Drug*, 17(2), 73-82.
11. **Holmes, A.H., Moore, L.S., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., Piddock, L. J.** (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet*, 387(10014), 176-187.
12. **Huemer M., Mairpady Shambat S., Brugger S.D., Zinkernagel A.S.** (2020). Antibiotic resistance and persistence- Implications for human health and treatment perspectives. *EMBO Rep.*, 21(12), e51034. doi: 10.15252/embr.202051034.
13. **Hughes, D., Andersson, D.I.** (2015). Evolutionary consequences of drug resistance: shared principles across diverse targets and organisms. *Nature Reviews Genetics*, 16(8), 459-471.
14. **Hutchings M.I., Truman A.W., Wilkinson B.** (2019). Antibiotics: past, present and future. *Curr Opin Microbiol*, 51, 72-80. doi: 10.1016/j.mib.2019.10.008.
15. **Klein, E.Y., Van Boeckel, T.P., Martinez, E. M., Pant, S., Gandra, S., Levin, S. A., Laxminarayan, R.** (2018). Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences*, 115(15), E3463-E3470.
16. **Larsson D.G.J., Flach C.F.** (2022). Antibiotic resistance in the environment. *Nat Rev Microbiol*, 20(5), 257-269. doi: 10.1038/s41579-021-00649-x.
17. **Laxminarayan, R.** (2019). The Coming Stewardship Crisis in Antimicrobial Resistance. *JAMA*, 321(20), 1971-1972.
18. **Lugagne J.B., Dunlop M.J.** (2022). Anticipating antibiotic resistance. *Science*, 25, 375(6583):818-819. doi: 10.1126/science. abn9969.
19. **O'Neill, J.** (2016). Tackling Drug-Resistant Infections Globally: Final Report and Recommendations. *Review on Antimicrobial Resistance*.
20. **Prestinaci, F., Pezzotti, P., Pantosti, A.** (2015). Antimicrobial resistance: a global multifaceted phenomenon. *Pathogens and Global Health*, 109(7), 309-318.

21. **Schmieder R, Edwards R.** (2012). Insights into Antibiotic Resistance Through Metagenomic Approaches. *Future Microbiology*, 7(1), 73-89.
22. **Spellberg, B., Blaser, M., Guidos, R.J., Boucher, H.W., Bradley, J.S., Eisenstein, B.I., Gilbert, D.N.** (2016). Combating Antimicrobial Resistance: Policy Recommendations to Save Lives. *Clinical Infectious Diseases*, 62(4), 479-483.
23. **Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D. L., Magrini, N.** (2018). Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *The Lancet Infectious Diseases*, 18(3), 318-327.
24. **Ventola, C.L.** (2015). The Antibiotic Resistance Crisis: Part 1: Causes and Threats. *Pharmacy and Therapeutics*, 40(4), 277.
25. **Ventola, C.L.** (2015). The Antibiotic Resistance Crisis: Part 2: Management Strategies and New Agents. *Pharmacy and Therapeutics*, 40(5), 344.
26. **Xiao R., Huang D., Du L., Song B., Yin L., Chen Y., Gao L., Li R., Huang H., Zeng G.** (2023). Antibiotic resistance in soil-plant systems: A review of the source, dissemination, influence factors, and potential exposure risks. *Sci Total Environ.* Apr 15, 869:161855. doi: 10.1016/j.scitotenv.2023.161855.