

BRIDGING THE GAP IN AMR: INTEGRATIVE CONTROL MEASURES FOR ANTIBIOTIC RESISTANCE IN HUMAN, ANIMAL AND ENVIRONMENTAL HEALTH

Cosmin ŞONEA¹, Dana TĂPĂLOAGĂ¹, Lucian ILIE¹,
Cristinel Gigi ŞONEA², Raluca-Aniela GHEORGHE-IRIMIA^{1#}, Elena-Nicoleta STANCIU¹, Paul-Rodian TĂPĂLOAGĂ¹

¹ University of Agronomic Sciences and Veterinary Medicine of Bucharest, 59 Mărăşti Blvd, District 1, Bucharest, Romania

² Ministry of Agriculture and Rural Development, Bucharest, Romania

REVIEW

Abstract

Antimicrobial resistance (AMR) represents a significant global health threat, driven by the improper use of antibiotics in human healthcare, veterinary medicine, and environmental systems. This review consolidates current evidence on the diverse factors contributing to AMR, emphasizing the interconnected nature of human, animal, and environmental health within the framework of the One Health approach. Proposed solutions to address AMR include prudent antibiotic usage, robust waste management strategies, the advancement of vaccines and alternative therapies, and widespread educational initiatives targeting both healthcare professionals and the general public. Furthermore, the review highlights the critical role of international collaboration in data sharing and the development of regulatory frameworks to monitor and control AMR effectively. By targeting the underlying drivers of resistance and implementing integrated strategies, stakeholders can collectively reduce the impact of resistant pathogens and protect global health. Special attention is needed in low- and middle-income countries, where the AMR problem is disproportionately high, underscoring the importance of equitable and coordinated action.

Keywords: Antimicrobial Resistance, One Health, antibiotics

#Corresponding author: raluca.irimia@fmv.usamv.ro

INTRODUCTION

Antimicrobial resistance (AMR) represents an escalating global health challenge, fuelled by the ability of microorganisms to withstand the antimicrobials that were once effective. The widespread and often inappropriate use of antimicrobial agents in clinical and agricultural settings has intensified this challenge, leading to infections that are becoming increasingly difficult to manage. Identified by the World Health Organisation (WHO) as one of the leading global public health threats, AMR could lead to an estimated 10 million deaths each year by 2050 if existing trends continue (Godinho, 2024). In addition to affecting personal health, AMR presents considerable challenges for healthcare systems, economies, and ecosystems (Vikesland et al., 2019; Ferri et al., 2015).

The intricacies of AMR arise from various elements, such as overprescription of antibiotics, inappropriate use in agriculture, and insufficient infection control measures. (Abbo &

Hooton, 2014, Brown et al., 2016; Saini et al., 2012). To tackle these challenges, it is essential to adopt a "One Health" approach that highlights the interrelation of human, animal, and environmental health (Matar et al., 2020).

The interconnected dynamics of AMR highlight the importance of understanding its transmission pathways and impacts. In agricultural contexts, antibiotic use not only fosters resistance in bacteria affecting livestock but also contaminates the environment, introducing resistant strains into ecosystems. These bacteria can enter the food supply and infect humans, complicating treatment efforts (Brown et al., 2016; Saini et al., 2012, Wang et al., 2023, Godinho, 2024; Wang et al., 2023, Vikesland et al., 2019; Wang et al., 2023).

Socioeconomic factors significantly influence the prevalence and control of AMR. In numerous low- and middle-income nations, the accessibility of over-the-counter antibiotics alongside insufficient healthcare infrastructure leads to misuse (Ayukekbong et al., 2017). The lack of awareness among healthcare providers and the general public about AMR poses significant challenges to prevention and

stewardship initiatives (Waseem et al., 2019; Abera et al., 2014; Kraker et al., 2011; Kraker et al., 2011; Waseem et al., 2019; Ferri et al., 2015).

The aim of this review is to explore the multifaceted drivers and impacts of AMR across human, animal, and environmental sectors, emphasizing the interconnected nature of the problem.

AMR ACROSS SECTORS

The misuse of antibiotics in healthcare drives AMR. These vital medications are misused due to overprescription, patient demand, and poor diagnostic tools. Studies show that many antibiotics are useless, especially for viral illnesses when they have no therapeutic benefit (Smit, 2023). Misuse fails to treat infections and selectively pressures bacterial populations, promoting resistance.

Lack of timely diagnostic tools worsens the issue. Empirical prescribing without bacterial illness typically leads to needless broad-spectrum antibiotic use, which increases resistance (Sjöström et al., 2020). Lack of information among healthcare providers regarding AMR's long-term effects perpetuates overuse and poor management (Waseem et al., 2019; Abera et al., 2014).

The clinical effects of AMR are significant. Resistant infections like MRSA and ESBL-producing *Escherichia coli* require sophisticated and expensive treatments with less effective or more hazardous alternatives (Kraker et al., 2011). AMR affects 33,000 Europeans annually, causing major economic and healthcare costs (Davies & Wales, 2019, Kasimanickam et al., 2021).

In many regions, antibiotics are administered not only to treat infections but also for growth promotion and disease prevention in healthy animals. These practices create selection pressure, encouraging the proliferation of resistant bacteria (Mshana et al., 2021; Tiseo et al., 2020).

Inadequate veterinary oversight and the indiscriminate use of antimicrobials exacerbate the problem. Resistant strains originating in animals can be transmitted to humans through direct contact, consumption of contaminated meat products, or environmental exposure (Smith et al., 2023; Rhouma et al., 2022). Moreover, antibiotic use in companion animals is a growing concern, as misuse by pet owners contributes to resistance in pathogens that can

cross the human-animal interface (Delalay et al., 2020).

The environmental impact of antibiotic use in agriculture is also significant. Resistant bacteria from livestock waste can contaminate soil and water systems, creating hotspots for resistance development (Nhung et al., 2015; Holvoet et al., 2013). Intensive farming practices with poor biosecurity measures further amplify the problem, necessitating stricter regulations and surveillance systems (Amin et al., 2020; Rhouma et al., 2022; Şonea, 2023a; Şonea, 2023b; Gheorghe-Irimia, 2023).

Agricultural runoff, hospital wastewater, and untreated sewage introduce resistant bacteria into natural ecosystems, where they persist and propagate (Holvoet et al., 2013; Guenther et al., 2011). Water systems, in particular, play a critical role in AMR dissemination. Contaminated water bodies not only affect aquatic ecosystems but also pose significant risks to human populations that rely on them for drinking and irrigation (Holvoet et al., 2013).

Soil contamination is another critical pathway. The application of manure from treated livestock can introduce resistant bacteria into agricultural soils, facilitating horizontal gene transfer and further resistance development within microbial communities (Nhung et al., 2015; Guenther et al., 2011). These bacteria can then affect crops, which may serve as another vector for AMR transmission to humans.

STRATEGIES FOR ANTIMICROBIAL RESISTANCE (AMR) REDUCTION

A critical strategy in combating AMR is ensuring antibiotics are used responsibly and only when necessary. This involves selecting the appropriate drug tailored to the specific infection. Evidence demonstrates that antimicrobial stewardship interventions, such as educational campaigns and clinical guidelines, can significantly improve antibiotic prescribing practices (Durkin et al., 2018; Gerber et al., 2013). For example, simple measures like displaying informational posters in outpatient clinics have successfully reduced inappropriate prescriptions for conditions like acute respiratory tract infections (Durkin et al., 2018).

Additionally, adopting a "wait-and-see" approach, where antibiotics are delayed unless clinically warranted, has been shown to lower unnecessary antibiotic use while encouraging

patients to understand their appropriate application (Liu et al., 2019). Establishing stringent prescribing guidelines across healthcare and veterinary sectors is essential. In healthcare, implementing protocols that include regular audits and feedback mechanisms can help ensure adherence to evidence-based prescribing practices (Bello et al., 2021; Alkhuzaei et al., 2018). In veterinary medicine, regulations should restrict antibiotic use to prescription by licensed veterinarians and prohibit their application as growth promoters in livestock (Wilkinson et al., 2018).

Educational campaigns targeting both healthcare providers and the public are vital in fostering responsible antibiotic use. Research indicates that such interventions can significantly reduce antibiotic consumption (Velden et al., 2013; Zetts et al., 2020). For example, public awareness initiatives can inform individuals about the dangers of antibiotic misuse, while healthcare providers benefit from continuous training on stewardship principles, including appropriate prescribing and the use of diagnostic tools.

For healthcare professionals and farmers, tailored training programs are crucial. Healthcare providers should receive ongoing education on stewardship practices, while farmers should be trained in responsible antibiotic use under veterinary supervision. Collaborative initiatives that bring together these stakeholders can advance the One Health approach to addressing AMR (Watkins et al., 2019; Alkhuzaei et al., 2018).

Effective prevention of antimicrobial resistance (AMR) dissemination via environmental pathways necessitates the implementation of comprehensive waste management systems across healthcare, agricultural, and industrial sectors. Hospitals have effectively reduced environmental contamination by adopting engineering controls, including closed-system transfer devices (CSTDs) (Sessink, 2024). In agriculture, effective management of waste products, including composting and anaerobic digestion, can reduce the effects of antibiotic residues on soil and water systems (Watkins et al., 2019; Sessink, 2024).

Vaccination is essential for infection prevention and decreasing dependence on antibiotics. Vaccination against bacterial diseases can markedly reduce the occurrence of infections necessitating antibiotic intervention. Investment in vaccine research is essential,

especially for diseases lacking effective vaccines (Alanazi, 2023).

Vaccines in agriculture can effectively prevent diseases in livestock, thereby reducing the reliance on antibiotics. Alternative therapies, including probiotics, bacteriophage therapy, and herbal remedies, demonstrate potential in preventing or treating infections and mitigating the risk of resistance development (Alanazi, 2023; Tudor, 2023). Investigation into these alternatives should emphasise their effectiveness in both human and veterinary medicine.

Countries must share surveillance data, best practices, and strategies for antibiotic regulation and resistance management. International organizations, such as the World Health Organization (WHO) and the Food and Agriculture Organization (FAO), provide critical frameworks for addressing AMR, offering resources to standardize interventions worldwide (Alanazi, 2023; Gerber et al., 2013).

Collaboration is particularly crucial for addressing socioeconomic disparities in low- and middle-income countries, where the AMR burden is often highest. Strengthening global research efforts to develop new antibiotics and alternatives, coupled with monitoring and regulating antibiotic use, is essential for mitigating the impact of AMR on public health systems (Alanazi, 2023; Gerber et al., 2013).

CONCLUSIONS

Antimicrobial resistance (AMR) represents a complex global health challenge that demands urgent, collaborative, and thorough intervention. To tackle this challenge, it is essential to combine efforts across human, animal, and environmental health using a holistic approach. Essential strategies, including careful antibiotic administration, effective waste management, vaccination efforts, and the creation of alternative therapies, should be integrated with educational initiatives to enhance awareness and encourage behavioural transformation. Moreover, international cooperation is crucial for developing regulatory frameworks, exchanging surveillance data, and assisting low- and middle-income countries that are disproportionately impacted by AMR. Through the application of these strategies, stakeholders can reduce the effects of AMR, protect the effectiveness of antimicrobials, and secure sustainable public health results for future generations.

REFERENCES

- Abbo, L. & Hooton, T., 2014. Antimicrobial stewardship and urinary tract infections. *Antibiotics*, 3(2), 174-192. <https://doi.org/10.3390/antibiotics3020174>
- Abera, B., Kibret, M. & Mulu, W., 2014. Knowledge and beliefs on antimicrobial resistance among physicians and nurses in hospitals in Amhara region, Ethiopia. *BMC Pharmacology and Toxicology*, 15(1). <https://doi.org/10.1186/2050-6511-15-26>
- Alanazi, A., 2023. Impact of antibiotic de-escalation on antibiotic consumption, length of hospitalization, mortality, and cost: a systematic review and meta-analysis. *Pharmacoepidemiology*, 2(4), 289-306. <https://doi.org/10.3390/pharma2040025>
- Alkhuzaei, A., Salama, R., Eljak, I., Chehab, M. & Selim, N., 2018. Perceptions and practice of physicians and pharmacists regarding antibiotic misuse at primary health centres in Qatar: A cross-sectional study. *Journal of Taibah University Medical Sciences*, 13(1), 77-82. <https://doi.org/10.1016/j.jtumed.2017.09.001>
- Amin, A., Hoque, M., Siddiki, A., Saha, S. & Mm, K., 2020. Antimicrobial resistance situation in animal health of Bangladesh. *Veterinary World*, 13(12), 2713-2727. <https://doi.org/10.14202/vetworld.2020.2713-2727>
- Ayukekbong, J., Ntemgwa, M. & Atabe, A., 2017. The threat of antimicrobial resistance in developing countries: causes and control strategies. *Antimicrobial Resistance and Infection Control*, 6(1). <https://doi.org/10.1186/s13756-017-0208-x>
- Bello, S., Aliyu, F., Yusuf, H. & Aliyu, B., 2021. Evaluation of knowledge, attitudes and practices of human healthcare students about antimicrobial drug use and resistance: A cross-sectional study in University of Maiduguri, Nigeria. *Journal of Pharmacy & Bioresources*, 18(3), 182-191. <https://doi.org/10.4314/jpb.v18i3.2>
- Brown, A., Grass, J., Richardson, L., Nisler, A., Bicknese, A. & Gould, L., 2016. Antimicrobial resistance in Salmonella that caused foodborne disease outbreaks: United States, 2003–2012. *Epidemiology and Infection*, 145(4), 766-774. <https://doi.org/10.1017/s0950268816002867>
- Davies, R. & Wales, A., 2019. Antimicrobial resistance on farms: A review including biosecurity and the potential role of disinfectants in resistance selection. *Comprehensive Reviews in Food Science and Food Safety*, 18(3), 753-774. <https://doi.org/10.1111/1541-4337.12438>
- Delalay, G., Berezowski, J., Diserens, N. & Schmidt-Posthaus, H., 2020. An understated danger: Antimicrobial resistance in aquaculture and pet fish in Switzerland, a retrospective study from 2000 to 2017. *Journal of Fish Diseases*, 43(10), 1299-1315. <https://doi.org/10.1111/jfd.13234>
- Durkin, M., Jafarzadeh, S., Hsueh, K., Sallah, Y., Munshi, K., Henderson, R., ... & Fraser, V., 2018. Outpatient antibiotic prescription trends in the United States: A national cohort study. *Infection Control and Hospital Epidemiology*, 39(5), 584-589. <https://doi.org/10.1017/ice.2018.26>
- Ferri, M., Ranucci, E., Romagnoli, P. & Giaccone, V., 2015. Antimicrobial resistance: A global emerging threat to public health systems. *Critical Reviews in Food Science and Nutrition*, 57(13), 2857-2876. <https://doi.org/10.1080/10408398.2015.1077192>
- Gerber, J., Prasad, P., Fiks, A., Localio, A., Grundmeier, R., Bell, L., ... & Zautis, T., 2013. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians. *JAMA*, 309(22), 2345. <https://doi.org/10.1001/jama.2013.6287>
- Gheorghe-Irimia, R. A., Tapaloaga, D., Sonea, C., Ilie, L. I., & Tapaloaga, P., 2023. Chicken meat production trends in Romania – A twelve-year forecast. *Annals of "Valahia" University of Târgoviște. Agriculture*, 15(1), 6–8. <https://doi.org/10.2478/aqr-2023-0002>
- Godinho, O., 2024. Antibiotic-resistant bacteria across a wastewater treatment plant. *Applied Microbiology*, 4(1), 364-375. <https://doi.org/10.3390/applmicrobiol4010025>
- Guenther, S., Ewers, C. & Wieler, L., 2011. Extended-spectrum beta-lactamases producing *E. coli* in wildlife, yet another form of environmental pollution? *Frontiers in Microbiology*, 2. <https://doi.org/10.3389/fmicb.2011.00246>
- Elger sma, A., 2015. Grazing increases the unsaturated fatty acid concentration of milk from grass-fed cows: A review of the contributing factors, challenges and future perspectives. *Eur J Lipid Sci Technol*. 117(9), 1345-1369.
- Holvoet, K., Sampers, I., Callens, B., Dewulf, J. & Uyttendaele, M., 2013. Moderate prevalence of antimicrobial resistance in *Escherichia coli* isolates from lettuce, irrigation water, and soil. *Applied and Environmental Microbiology*, 79(21), 6677-6683. <https://doi.org/10.1128/aem.01995-13>
- Kasimanickam, V., Kasimanickam, M. & Kasimanickam, R., 2021. Antibiotics use in food animal production: Escalation of antimicrobial resistance: Where are we now in combating AMR? *Medical Sciences*, 9(1), 14. <https://doi.org/10.3390/medsci9010014>
- Kraker, M., Davey, P. & Grundmann, H., 2011. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: Estimating the burden of antibiotic resistance in Europe. *PLOS Medicine*, 8(10), e1001104. <https://doi.org/10.1371/journal.pmed.1001104>
- Liu, C., Liu, G., Wang, D. & Zhang, X., 2019. Intrinsic and external determinants of antibiotic prescribing: A multi-level path analysis of primary care prescriptions in Hubei, China. *Antimicrobial Resistance and Infection Control*, 8(1). <https://doi.org/10.1186/s13756-019-0592-5>
- Matar, G., Andreumont, A. & Bazzi, W., 2020. Editorial: Combating antimicrobial resistance - A One Health approach. *Frontiers in Cellular and Infection Microbiology*, 9. <https://doi.org/10.3389/fcimb.2019.00458>
- Mshana, S., Sindato, C., Matee, M. & Mboera, L., 2021. Antimicrobial use and resistance in agriculture and food production systems in Africa: A systematic review. *Antibiotics*, 10(8), 976. <https://doi.org/10.3390/antibiotics10080976>
- Nhung, N., Cuong, N., Campbell, J., Hoa, N., Bryant, J., Truc, V., ... & Carrique-Mas, J., 2015. High levels of antimicrobial resistance among *Escherichia*

- coli* isolates from livestock farms and synanthropic rats and shrews in the Mekong Delta of Vietnam. *Applied and Environmental Microbiology*, 81(3), 812-820. <https://doi.org/10.1128/aem.03366-14>
- Rhouma, M., Soufi, L., Cenatus, S., Archambault, M. & Butaye, P., 2022. Current insights regarding the role of farm animals in the spread of antimicrobial resistance from a One Health perspective. *Veterinary Sciences*, 9(9), 480. <https://doi.org/10.3390/vetsci9090480>
- Saini, V., McClure, J., Scholl, D., DeVries, T. & Barkema, H., 2012. Herd-level association between antimicrobial use and antimicrobial resistance in bovine mastitis *Staphylococcus aureus* isolates on Canadian dairy farms. *Journal of Dairy Science*, 95(4), 1921-1929. <https://doi.org/10.3168/jds.2011-5065>
- Sessink, P., 2024. Evaluation of environmental antibiotic contamination by surface wipe sampling in a large care centre. *Journal of Antimicrobial Chemotherapy*, 79(7), 1637-1644. <https://doi.org/10.1093/jac/dkae159>
- Sjöström, K., Hickman, R., Tepper, V., Antillón, G., Järhult, J., Emanuelson, U., ... & Lewerin, S., 2020. Antimicrobial resistance patterns in organic and conventional dairy herds in Sweden. *Antibiotics*, 9(11), 834. <https://doi.org/10.3390/antibiotics9110834>
- Smit, C., 2023. One Health determinants of *Escherichia coli* antimicrobial resistance in humans in the community: An umbrella review. *International Journal of Molecular Sciences*, 24(24), 17204. <https://doi.org/10.3390/ijms242417204>
- Smith, R., May, H., AbuOun, M., Stubberfield, E., Gilson, D., Chau, K., ... & Anjum, M., 2023. A longitudinal study reveals persistence of antimicrobial resistance on livestock farms is not due to antimicrobial usage alone. *Frontiers in Microbiology*, 14. <https://doi.org/10.3389/fmicb.2023.1070340>
- Şonea, C., Gheorghe-Irimia, R. A., Tapaloaga, D., Gurau, M. R., Udrea, L., & Tapaloaga, P., 2023a. Optimizing animal nutrition and sustainability through precision feeding: A mini review of emerging strategies and technologies. *Annals of "Valahia" University of Târgoviște. Agriculture*, 15(2), 7-11. <https://doi.org/10.2478/agr-2023-0011>
- Şonea, C., Gheorghe-Irimia, R., Tăpăloagă, D., & Tăpăloagă, P., 2023b. Nutrition and animal agriculture in the 21st century: A review of future prospects. *Annals of the University of Craiova - Agriculture Montanology Cadastre Series*, 53(1), 303-312. <https://doi.org/10.52846/aamc.v53i1.1482>
- Tiseo, K., Huber, L., Gilbert, M., Robinson, T. & Boeckel, T., 2020. Global trends in antimicrobial use in food animals from 2017 to 2030. *Antibiotics*, 9(12), 918. <https://doi.org/10.3390/antibiotics9120918>
- Tudor, L., Pițuru, M. T., Gheorghe-Irimia, R. A., Şonea, C., & Tăpăloagă, D., 2023. Optimizing milk production, quality and safety through essential oil applications. *Farmacia*, 71(5), 900-910. <https://doi.org/10.31925/farmacia.2023.5.3>
- Velden, A., Duerden, M., Bell, J., Oxford, J., Altiner, A., Kozlov, R., ... & Essack, S., 2013. Prescriber and patient responsibilities in treatment of acute respiratory tract infections — Essential for conservation of antibiotics. *Antibiotics*, 2(2), 316-327. <https://doi.org/10.3390/antibiotics2020316>
- Vikesland, P., Garner, E., Gupta, S., Kang, S., Maile-Moskowitz, A. & Zhu, N., 2019. Differential drivers of antimicrobial resistance across the world. *Accounts of Chemical Research*, 52(4), 916-924. <https://doi.org/10.1021/acs.accounts.8b00643>
- Wang, W., Weng, Y., Luo, T., Wang, Q., Yang, G. & Jin, Y., 2023. Antimicrobials and the resistances in the environment: Ecological and health risks, influencing factors, and mitigation strategies. *Toxics*, 11(2), 185. <https://doi.org/10.3390/toxics11020185>
- Waseem, H., Ali, J., Sarwar, F., Khan, A., Rehman, H., Choudri, M., ... & Ali, M., 2019. Assessment of knowledge and attitude trends towards antimicrobial resistance (AMR) among the community members, pharmacists/pharmacy owners and physicians in District Sialkot, Pakistan. *Antimicrobial Resistance and Infection Control*, 8(1). <https://doi.org/10.1186/s13756-019-0517-3>
- Watkins, J., Wagner, F., Gómez-Olivé, F., Wertheim, H., Sankoh, O. & Kinsman, J., 2019. Rural South African community perceptions of antibiotic access and use: Qualitative evidence from a health and demographic surveillance system site. *American Journal of Tropical Medicine and Hygiene*, 100(6), 1378-1390. <https://doi.org/10.4269/ajtmh.18-0171>
- Wilkinson, A., Ebata, A. & MacGregor, H., 2018. Interventions to reduce antibiotic prescribing in LMICs: A scoping review of evidence from human and animal health systems. *Antibiotics*, 8(1), 2. <https://doi.org/10.3390/antibiotics8010002>
- Zetts, R., García, A., Doctor, J., Gerber, J., Linder, J. & Hyun, D., 2020. Primary care physicians' attitudes and perceptions towards antibiotic resistance and antibiotic stewardship: A national survey. *Open Forum Infectious Diseases*, 7(7). <https://doi.org/10.1093/ofid/ofaa244>