REVIEW ARTICLE

Antimicrobial Resistance in Human Health: A Comprehensive Review of One Health Approach

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Received on: 18 March 2024; *Accepted on:* 10 April 2024; *Published on:* 18 April 2024

Abstract

Antimicrobial resistance (AMR) poses a complex and interconnected global challenge affecting human health, animal health, and the environment. This comprehensive review explores the multifaceted dimensions of AMR and highlights the pivotal role of the One Health approach in addressing this pressing issue. The discussion emphasizes evidence-based strategies, integrated surveillance, and effective communication to inform decision-making and policy formulation. Furthermore, the economic implications of AMR and the need for a paradigm shift toward holistic One Health models are examined. The World Health Organization's (WHO) Global Action Plan and stakeholder engagement across various sectors are emphasized as critical components of AMR control. The review also delves into the importance of research and surveillance in understanding AMR drivers and developing alternatives to antibiotics. Promising approaches, such as microbiota modulation, gene editing, vaccines, antivirulence inhibitors, and bacteriophages, are explored as innovative means to combat AMR. Overall, this review underscores the urgency of a coordinated, multidisciplinary One Health approach in mitigating the global threat of AMR.

Keywords: Antimicrobial resistance, Eco-epidemiology, Interconnected, One health, Threat.

Bengal Physician Journal (2024): 10.5005/jp-journals-10070-8039

Introduction

Antibiotic resistance (AMR) stands as one of the most pressing global health challenges of our time. It is a complex issue that is deeply intertwined with human, animal, and environmental factors. This chapter delves into the latest developments in AMR with a focus on human health and the One Health approach—A comprehensive and integrated strategy that recognizes the interconnectedness of human, animal, and environmental health.

The One Health Paradigm: A Holistic Approach to AMR

In recent years, the One Health paradigm has gained prominence as a holistic approach to addressing AMR. The One Health approach underscores the need for multidisciplinary and multisectoral collaboration, aligning seamlessly with the overarching principles of the One Health concept.[1] One Health recognizes the inherent interconnectedness between humans, animals, and the environment and seeks to enhance overall community health and well-being through integrated efforts.

Prominent international organizations, including the International Monetary Fund (IMF), the World Bank, the World Health Organization (WHO), and the G8, have officially recognized AMR as a significant global health concern. These organizations have reached a consensus that tackling AMR requires a collaborative and interdisciplinary approach, acknowledging the role of multiple ecosystems in the development, emergence, and spread of AMR.[2]

Local and Global Dynamics of AMR

The dissemination of AMR is influenced by a myriad of factors, ranging from socioeconomic drivers like world trade, conflict, displacement, and travel, to local factors like contaminated habitats and inadequate infection control measures. Both the irrational use of antibiotics in human and animal populations and the presence of drug residues or resistance genes in the environment contribute to the local and worldwide spread of AMR.[3,4]

Antibiotic resistance is not confined to a single domain; it extends across various environmental reservoirs, including soil, water, hospital settings, industrial areas, farm waste, and polluted

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How to cite this article: Samajdar SS, Chatterjee N, Sarkar S, *et al.* Antimicrobial Resistance in Human Health: A Comprehensive Review of One Health Approach. Bengal Physician Journal 2024;11(1):18–23.

Source of support: Nil

Conflict of interest: Dr Nandini Chatterjee, Dr Jyotirmoy Pal and Dr Shashank R Joshi are associated as the Editorial board members of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of these Editorial board members and their research group.

ecological niches. These reservoirs play a crucial role in the persistence and propagation of AMR.[3,5]

While there is a consensus on the interconnectedness of AMR with human, animal, and environmental health, some scholars have questioned the extent of the contribution of animal agriculture to the AMR challenge, citing a lack of evidence linking livestock or aquaculture-related diseases to human cases.[6]

One Health as a Strategy for Tackling AMR

One promising strategy for combating AMR is the adoption of a comprehensive and integrated One Health approach. This approach, championed by figures like Lord Jim O'Neill and Holmes et al., recognizes that the growth of the human population is intrinsically linked to climate change and resource depletion, necessitating collaboration among diverse fields of study to safeguard global health security.[7,8]

Within the context of AMR, the health of humans is intricately intertwined with that of animals and the environment. This interconnectedness is especially significant in light of the rising prevalence of multidrug-resistant (MDR) superbugs like *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*, which impose a substantial burden on global public health.[9]

In this regard, the United Nations has also recognized the gravity of the AMR challenge, with reports of hundreds of thousands of infant deaths attributed to sepsis caused by MDR pathogens.[10]

We will provide an in-depth exploration of the "One Health One World" perspective on AMR, highlighting its multifaceted and multisectoral nature. It sheds light on the challenges associated with implementing the One Health strategy to contain AMR at both local and global levels.

Furthermore, it offers a comprehensive summary of the key recommendations and action plan established by the Tripartite's commitment, comprising the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and the WHO. These guidelines and action plans aim to effectively manage zoonotic diseases and AMR.[11–14]

The overarching goal of this chapter is to provide a comprehensive understanding of the various domains encompassed within the One Health approach, specifically in the context of AMR. It also underscores the critical role of surveillance, awareness, education, policy decisions, and workforce training in mitigating AMR within the One Health framework.

Precision in Terminology: Antibiotic-resistant Bacteria

To maintain precision in terminology, it is advised, following the WHO recommendations, to use the term "antibiotic-resistant bacteria" (ABR) exclusively to refer to bacteria that have developed resistance to antibiotics, as opposed to implying antibiotic resistance in people and animals themselves.[14]

We will delve into the molecular epidemiology and genetic relatedness of AMR in the human–animal–environment interface, the strategies for surveillance, and the political recognition of AMR as a One Health concern. It will also explore the interplay between antibiotics and the interconnected dimensions of the One Health triad.

Antibiotic Use in Human and Veterinary Medicine

The utilization of antibiotics holds a central position in the realm of medicine, encompassing both human and veterinary contexts. In human medicine, antibiotics are predominantly employed for clinical infections and as prophylactic measures, typically in post-surgical scenarios. The administration of antibiotics to humans is often reserved for treating severe contagious illnesses, and even in such cases, they are prescribed selectively to individuals with intimate and extended exposure to infected individuals.[15]

In stark contrast, the veterinary landscape exhibits notable distinctions in antibiotic use when comparing pets and food-producing animals. The application of antibiotics in pets closely mirrors human medical practices.[16] They are used for treating clinical diseases and, to a lesser extent, as prophylactics in certain situations.[17]

However, in the context of food-producing animals, the scenario diverges significantly. Antibiotics are not only used therapeutically, but also as feed additives and growth promoters. For instance, in poultry farming, antibiotics are frequently administered prophylactically, without specific therapeutic grounds, to the entire group through water or feed. This practice is commonplace in broilers, layers, and pig pens.[18,19]

Prophylactic Use of Antibiotics in Veterinary Medicine

Prophylactic antibiotic use in veterinary medicine is recommended in situations where there is a significant risk of bacterial infections, often arising from factors such as the introduction of new animals, overcrowded or unsanitary conditions, transportation stress, and age-related vulnerabilities.[20] However, this prophylactic approach is a double-edged sword, as it has been recognized as a significant contributor to the development of antibiotic resistance.

The practice of administering antibiotics as growth promoters in animals, especially in food production, has been strongly linked to the emergence of antibiotic resistance. This is primarily attributed to the sub-therapeutic use of antibiotics over extended durations. Such conditions foster the emergence and dissemination of drug-resistant microorganisms within animal populations and across different animal groups. Importantly, these drug-resistant microorganisms can find their way into human populations through environmental sources or the animal food chain.[19]

Economic Considerations and Shifting Practices

The use of antibiotics as growth promoters in poultry production, for instance, has been associated with economic benefits ranging from 1 to 10%. However, these advantages are primarily derived from the prophylactic aspect of antibiotics rather than substantial improvements in feed efficiency or production gains. As a result, some major poultry production companies are now advocating for the sale of antibiotic-free chicken products.[21]

In the realm of aquaculture, where the transfer of fish from hatchery to farms is a critical phase, concerns over antibiotic use have been extensively studied. Researchers have pointed out that antibiotics are sometimes employed to compensate for deficiencies in hygiene practices, suboptimal housing conditions, and inadequate animal health management.[22] Recognizing the gravity of this issue, the FAO, OIE, and the WHO have jointly advised against the use of antibiotics for the purpose of promoting growth in order to address the escalating problem of antibiotic resistance.

Global Antibiotic Consumption and the One Health Perspective

The global distribution of AMR through the lens of the One Health approach reveals numerous interconnected factors contributing to the proliferation of antibiotic resistance genes (ARGs) and AMR. These factors encompass intensive food production, globalization of food distribution, international travel, climate change, population growth, urbanization, and the release of non-metabolized antibiotics or their remnants into the environment.

These variables exert genetic selection pressure on bacteria, leading to the vertical and horizontal transmission of drug resistance genes among bacteria of various origins. This dynamic contributes to the dispersion of ARGs in the environment and facilitates the dissemination of MDR pathogens within communities.

Despite national and international restrictions on antibiotic use, global antibiotic consumption witnessed a substantial increase between 2000 and 2015. Predictions indicate a doubling of consumption by 2030, with low- and middle-income countries (LMICs) expected to experience the most significant surge due to development initiatives and improved healthcare accessibility. The sale of antibiotics without prescriptions, especially common in LMICs, contributes to the proliferation of ABR.[23]

Antibiotics in Animal Agriculture

Antibiotics are also extensively used in animal agriculture, with approximately two-thirds of all antibiotics consumed worldwide allocated to this sector. The intensification of meat consumption driven by rising incomes in LMICs has led to increased demand for antibiotics in animal agriculture.[24]

For example, the United States has witnessed a significant surge in antibiotic consumption, with approximately 80% of these antibiotics used for fish farming and cattle production. The management of waste in cattle farming has proven inadequate in eradicating resilient superbugs and ARGs, raising concerns about the transmission of these pathogens and genetic elements through water and soil. This phenomenon contributes to the increasing prevalence of MDR diseases in humans.[25]

Addressing the intricate interplay between antibiotic use in human and veterinary medicine, and its impact on AMR, is essential within the One Health framework. Understanding how superbugs and ARGs are maintained, survive, and transmit at the interface between the environment and human populations is crucial for developing effective strategies to combat AMR.[26]

Antimicrobial resistance poses a substantial threat to public health worldwide, affecting both developed and underdeveloped countries. Among the various pollutants contributing to AMR, heavy metals and biocides have emerged as significant concerns, especially in livestock production. These pollutants not only exert selective pressure, promoting ARGs but also facilitate horizontal gene transfer among bacteria. Understanding the role of heavy metals and biocides in AMR selection and dissemination is critical, and stringent measures are required to minimize metal-induced co-selection of ARGs. The global increase in economic activity in LMICs has led to a surge in antibiotic consumption, elevating the risk of AMR development. Pathogens with antibiotic resistance can enter natural ecosystems through human and animal waste, contaminating the environment. Addressing this challenge requires public health interventions to improve water and food quality and enhance sewage disposal in emerging economies.

Wastewater treatment plants, drinking water sources, and coastal waters have become reservoirs for AMR genes and microbes. The dissemination and management of AMR in these environments are challenging, as evidenced by the similarity between AMR gene profiles in wastewater treatment plants and clinical settings. To mitigate this issue, guidelines should define threshold levels for ABR bacteria and genes to ensure safe drinking water and sewage disposal.

Drug residues in wastewater can also contribute to water pollution, necessitating the development of rapidly degradable antibiotics and improved wastewater treatment techniques. On-site wastewater treatment plants can play a crucial role in reducing antibiotic levels, ABR, and ARGs downstream.

Environmental alterations, both natural and human-induced, can significantly impact the spread of antibiotic resistance. Factors such as weather patterns, ocean variations, and natural disasters can alter the distribution of pathogenic bacteria, including antibiotic-resistant strains. These phenomena require further investigation to understand their role in AMR and MDR pathogen dissemination.[27]

Antibiotic Resistance Mechanisms in Bacteria

Bacteria employ two primary mechanisms to resist antibiotics: intrinsic resistance and acquired resistance. Intrinsic resistance is based on the bacteria's inherent functional characteristics or structural components that make them less susceptible to antibiotics. For instance, some bacteria have insensitive targets for specific antibiotics, rendering them ineffective. Intrinsic resistance can also involve barriers preventing antibiotics from crossing the bacterial membrane.

Acquired resistance, on the other hand, occurs when bacteria acquire resistance mechanisms from external sources. This type of resistance can result from inadequate antibiotic penetration, drug efflux systems reducing antibiotic concentrations within the cell, target modification, or antibiotic inactivation/hydrolysis. Acquired resistance has become increasingly prevalent, with enzymes like extended-spectrum β-lactamases (ESBLs) and metallo-β-lactamases (MBLs) playing key roles in resistance against cephalosporins and carbapenems.[28]

Estimation of ABR in a One Health Context

Understanding the extent of antibiotic resistance at the human–animal–environment interfaces is crucial for implementing effective control measures. Whole-genome sequencing (WGS) has emerged as a valuable tool for estimating antibiotic resistance in these interfaces. Large genomic datasets have revealed connections between *E. coli* outbreaks and contaminated animal and plant food products. The WGS-based genetic relatedness analysis among isolates from various sources aids in understanding potential transmission routes.

Metagenome sequencing, which detects the entire genetic material in a sample, offers an alternative approach. However, its sensitivity depends on sample composition and sequencing procedures. Target-based sequencing with specific probes for different ARGs can enhance its accuracy. Metagenomics, combined with innovative techniques like metagenome Hi-C, provides insights into pathogen-ARG associations.

Accurate metadata recording following harmonized procedures is essential for comprehensive understanding and monitoring of antibiotic resistance within the One Health framework. Maintenance and Dissemination of Drug-Resistant Bacterial Clones at the human–animal–environment Interface. Drug-resistant bacterial clones can be maintained and disseminated across the human–animal–environment interface, driven by factors such as antibiotic exposure, genetic background, and fitness costs. Mobile genetic elements (MGEs) play a crucial role in the dissemination of resistance. For example, *K. pneumoniae* acts as a host for various mobile ABR genes, facilitating their spread across different One Health domains.[23,26]

High-risk ABR clones are often spread through animal–human contact and diverse farm animal populations. Cross-species ABR transmission is rare, but certain clones act as shuttles of ABR, infecting, and colonizing both humans and animals. Studies have revealed limited relatedness of MDR bacterial pathogens at the human–animal interface, suggesting that ABR transmission patterns vary based on factors like geographic location and genetic diversity.

Risks of ABR for Public, Animal, and Environmental Health

Antimicrobial resistance significantly reduces the efficacy of antibiotics, leading to increased infection rates, and severity. In animals, misuse of antibiotics contributes to ABR, affecting both livestock and companion animals. Public health risks arise from the transmission of ABR bacteria through food, water, and direct contact. Non-typhoidal *Salmonella* and *Campylobacter*, among others, are foodborne pathogens associated with ABR, posing a substantial public health risk. Additionally, MRSA infections, both in healthcare and community settings, are a growing concern.

In the environmental context, ABR microbes and genes originate from sources like soil and water, with human activities amplifying the "global resistome." Inadequate sewage and pharmaceutical waste treatment release antibiotics into water sources, contributing to the transmission of resistance genes and bacteria. International travel and trade further facilitate the global dissemination of resistance.[28]

Antimicrobial Resistance and One Health in Low and Middle-income Countries (LMICs)

Low- and middle-income countries face unique challenges in combatting AMR due to the convergence of factors such as economic growth, antibiotic misuse, and inadequate healthcare infrastructure. Misuse of antibiotics in veterinary practice, especially as growth promoters, has led to the emergence of MDR pathogens in animals. Occupational risks for individuals handling animals are high, highlighting the need for a One Health approach.

To address these challenges, a multidimensional One Health approach involving human and animal health, food production, and environmental factors is essential. Collaborative efforts, including the FAO–OIE–WHO alliance, aim to mitigate the global threat of AMR by fostering integrated surveillance systems and control measures across the animal–human–environment nexus.

In conclusion, the global challenge of AMR poses a significant threat to human health, animal health, and the environment. The One Health approach, which recognizes the interconnectedness of these domains, has emerged as a critical strategy in combating AMR. The FAO–OIE–WHO action plan,[11–14] as well as initiatives like the global antibiotic resistance partnership (GARP), underscore the importance of evidence-based eco-epidemiology, integrated surveillance, and reporting in the fight against AMR. Moreover, communication to raise awareness among the masses and the promotion of good practices such as biosecurity, agro-ecology, and alternatives to antibiotics are essential components of this approach.

Economics plays a pivotal role in addressing AMR. Economic development and technology influence the distribution of AMR, making it imperative for organizations like the World Economic Forum to contribute by establishing regulations, infrastructure, and public health interventions. Policymakers are tasked with implementing measures across various sectors, including travel and tourism, food and agriculture, and healthcare, to control AMR effectively.

अयं निजः परो वेति गणना लघुचेतसाम्।
उदारचरितानां तु वसुधैव कुटुम्बकम्।

Fig. 1: The shloka from Maha Upanishad, chapter 6, verse 71

The transition from the current health paradigm to the One Health model is challenging but essential. A thorough assessment of net benefits is crucial in this transformation, emphasizing the efficient use of resources and the comparative analysis of marginal benefits vs VPS marginal costs. Reduction in disease burden and decreased incidence/prevalence rates are potential outcomes of the One Health paradigm, and these can be evaluated using economic standard methods.

The WHO's Global Action Plan, based on the One Health approach, serves as a guideline for nations worldwide in their efforts to combat AMR. Awareness, understanding, and engagement of all stakeholders in One Health, including clinicians, veterinarians, farmers, industrialists, and policymakers, are imperative to reduce antibiotic usage and curb the spread of AMR. Evidence-based research and surveillance are essential to recognize the drivers of AMR, develop cost-effective alternatives to antibiotics, and support antibiotic stewardship.[29]

Hygiene and sanitation are crucial in healthcare settings to control infections, while prudent antibiotic use is vital in veterinary and farm settings. Control measures to improve food and water quality can reduce the dissemination of resistant pathogens and ARGs. Monitoring antibiotic consumption and continuous efforts to improve antibiotic utilization are critical components of AMR management.[13]

Furthermore, exploring alternatives to antibiotics is essential. Microbiota modulation, gene editing techniques, vaccines, AV (antivirulence) inhibitors, and bacteriophages offer promising avenues to control resistant bacterial pathogens. These approaches, when combined with advanced genomic tools and sequencing techniques, provide new opportunities to combat AMR effectively.[30]

Despite the progress made, numerous challenges remain, including motivation inadequacy, limited awareness, and malpractices in antibiotic usage. Developing nations face slower adoption of scientific advancements and the evidence of public and animal health impacts related to excessive antibiotic use. Regulatory and policy measures must be implemented to address these challenges effectively.

Vasudhaiva Kutumbakam's Role in One Health and Collective Well-being

The ancient Sanskrit shloka from Maha Upanishad depicted in Figure 1 encapsulates a profound philosophy that resonates deeply with the ethos of Indian civilization. Translated, it means "This is mine, and that is a stranger's, is the consideration of the narrow-minded. For the magnanimous hearts, however, the entire earth is but a single family." This principle, known as "Vasudhaiva Kutumbakam," symbolizes the essence of universal brotherhood and inclusivity, advocating that the entire world is one single family without the boundaries of mine and thine. It aligns seamlessly with core Indian values such as *Satya* (truth), *Ahimsa* (non-violence), *Asteya* (non-stealing), and *Aparigraha* (non-possessiveness), which collectively promote a life of honesty, compassion, respect, and minimalism.[31]

In the context of contemporary challenges such as AMR, the relevance of "Vasudhaiva Kutumbakam" becomes even more critical. It underlines the imperative for a global community to work together in harmony, transcending geographical, cultural, and political barriers to address issues that threaten our collective well-being. Just as the philosophy teaches us to view the world as a single family, tackling AMR requires a unified approach that embodies the principles of One Health. This approach acknowledges the interconnectedness of human, animal, and environmental health and calls for collaborative efforts across disciplines and nations to develop sustainable solutions. In essence, "Vasudhaiva Kutumbakam" serves as a guiding light for fostering cooperation, empathy, and altruism, essential qualities for combating global health challenges and achieving a harmonious coexistence on this planet.

Conclusion

In conclusion, the global community must continue to prioritize the One Health approach to combat AMR comprehensively. Collaborative efforts among nations, interdisciplinary research, and the practical implementation of antibiotic stewardship plans are essential to reduce antibiotic use and mitigate the adverse impacts of AMR on human health, animal health, and the environment. The ongoing commitment of organizations like the FAO, OIE, and WHO, coupled with the engagement of stakeholders from all sectors, holds the key to a sustainable future in which AMR is effectively managed and controlled.

Take-home Messages

- Interconnected threat: Antimicrobial resistance is a global threat that affects human health, animal health, and the environment. Recognizing the interconnectedness of these domains is essential for effective mitigation.
- One health approach: The One Health approach, championed by organizations like FAO, the OIE, and WHO, is pivotal in addressing AMR. It emphasizes collaboration across sectors to combat this multifaceted challenge.
- Evidence-based strategy: Successful AMR control relies on eco-epidemiology, integrated surveillance, and evidence-based reporting. These data-driven approaches inform decision-making and policy formulation.
- Communication and awareness: Raising awareness among the public, clinicians, veterinarians, farmers, and policymakers is crucial. Effective communication is key to understanding and addressing AMR.
- Economic implications: The economic development and technology of regions influence the spread of AMR. Organizations like the World Economic Forum can play a significant role in addressing AMR through infrastructure, regulations, and public health interventions.
- Paradigm shift: Transitioning from the current health paradigm to the holistic One Health model is challenging but necessary. Assessing net benefits, resource efficiency, and cost-effectiveness are essential components of this shift.
- Global action plan: The WHO's Global Action Plan, based on the One Health approach, provides a framework for nations to combat AMR. It emphasizes collaborative efforts and guideline adherence.
- Stakeholder engagement: Engagement of stakeholders across various sectors, from healthcare to agriculture, is paramount in reducing antibiotic usage and mitigating AMR's spread.
- Research and surveillance: Evidence-based research and surveillance are essential for understanding the drivers of AMR, developing alternatives to antibiotics, and supporting antibiotic stewardship.
- Alternative approaches: Exploring alternatives to antibiotics, such as microbiota modulation, gene editing, vaccines, AV inhibitors, and bacteriophages, offers promising avenues to control resistant pathogens and reduce antibiotic dependence.

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