Editorial

Antibiotic Use and Resistance: Situation, Strategies, Innovation and Research in the 21st Century

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Antibiotics, once considered miracle drugs, are facing an alarming threat of antimicrobial resistance (AMR) globally. It is largely driven by inappropriate and unindicated antibiotic use in both hospital and community settings. However, the impact is dire in low- and middle-income countries, including India, due to strained healthcare infrastructure, high burden of infectious diseases, easy accessibility and limitations of data and regulatory monitoring. However, AMR does not respect the geographical boundaries and poses a serious global challenge. This article presents the current global and national landscape of antibiotic use and resistance, highlights the research gaps, and the importance of research that helps to identify opportunities for interventions in the global scenario. Finally, it outlines a comprehensive way forward and summarizes the key recommendations to address AMR.

Access this article online

Website:
www.cijmr.com

DOI:
10.58999/cijmr.v4i03.317

Keywords:
Antimicrobials, antibiotics, antibiotic resistance, AWaRe classification, solutions, diagnostics, innovations

Introduction

Antibiotic Use and Resistance: The Global Crisis and Diverse Challenges

The discovery of antibiotics, tagged as wonder drugs, and their integration into routine clinical practice marked the onset of a dramatic reduction in global morbidity and mortality due to infectious diseases.[1] However, the regular misuse of antibiotics has magnified selective pressures on bacteria and conferred a competitive advantage to resistant phenotypes. The term antimicrobial resistance (AMR) denotes the result of these enhanced evolutionary processes in microorganisms (including bacteria, virus, fungus and parasites) to develop the ability to survive against antimicrobial drugs.[2] However, the term AMR broadly refers to antibacterial resistance (ABR), which is the most widespread threat to global public health.

In 2019, about 1.27 million deaths were directly related to AMR, making it the third leading cause of death after ischaemic heart disease and stroke.[3,4] Nonetheless, infections caused by resistant bacteria are associated with increased mortality due to the risk of treatment failure. Therefore, it is necessary to explore alternative options or develop higher-class antibiotics to treat resistant infections. However, these alternative options might place a financial strain on patients and health systems and carry severe adverse effects; thus, to be weighed against risks and benefits.[5,6]

Evidence indicates inconsistent and often unjustified antibiotic use across the globe.[1,4] Yet, there is considerable variation in situations between countries around the world. Despite the World Health Organisation's (WHO) advice through *AWaRe* (Access, Watch and Reserve), narrow-spectrum antibiotics, including those in the *Access* class, should constitute 60% of the total antibiotic prescriptions, and broad-spectrum third-generation cephalosporins and fluoroquinolones are widely used.[7,8] Moreover, prescribing antibiotics in the absence of a clear indication of bacterial infection is injudicious, fosters the development of ABR, and rarely provides any clinical benefit. A pertinent example is the treatment of upper-respiratory tract infections, which are predominantly of viral aetiology and self-limiting nature, yet, 97% of upper RTIs were reported to use antibiotics.[9-11]

Another example of poor practice is the use of certain fixed-dose combinations (FDCs) of antibiotics. FDC formulations contain fixed ratios of medicines and

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Submitted: 05/11/2025 Revision: 18/11/2025
Accepted: 28/11/2025 Published: 20/12/2025

How to cite this article: Sharma M. Antibiotic Use and Resistance: Situation, Strategies, Innovation and Research in the 21st Century. Central India Journal of Medical Research. 2025;4(3):2-5.

have proven benefits in improving treatment adherence for specific conditions associated with polypharmacy, such as tuberculosis. Nevertheless, the FDCs containing multiple broad-spectrum antibiotics are of concern. The recognition of the risks of suboptimal doses, additive toxicity, potential to select co-resistant organisms, and lack of medical merits of FDCs of antibiotics was delayed by WHO (2019) to discourage the use of several FDCs by labelling those as *'Not Recommended'* in the *AWaRe* classification.[12,13] The FDCs have been a significant component of the pharmaceutical markets in Low-and Middle-Income Countries (LMICs). In a comparative analysis of 75 countries, LMICs ranked as top 3 consumers.[15]

Large international studies report weak links between antibiotic use and culture-confirmed diagnosis, with up to nine-fold exposure variation between countries, worldwide.[16,17] Lack of standardized prescribing guidelines fosters a low threshold for initiating antibiotics in healthcare facilities, and poor enforcement of regulations supports over-the-counter availability of antibiotics, exposing patients to routine antibiotic use.[5,18] The gold standard includes diagnostic sampling followed by empiric broad-spectrum therapy, thereby culture and susceptibility results within 24–72 hours guide rational prescribing of antibiotics.[18,19] However, in resource-limited settings, poor lab infrastructure, limited capacity, and consumable shortages hinder microbiological testing, restrict therapy rationalization and amplify AMR burden.

India: The storm's first lightning

The impact of AMR is universal, yet the burden is disproportionately amplified in LMICs. A systematic analysis reported higher AMR-related mortalities in Sub-Saharan Africa and South Asia than in high-income countries, despite notably lower per capita antibiotic use.[4] India, an LMIC and the most populous country, ranked on top of the Drug Resistance Index for various clinically significant pathogens among 41 countries (2019, 20). A One Health Trust study focused on India shows that the *Klebsiella pneumoniae* resistance to carbapenems, last-line antibiotics, increased from 9% in 2008 to 57% in 2020.[21] These trends indicate towards high and increasing AMR-related morbidities and mortalities in India.[21-23] The reasons underlying the alarming AMR situations in LMICs, including India, are multifactorial, among which are inappropriate prescribing practices and self-medication and over-the-counter availability of antibiotics, specifically broad-spectrum antibiotics, such as third-generation cephalosporins.[24,25] These antibiotics are effective against a wide range of bacteria, but also are prone to developing resistance.

In view of the abovementioned factors, the WHO ranked bacterial AMR among the top 10 global health threats. There have been multiple warnings of the initial coughs in the crowd. However, data on antibiotic use patterns and prescribing correctness remain scarce, hindering essential antimicrobial stewardship programmes (ASP) for reducing unnecessary use and optimising therapy.[26] This gap is most pronounced in LMICs, where data collection is resource- and time-intensive, and the lack of information intensifies the existing AMR inequalities. Robust monitoring and surveillance are essential for ASP implementation, providing evidence to target interventions and benchmark effectiveness.[27]

In view of the ethnic, geographical and economic diversities, LMICs need context-specific research to guide policymakers. Studies from India highlight data scarcity, poor justification through prescribing patterns and trends, ASP barriers, and inadequate focused interventions, which place India at the frontline of the AMR crisis.[5,8,12,24,28]

Way Forward: A map with marked paths and blank spaces

It has been paraphrased many times, and rightly so, that developing and implementing contextualized prescribing guidelines for the local settings, ASP, robust infection prevention measures, prescription audits, education and awareness for healthcare providers and community, surveillance, monitoring and feedback, remain proven, and cost-effective fundamental pillars to rationalize antibiotic use and curb resistance. Nonetheless, emerging technological innovations offer promising strategies to limit inappropriate use of antibiotics and minimize ABR.[29]

Possibilities and Opportunities

- The Role of Electronic Medical Record (EMR) System and Electronic Prescribing and Medicines Administration (ePMA) systems represent a transformative tool for combating AMR in resource-constrained settings. By standardizing documentation, supporting clinical decision-making, and enabling real-time surveillance of prescribing patterns, EMR and ePMA can improve continuity of care and accountability, facilitate ASP and research.[30] Therefore, prioritizing electronic and digital systems could deliver substantial gains in rational antibiotic use and patient outcomes.

- The appropriate disposal of medicines, particularly antibiotics, is another ignored area. The open disposal contaminates the environment and contributes to the development of resistance among microorganisms living in natural reservoirs such as water and soil. The resistance can subsequently spread to animals and humans, posing a significant public health risk.
- Use of rapid diagnostic tools, including point-of-care biosensors and smart biomaterials, will enable timely identification and susceptibility profiles of pathogens, facilitating targeted treatment instead of empirical use of broad-spectrum antibiotics.[31]
- Innovative therapeutic approaches such as bacteriophage therapy, which selectively eliminate resistant bacteria and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) sequences and Cas (CRISPR-Associated) systems, which detaches resistance genes from bacterial genomes should be explored and evaluated.[32,33]
- Interventions using metal and carbon-based nanoparticles disrupt bacterial membranes and biofilms while enhancing drug delivery, reducing the possibilities of developing resistance.[33]
- Synthetic antimicrobial peptides and immuno-modulators complement these efforts by strengthening host defenses.[34]
- Artificial intelligence and big-data analytics can further support antibiotic stewardship by predicting resistance patterns and improving prescribing practices.[35]
- Hence, in addition to the conventional strategies, the future demands bold, coordinated and focused strategies such as prioritizing prolonged investment in ASP, equitable access to diagnostics, and digital health infrastructure. Innovations should be motivated and researched, and their affordability and scalability should be ensured for resource-constrained settings where they are most needed. International cooperation is critical for unified progress and can be cooperated through setting common national and global research agendas; sharing technologies, surveillance systems, resources, and regulatory frameworks. Integrating established measures with innovations can foresee a future where AMR is controlled, with efficient global health systems to safeguard future generations.

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