The Battle Against Antimicrobial Resistance

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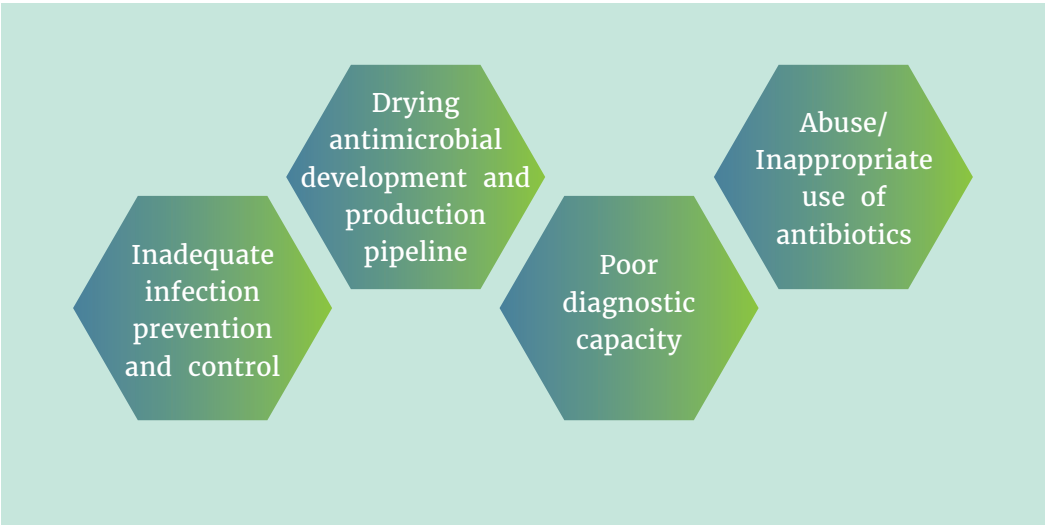
Antibiotics have revolutionised modern medicine by reducing morbidity and mortality caused by bacterial infections. However, the overuse and misuse of antibiotics has accelerated the development of antibiotic resistance, making once-treatable infections increasingly difficult to manage.[1] Antimicrobial resistance (AMR) is a grave global health crisis, posing significant challenges to achieving health equity on a global scale. In 2019 alone, bacterial AMR was directly responsible for 1.27 million deaths worldwide.[2] If left unchecked, this is predicted to cause a staggering 10 million deaths by 2050,[3,4,5] underlining the urgent need for action. An increase in AMR will significantly impact the global economy and is expected to push an additional 24 million people into extreme poverty by 2030.[6] Although reliable estimates from developing nations remain limited, perhaps due to inadequate surveillance, the burden of AMR is suspected to be highest in low-income countries. Unless suitable interventions are implemented, certain susceptible bacterial pathogens will eventually become resistant to antimicrobials, thereby rendering treatments ineffective.[7] This essay explores the multifaceted nature of AMR and its impact on healthcare systems and patient outcomes. The focus is on accelerating efforts to combat AMR, with the recognition that addressing this issue is crucial for ensuring health equity for all.

Understanding Antimicrobial Resistance

The emergence of AMR impedes the prevention and/or treatment of persistent infectious diseases. Although a number of measures have been initiated at the global, national, and regional levels, AMR persists.[8] To effectively combat AMR, it is essential to comprehend its fundamental aspects. AMR refers to the ability of microorganisms, such as bacteria, viruses, fungi, and parasites, to withstand the effects of antimicrobial drugs. The development of resistance is part of the natural biological evolution as this is part of the defence system of microorganisms. Resistance can be inherent (i.e. no target for the antibiotic) or it can arise through various mechanisms, including genetic mutations, horizontal transfer of resistance genes between microorganisms, target modification, membrane permeability alteration, drug modification, and antibiotic efflux. Exposure to antimicrobials accelerates the generation of resistance by increasing rates of mutation and exchange of genetic resistance mechanisms as well as the killing of susceptible microorganisms (including many bacteria of the normal flora), thereby giving resistant microorganisms a competitive advantage (also known as 'selection'). Resistance affects all types of antimicrobial agents, including antibiotics, antivirals, antifungals, and antiparasitic drugs. There are five key factors that contribute to the rise of AMR (see Figure 1).

Figure 1: Factors Contributing to the Rise of AMR



Source: Authors' own

a) Inadequate infection prevention and control: The spread of AMR is closely linked to the ability of bacteria and other microorganisms to rapidly multiply and spread their population through various vectors/hosts. Poor hand hygiene, improper disinfection and sterilisation practices, and inadequate sanitation can lead to the rapid spread of these drug-resistant pathogens. Strict adherence to infection control measures can lower the occurrence of hospital-acquired infections.[9] Therefore, appropriate measures need to be taken to enhance the existing infection prevention framework and reduce the risk of the spread of AMR. A significant hurdle in implementing infection prevention and control (IPC) practices, especially in low- and middle-income countries (LMICs), is the presence of adequately-trained human resources. To address this, institutions such as the World Health Organization (WHO) and US Centers for Disease Control and Prevention have developed training modules, while the Infection Control Academy of India (IFCAI) has developed a diploma course to build the capacity of infection preventionists.

b) Abuse/inappropriate use of antibiotics: In addition to the selection pressure on microbes due to the use of antimicrobial drugs, social and administrative factors also contribute to, and exacerbate the emergence of AMR. One of the contributing factors is the availability, in many countries, of antimicrobials through over-the-counter (OTC) sales without requiring prescriptions. Furthermore, the inappropriate prescription of antibiotics by physicians contribute to the overuse of antibiotics. A study conducted by WHO highlighted that a significant proportion of antimicrobials prescribed in outpatient departments of various hospitals were unnecessary or inappropriate.[10] Rampant use of antibiotics in the livestock sector, pressure from patients to be prescribed an antibiotic for immediate relief from symptoms, self-medication, and the discontinuation of antibiotic course after relief from symptoms—all worsen drug resistance in pathogens.[11,12] New legislation and the enforcement of existing regulations to prevent the OTC sale of antimicrobials is crucial, as are stricter antibiotic prescription and consumption measures.

c) Drying antimicrobial development and production pipeline: The complete antimicrobial drug development process, from discovery to market entry, takes an average of eight to 12 years. Although advancements in computational

chemistry and artificial intelligence (AI) have aided in drastically cutting down the timelines for the discovery of new antimicrobials, the in vitro and in vivo trials take time. Even after such laborious efforts, bacteria swiftly develop resistance to these antibiotics. Quicker and more efficient antibiotic testing and approval pipelines need to be established to combat AMR.[13]

Recent advances in antimicrobial discovery—including the repurposing of existing drugs, exploration of natural products, employing alternate treatment strategies, the use of computational approaches for drug design, interdisciplinary collaborations, and the integration of new technologies may help in accelerating the discovery process[14] and in the mitigation of AMR.

Despite the recent advantages, investment in antibiotic research and development remains limited, resulting in a clinical antibacterial pipeline that is insufficient to address the emergence and spread of AMR infections. In 2021,[15] there were only 77 antibacterials in the clinical pipeline that target WHO priority pathogens (Enterobacteriaceae, *Acinetobacter* and *Pseudomonas*) including tuberculosis.[16] Of these, 45 are traditional antibacterial agents and 32 are non-traditional. Of the 45 traditional antibiotics, 27 are reported to be active against the WHO bacterial priority pathogens, 13 against Mycobacterium tuberculosis, and five exclusively against Clostridium difficile. Only six of the 27 antibacterials targeting the priority pathogens fulfil at least one of WHO's four innovation criteria (i.e., absence of known cross-resistance, new class of drug, new target site, and new mode of action).[17]

However, a robust pipeline of novel antibiotics is critical to tackling the increasing emergence and spread of AMR. The Global AMR R&D Hub and WHO[18] reported on the progress and challenges for incentivising the development of new antibacterial treatments to tackle the emerging threat of AMR. The return on investment for new antibiotics fails to cover the costs of their development, manufacturing, and distribution.[19] As a result, big pharmaceutical companies have exited the antibiotic market, and companies remaining in the space (often small or micro biotech firms) face challenges to sustain their operations given the cost and time for drugs to reach the market. Novel reimbursement models addressing the market failures are needed to make antibiotic development more economically sustainable.

Innovative financing mechanisms play a crucial role in addressing the lack of financial incentives for the private sector to develop, test, and roll out new antimicrobials. One potential solution is the implementation of advance market commitment–type investments, such as those undertaken by organisations like DNDi (Drugs for Neglected Diseases Initiative), CEPI (Coalition for Epidemic Preparedness Innovations), and Gavi (Global Alliance for Vaccines and Immunization).

Under this model, governments pool funding to support manufacturers and the private sector in creating antibiotics, thereby reducing innovation risks and ensuring equitable pricing and access. This approach incentivises private-sector investment, overcomes financial barriers, and contributes to the fight against AMR, securing effective treatments for all.

d) Poor diagnostic capacity: Accurate and timely diagnostics are critical for identifying and managing infectious diseases effectively. Poor diagnostic capacity can lead to delayed or inappropriate treatment, increased morbidity, mortality, and spread of infectious diseases, including outbreaks. Poor diagnostics encompass several aspects, including limited access to diagnostic technologies, inadequate laboratory supplies and equipment, poor quality of chemicals and equipment, absence of reliable quality assurance systems, limited access to reference laboratories, inadequate infrastructure, lack of trained personnel, and delays in obtaining test results.[20] Poor diagnostic capacity is one of the biggest challenges of the health sector in developing countries.[21] Lack of timely diagnostics is also a challenge in vulnerable populations in high-income countries (HIC). Therefore, improving diagnostic capacity is essential, especially in LMICs, as is ensuring equitable access to diagnostics for vulnerable populations to enhance the quality and efficiency of healthcare delivery and for achieving the global health goals of reducing the burden of communicable and non-communicable diseases.[22]

Innovations Related to AMR

a) Exploration of alternative therapies: Alternate ways of treatment like "bacteriophages,[23] antimicrobial peptides (AMPs) or bacteriocins,[24] antimicrobial adjuvants, faecal microbiota transplant (FMT) and competitive exclusion of pathogens through genetically modified probiotics and

postbiotics"[25] rather than antibacterial agents alone, could be an alternate way to reduce the use of antimicrobials.

b) Streamlined approval of new antimicrobials: Efficient and streamlined clinical trial processes are crucial for expediting the development timeline of new antimicrobials, including regulatory processes and innovative trial designs, such as adaptive dose-ranging studies and seamless phase transitions. This calls for better collaboration between regulatory agencies, researchers, and industry stakeholders to establish harmonised protocols, reduce administrative burden, and expedite patient recruitment, leading to faster completion of clinical trials.[26]

c) Repurposing of existing drugs: Drug repurposing, or identifying new therapeutic applications for existing drugs offers another strategy to expedite antibacterial production. By leveraging the extensive knowledge and safety profiles of approved drugs, researchers could bypass certain preclinical and early clinical development stages, significantly reducing the overall timeline. Repurposing can be achieved through in-silico analyses, high-throughput screening, and exploring drug libraries, aiming to identify existing drugs with potential antibacterial activity.[27]

d) Harnessing the power of AI: Machine learning (ML) and AI offer possibilities to accelerate drug repurposing in several ways, including the detection of the relationships among various biological components (such as genes, proteins, diseases, and drugs) and through the analysis of molecular fingerprints of compounds. Furthermore, neural network-based approaches can be trained to learn the patterns and properties of fingerprints, enabling prediction of drug activities and identifying potential drug candidates.[28]

AI can also be harnessed to streamline the diagnostic process. An academic–industry collaboration in India (between Sri Sathya Sai Institute of Higher Learning, IFCAI and SCIINV Biosciences Private Limited) has developed AMRx™, an AI/ML-based culture-free prediction system in the context of urinary tract infections. It is a clinical decision support system to improve empirical antibiotic prescriptions and to reduce unnecessary laboratory testing of samples.

e) Collaborative research and funding initiatives: Global efforts are urgently needed to address the complex elements of AMR. These include coordinated leadership at the global, regional, and national level, involving diverse government agencies, academia, practitioners, and industry.[29,30] Recognising the spread of AMR, WHO, the Food and Agriculture Organization, the United Nations Environment Programme, and the World Organisation for Animal Health have formed the Quadripartite to promote a 'One Health' approach[31] that aims to align actions across the human, animal, and environmental sectors. Several initiatives are ongoing, and 170 countries have developed national action plans (NAPs). However, only 10 percent of these plans are fully costed. Converting the NAPs to concrete AMR mitigation actions has proved to be difficult, including in the LMICs.

In response, Denmark initiated the establishment of the International Centre for Antimicrobial Resistance Solutions (ICARS) to support these countries with funding and expertise to develop evidence-based, context-specific and cost-effective solutions that can be scaled to establish sustainable AMR mitigation. The AMR Multi-Partner Trust Fund (MPTF) was launched in 2019 by the Quadripartite members to catalyse the implementation of One Health NAPs and to provide effective leadership and coordination of multisectoral One Health response to AMR. Additionally, the Global AMR R&D Hub in Berlin is promoting collaboration and coordination of research and development on AMR, and is cataloguing the present funding in AMR R&D to provide the landscape of present funding for future prioritisation. Organisations such as CARB-X, Global Antibiotic Research & Development Partnership (GARDP), and the AMR Action Fund work to stimulate drug discovery and equitable access. To solve the market failure for antimicrobials, new models for financing the development of novel antimicrobials, where countries pay for the accessibility of drugs, are currently being explored.[32]

f) Rapid Diagnostic Tests and Point-of-Care Technologies in AMR: Absolute, concrete, and timely diagnosis detection, and management of infection-causing pathogens will significantly decline morbidity, mortality, and the cost burden. Rapid diagnostic tests (RDTs)[33] and point-of-care technologies (POC) are tools that can be employed in achieving timely diagnostics. The integration of RDTs and POC technologies, such as polymerase chain reaction-based tests, genotypic assays, and phenotypic assays, in AMR

management can potentially transform clinical practice and public health interventions.[34]

Accelerating Efforts to Combat AMR

Combating AMR requires a multipronged approach the comprises all critical components—from policy to implementation.

- Development of new antibiotics and alternative treatments in the era of Antimicrobial Resistance
- Overcoming difficulties in finding new drugs
- Antibiotic repurposing
- Development of alternate therapies like Bacteriophages
- Improving infection prevention and control practices
- Optimising antimicrobial use
- Strengthening surveillance and data collection
- Integrated One Health approach to unify and integrate multiple sectors
- Incorporating AMR into national and global health plans
- Engaging stakeholders and raising awareness about AMR
- Mobilising political will and fostering multi-sectoral collaboration

Conclusion

AMR is an ongoing and evolving pandemic that impacts LMICs and vulnerable populations in HICs the hardest. This is aggravated by a drying pipeline of antimicrobials and the industry leaving the field of antimicrobial drug discovery due to lack of economic sustainability. The consequences of the AMR pandemic are already severe, but will become even more dire if not reversed. There is an urgent need for increased and focused action. Due to the complex nature of AMR, this effort needs to be multifaceted, both in reducing the circulation and spread of existing resistant microorganisms and in slowing the increase of novel resistance mechanisms. Key to this is lowering the overall use of antimicrobials (i.e. infection prevention), antimicrobial stewardship (including accessibility of affordable and timely diagnostics), and strengthening IPC and biosecurity procedures, all of which need to be carried out through the 'One Health' approach. This needs involvement at all levels and of all stakeholders, including civil society.

Exploring alternative therapies such as bacteriophage therapy, repurposing existing drugs, harnessing the power of AI, and fostering collaborative research initiatives are key strategies in tackling AMR. These innovative approaches provide hope for the future, where a robust antibacterial pipeline can meet the challenges posed by evolving bacterial infections and ensure effective treatment options for patients worldwide.

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