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Review Article

The silent pandemic: understanding the global burden of antimicrobial resistance

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ABSTRACT

Antimicrobial resistance (AMR) is one of the most severe public health concerns of the 21st century and is reversing decades of progress made in the prevention and treatment of infectious diseases. AMR is a so-called "silent pandemic" since the condition progresses slowly and is completely unnoticed. But even AMR worldwide leads to considerable health, mortality and economic losses, with the most recent global report showing millions of such infectious diseases worldwide, and a very high number of deaths resulting from them, most of which are in the low- and middle-income countries. This review presents a global picture of AMR, clinical and public health-related issues along with key issues in terms of epidemiological surveillance, innovation and policy response. Factors driving the emergence and spread of resistance include the overuse and inappropriate use of antibiotics in human and animal health, poor infection control, substandard drugs, and environmental pollution. Also, we report that the health care sector is at significant risk due to AMR, which is a serious threat to the outcomes of routine surgeries, organ transplants, cancer treatment and the care of vulnerable patients. This in turn places substantial strain on health care systems. Worldwide and in different regions, monitoring programmes have been established that use genomics and Artificial Intelligence (AI) to study resistance pattern although they are still in a developing stage. Also, the development of new antibiotics in the pharma sector is a limited field, which in turn is pushing research into alternative options like phage therapy, nanotech-based solutions, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and vaccines that target priority pathogens. Although the World Health Organisation's (WHO) Global Action Plan and national AMR strategies play a key role in shaping the international policy landscape for this issue, significant gaps still exist in implementation, regulation, financing and stewardship. The solution lies in better data collection on health issues, responsible use of antibiotics, infection control, innovation and sustained political commitment, which will not only slow down the AMR pandemic but also help secure the health of future generations.

Keywords: Drug resistance, Microbial, Anti-bacterial agents, Global burden of diseases, One health, Vaccines and bacteriophages

INTRODUCTION

Antibiotic resistance is a form of antimicrobial resistance (AMR) that involves bacteria, viruses, fungi and parasites. It arises when these microorganisms develop mechanisms that render antibiotics and other antimicrobial agents ineffective, thereby causing persistent infections and spread to others. While AMR is a natural part of the evolutionary process, a greater surge in AMR can be seen due to improper use of antibiotics in human and animal health care as well as in agriculture. this is due to many infections that once readily treatable are now often difficult and impossible to cure. also, routine medical procedures depend on a progressively smaller pool of effective antibiotics.[1-3] AMR is often referred to as a

pandemic in a state of dormancy as it represents a slow-progressing crisis rather than an acute disease outbreak. consequently, receives insufficient attention despite the substantial burden it creates in society. Modelling studies across the world suggest that bacterial AMR is associated with a large number of deaths across the world which is even complicated by considerable geographical imbalance. Numerous nations, especially those with low- and middle-income countries, tend to have the extra problems of limited or absent laboratory infrastructure, as well as unsatisfactory surveillance, which results in the current statistics being a significant under-representation of the actual toll being taken. The issue of AMR goes beyond the scope of individual treatment failure. Effective antibiotics are a cornerstone of modern health care, which includes major surgery, organ transplantation, intensive care and cancer chemotherapies. As resistance rises, we see that these services are put at risk, which in turn leads to prolonged hospital stays, increased health care costs, and greater risk of complications and death. Also at high risk are vulnerable populations, which include neonates, young children, older adults and immunocompromised patients, also in settings that have little access to diagnostic and supportive care.[4-7]

Improving awareness and understanding of AMR contributes to better surveillance and research, reduced infection incidence, more optimal use of antibiotics and development of sustainable investment in new medicines, diagnostics, vaccines and other Interventions. However, implementation still remains uneven, thus many countries are struggling with weak regulatory structures, limited resources and competing health priorities. In this regard, a comprehensive and up-to-date review of existing antimicrobial agents is essential.

This review summarises current data on the global scale of AMR, examines its principal drivers and their health care and public health implications and evaluates progress in surveillance and emerging solutions, includes novel therapeutics and vaccines. We also present an overview of the existing policy and governance structures in place, highlight ongoing challenges in antibiotic stewardship and public awareness and propose future directions and research priorities to improve global preparedness for AMR.[8-11]

CORE MECHANISMS OF ANTIMICROBIAL RESISTANCE

Most resistance determinants fall into several core categories of mechanisms by which bacteria can avoid the action of antibiotics. An understanding of these mechanisms is thus key not only for the interpretation of susceptibility data but also for the rational design of new drugs and the appropriate use of existing agents. A schematic overview of the principal resistance mechanisms is presented in Figure 1, while Table 1 provides examples of key microorganisms commonly associated with clinically significant resistance patterns.

Reduced drug uptake (limited permeability)

Many gram-negative bacteria develop resistance to antibiotics through reduced entry across their outer membrane. The loss or change of porin channels lowers the entry of hydrophilic antibiotics like β-lactams and some fluoroquinolones. Structural traits such as the lipopolysaccharide layer found in gram-negative bacilli act as a natural barrier and contribute to baseline resistance against several agents.[12]

Active efflux pumps

Membrane proteins known as efflux pumps actively export antibiotics from inside the bacterial cell to outside. These are so effective that the intracellular concentrations never reach inhibitory levels. Many multidrug efflux systems (for example, AcrAB-TolC in Enterobacterales or Mex pumps in Pseudomonas) can extrude several different classes of drugs. Overexpression of efflux pumps often acts together with decreased permeability or target mutations to confer high-level multidrug resistance.[13]

Enzymatic inactivation or modification of the drug

Drugs can be hydrolysed or modified by enzymes produced by bacteria. β-lactamases, including extended-spectrum β-lactamases (ESBLs) and carbapenemases, hydrolyse β-lactam antibiotics, and such resistance has now spread in enterobacterales and non-fermenters. Aminoglycoside-modifying enzymes include acetyltransferases, phosphotransferases, and nucleotidyltransferases, which change the drug so that it cannot bind to the ribosome.[14]

Modification of the antibiotic target site

Resistance may arise from genetic changes that remodel the target binding site so that the drug does not bind efficiently. Altered penicillin-binding proteins, for example, Penicillin-Binding Protein 2a(PBP2a) encoded by mecA in Methicillin-Resistant *Staphylococcus aureus (*MRSA), have reduced affinity for β-lactams. Deoxyribonucleic Acid (DNA) gyrase or topoisomerase IV mutations confer resistance to fluoroquinolones, while Ribosomal Ribonucleic Acid (Rrna) methylation (Erythromycin Ribosomal Methylase genes) mediates macrolide, lincosamide, and streptogramin resistance.[15]

Biofilm formation and adaptive mechanisms

Biofilms produce an extracellular matrix outside the cell that limits antibiotic entry and permits slow-growing or resting cells to survive. Nutrient and oxygen gradients in biofilms give rise to subpopulations with different metabolic states, most of which are less sensitive to antibiotics. Biofilms growing on medical device surfaces (catheters, prostheses) are major reservoirs for chronic and recurrent infections with multidrug-resistant organisms.[16,17]

Genetic basis: intrinsic and acquired resistance

Intrinsic resistance refers to resistance naturally present in a species, while acquired resistance is gained through mutation and horizontal gene transfer. Intrinsic resistance reflects chromosomal features-impermeable outer membrane, constitutive efflux pumps or simply the absence of the antibiotic target. Acquired resistance occurs via spontaneous mutations and gene acquisition on plasmids, transposons, and integrons. This allows the rapid spread of resistance determinants such as bla_NDM, bla_CTX-M or mcr not only within one species but also among different species in large regions.[18-20]

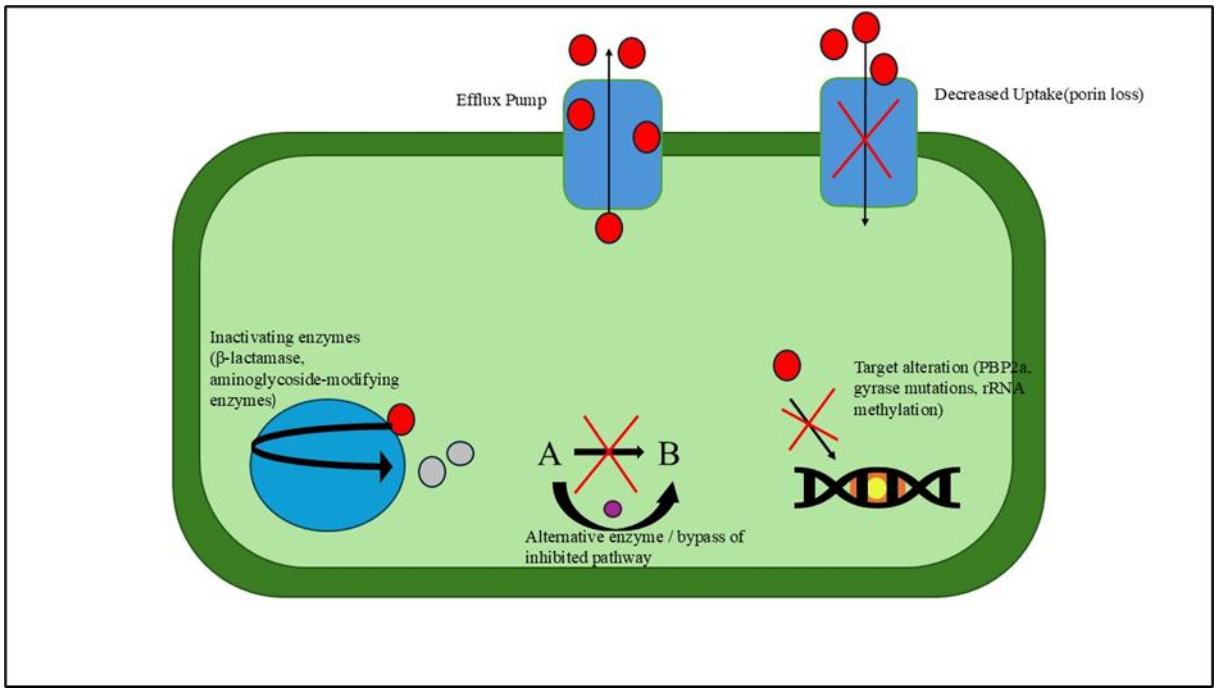

Figure 1: Mechanisms of antimicrobial resistance.

GLOBAL EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE

Current burden of drug-resistant infections

Bloodstream infections, intra-abdominal infections, bacterial lower respiratory tract infections, and other syndromes caused by priority bacterial pathogens such as Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, and Acinetobacter baumannii contribute greatly to the growing problem of antimicrobial resistance. Bacterial AMR has been projected to cause up to 10 million deaths per year and enormous economic losses due to declines in productivity and the strain placed on health care systems, over the next 30 years.

Most deaths due to bacterial AMR and the highest associated mortality and morbidity burden arise from lower respiratory infections. Although resistant infections in other common bacterial syndromes are also linked with substantial mortality, these projections of AMR-related deaths and economic losses assume that current trends continue or worsen. More recent analyses indicate that bacterial AMR is already among the leading causes of morbidity and mortality worldwide, with deaths attributable to or associated with resistant infections estimated in the millions each year.[21-24]

Regional variations and hotspots

The global AMR profile is highly heterogeneous: sub-Saharan Africa and South Asia report the highest rates of deaths attributable to bacterial resistance, followed by parts of Latin America and Eastern Europe. Also, many low- and middle-income countries face a dual challenge of high burden of infectious diseases, a substantial proportion of which are resistant to available treatments, combined with poor diagnostic capacity, weak surveillance system and limited access to second-line drugs; together, these factors intensify the impact of resistant infections. In high-income regions, overall mortality from AMR is generally lower, but health care institutions frequently report high levels of multidrug-resistant bacteria, driven in part by intensive antibiotic use and complex medical care, which also contributes significantly to the global AMR problem.[25-27]

Mortality, morbidity and economic impact

AMR results in longer hospital stays for patients, more complex cases requiring additional interventions, and

higher case-fatality rates compared with infections caused by susceptible organisms across all specialities and regions. Infected patients experience substantial disability-adjusted life years (DALYs) lost and increased medical costs, which are compounded by long- term reductions in economic productivity. Analyses suggest that improving control of AMR would positively impact global GDP and healthcare expenditure, rather than the current negative trajectory, where AMR predominantly affects already resource-constrained health systems.[28-29]

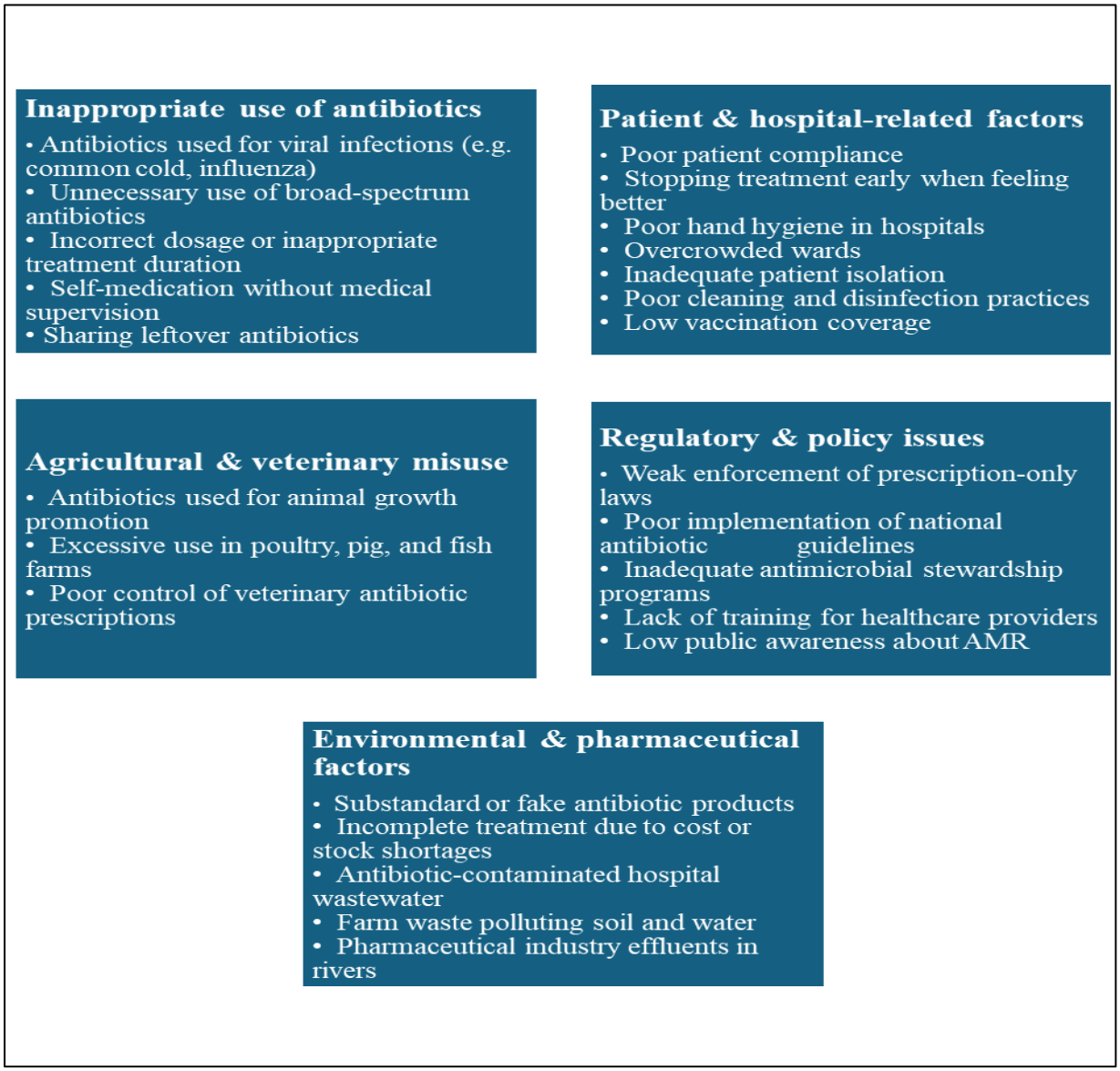

Figure 2: Major causes of antimicrobial resistance.

DRIVERS OF ANTIMICROBIAL RESISTANCE

Overuse and misuse of antibiotics in humans

One of the leading contributing factors to the global problem of AMR is the misuse of antibiotics. Prescribing antibiotics during viral infections, incorrect prescription of the drug (wrong dosage, wrong duration, etc.), self-medication, and self-prescribing are important problems. There is also an issue with over-the-counter antibiotics being sold in several countries with no prescription needed. In many low- and middle-income countries, there is a lack of diagnostic equipment, which leads to an encouragement of empirical use of broad-spectrum antibiotics. There are also problems in high-income countries, such as misuse of protective prescribing and pressure to prescribe antibiotics to meet the patients' expectations.[30]

Veterinary, agricultural and environmental factors

Large-scale antimicrobial use in food-producing animals is for therapy, prophylaxis and in some regions for growth promotion, which in turn places considerable selective pressure on animal and environmental microbiota. Resistant bacteria and resistance genes being transmitted to humans via the food chain, direct animal contact and

contamination of water, soil and crops with animal waste or pharmaceutical byproducts. Also, inadequate wastewater treatment and discharge of hospital and industrial effluents play a role in the environment, which in turn becomes a major reservoir for resistance determinants, which reinforces the One Health idea that human, animal and environmental health are very much interconnected.[31-33]

Table 1: Examples of microorganisms prone to resistance.

S.no.	Name of microorganism	Type	Type of resistance/resistant strains
1	Staphylococcus aureus	Gram-positive cocci	MRSA (methicillin-resistant), VISA/VRSA
2	Enterococcus faecium	Gram-positive cocci	Vancomycin-resistant strain
3	Escherichia coli	Gram-negative bacilli	– ESBL-producing plus carbapenem-resistant strains.
4	Klebsiella pneumoniae	Gram-negative bacilli	ESBL-producing and carbapenemase producers (KPC, NDM, etc.).
5	Enterobacter spp.	Gram-negative bacilli	Members of the ESKAPE class are often multidrug-resistant.
6	Acinetobacter baumannii	Gram-negative coccobacilli	Frequently, carbapenem plus multidrug-resistant.
7	Pseudomonas aeruginosa	Gram-negative bacilli	Multidrug and extensively drug-resistant hospital pathogen.
8	Enterobacterales group	Gram-negative bacilli	Proteus, serratia, citrobacter W/ESBL/CRE phenotype
9	Streptococcus pneumoniae	Gram-positive cocci	Macrolide and multidrug-resistant strains.
10	Group a streptococci	Gram-positive cocci	Strains resistant to macrolides.
11	Salmonella typhi and nontyphoidal salmonella	Gram-negative bacilli	Resistant to fluoroquinolone and multidrug drugs.
12	Shigella species	Gram-negative bacilli	Resistant to fluoroquinolone and multidrug.
13	Group B streptococci	Gram-positive cocci	Emerging isolates resistant to penicillin.
14	Neisseria gonorrhoeae	Gram-negative diplococci	Resistant to third-generation cephalosporins and fluoroquinolones

Health system and regulatory gaps

Low-quality health systems and weak regulations drive AMR when the quality, supply, and use of antibiotics are poorly managed and controlled. In several countries, substandard and falsified medicines, lack of standard treatment guidelines, poor infection prevention and control, and weak governance, lead to antimicrobials being both underused and overused. Poor enforcement of prescription-only policies, along with financial pressures related to antibiotic sales, limited continuing education for prescribers and pharmacists, and weak financial controls, sustain the irrational use of antimicrobials.[34]

Microbiological and genetic mechanisms

Where bacteria are exposed to antibiotics, cells that possess resistance mechanisms such as drug-inactivating enzymes, target modification, reduced permeability or active efflux. Also note that horizontal gene transfer via plasmids, transposons and integrons enables the rapid spread of resistance genes within and between bacterial species, which in some cases leads to global dissemination of determinants such as extended-spectrum β-lactamases and carbapenemases. Biofilm formation is also important as resistant subpopulations can persist on hospital and community surfaces and medical devices where the biofilm matrix protects them and makes eradication difficult, thereby promoting chronic and recurrent infections.[35,36]

CLINICAL AND PUBLIC HEALTH IMPLICATIONS

Impact on healthcare systems and costs

Infections that are resistant to medications lead to prolonged hospital stays, increased need for critical care, and greater use of last-line antibiotics, thereby increasing health care costs. National-level studies on the burden of AMR have shown higher in-hospital mortality rates and greater resource use among patients with resistant infections, whereas those with susceptible infections require fewer diagnostic tests and procedures. Failure to control AMR is projected to result in direct economic losses amounting to tens of trillions of US dollars by mid-

century, together with substantial losses in productivity and further increases in medical costs.[37-40]

Threats to surgery, transplantation and cancer care

In the current era of advanced medical procedures such as major surgery, organ and stem cell transplants, and intensive chemotherapy, reliable prophylactic and therapeutic antibiotics are essential to prevent and treat bacterial infections. We are seeing an increase in resistance to gram-negative bacilli, staphylococci and enterococcus, which in turn is a challenge to our present prophylaxis practices and is greatly increasing the risk of postoperative and device-associated infections, some of which are very difficult or even impossible to treat. even small increases in resistance rates can substantially raise postoperative infection rates and procedure-related mortality in some cases, which in turn prompts clinicians to reconsider, modify or postpone high-risk interventions.[41]

AMR in vulnerable populations

The issue of AMR disproportionately affects vulnerable groups, including neonates, young children, older adults, pregnant women and people living with HIV, immunocompromised patients, cancer patients and those on long-term immunosuppression. In neonatal and paediatric sepsis, we see very high rates of multidrug resistance in common pathogens, which in turn are associated with high case-fatality rates, particularly in low- and middle-income countries that lack access to second-line drugs and adequate critical care. In long-term care facilities and oncology units, high levels of colonisation and infection by multidrug-resistant organisms, which in turn cause outbreaks, create complex infection-control challenges and cause substantial psychological and financial stress for patients and their families.[42]

SURVEILLANCE AND MONITORING OF ANTI-MICROBIAL RESISTANCE

Global and regional surveillance programmes

Surveillance of AMR aims to monitor the resistance pattern over time and geography with a view to informing empirical therapy, stewardship, and policy. WHO AMR and antibiotic use surveillance system (GLASS) collates and systematises information from participating countries, while regional networks and systems, such as European Antimicrobial Resistance Surveillance Network (EARS-Net) in Europe, and national laboratory networks, contribute additional data on sentinel pathogens and important drug–bug combinations.[43]

Challenges in data collection and reporting

Despite growth in this field, major disparities persist, particularly in low- and middle-income countries, where we find that infrastructure for laboratories, trained personnel and quality assurance is lacking. We also see a wide variation in what is monitored and how, which complicates comparison of results between sites. Also, many settings do not have robust community-based surveillance, which is weak, leading to over-reliance on hospital-based data and underestimation of the true burden. reporting may be incomplete or delayed, and data on resistance, antimicrobial use and clinical outcomes are not integrated, which in turn reduces the current systems' use for real-time decision making.[44]

Role of genomic and AI-based tools

Recent improvements in genome sequencing make it possible to track, in near real time, resistant strains, resistance genes, and mobile genetic elements within human, animal, and environmental reservoirs. Combined genomic, clinical, and epidemiological support outbreak investigation, source tracking and surveillance for the emergence of novel mechanisms such as carbapenemases or colistin resistance. At the same time, machine-learning and other AI-based analytical approaches are being explored to detect resistance patterns and to analyse genomic and routine laboratory data for early-warning systems and resistance prediction. Most of these systems, however, are still in the early pilot or development stages.[45,46]

INNOVATIONS AND EMERGING SOLUTIONS

New antibiotics and optimisation of existing agents

The current antibiotic clinical pipeline remains insufficient to address the scale of the global threat posed by critical priority gram-negative pathogens. Most agents in development consist of modifications of existing molecules or β-lactam/β-lactamase inhibitor combinations. While these therapies provide important short-term benefits, resistance may rapidly emerge if antimicrobial stewardship efforts are not rigorously maintained. Therefore, it is essential to maximise the effectiveness of existing antibiotics through pharmacokinetic/pharmacodynamic (PK/PD)-based dose optimisation, therapeutic drug monitoring, and the appropriate use of combination therapy, in order to preserve their clinical utility.[47]

Phage therapy, nanotechnology and CRISPR-based tools

Bacteriophage therapy using lytic viruses that infect bacteria has seen a re-emergence as a promising field for multidrug-resistant infections, which has been reported in case reports and small-scale studies that report benefit in hard-to-treat infections when the treatment is tailored to pathogen susceptibility. In the nanotechnology field, there is development of metallic nanoparticles, nano carriers and surface coatings which are aimed at improving drug delivery, increasing biofilm penetration and reducing toxicity; however, issues of safety, manufacturing and regulation still need careful evaluation. CRISPR-based

antimicrobials which aim to target resistance genes or essential bacterial functions via gene editing systems delivered by bacteriophages or other vectors, do offer high specificity but are at present some way from the market due to issues of delivery, off-target effects and scalability.[48-50]

Vaccine development against resistant pathogens

Vaccines play a role in reducing AMR by decreasing the incidence of bacterial infections, thereby reducing the need for antibiotic use, as seen in the case of pneumococcal and Haemophilus influenzae type B vaccines. Also in the works is research into vaccines for priority resistant pathogens such as extraintestinal pathogenic Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus, as well as improved influenza and respiratory syncytial virus vaccines, which in turn will reduce secondary bacterial infections. Also, to this point, wide-scale use of present vaccines in low- and middle-income countries, along with the development of new vaccines, is a recognised component of global AMR strategies.[51,52]

POLICY AND GOVERNANCE FRAMEWORKS

Global action and One Health governance

AMR has been recognised as a major global health security threat, which has in turn led to high-level political commitments, including the WHO Global Action Plan on AMR and also statements from the United Nations and G20. These frameworks promote a One Health approach, which integrates the human, animal, and environmental health sectors, and emphasize the need for integrated national action plans, improved surveillance, rational use of antibiotics and sustained investment in research and development.[53]

National strategies, successes and gaps

Many countries have developed AMR action plans and begun implementing policies on infection, prevention and control, public awareness, regulation of antibiotic sales, and antimicrobial stewardship. From the experiences in Europe and some high- and middle-income countries, learning that the presence of strong laboratory networks, clear policies and stringent antimicrobial regulations can positively change the resistance trends. But in countries with weak governance, fragmented control, and poor financing the policies are stagnant.[54,55]

PUBLIC AWARENESS AND ANTIBIOTIC STEWARDSHIP

Community engagement and education

Public awareness of AMR is still at a low level in many settings, which in turn contributes to self-medication, demand for antibiotics for viral illnesses and poor compliance with prescribed regimens. In the community mass media campaigns, school-based education and the role of pharmacists as front-line counsellors have been shown to improve knowledge and reduce inappropriate use when sustained and tailored to the setting.[56]

Hospital-based stewardship programmes

Antimicrobial stewardship programmes (ASPs) in hospitals ensure that patients receive the correct antibiotics at the appropriate dosage, route, and duration, considering the local epidemiology and clinical evidence. Successful ASPs commendably include and rely on interdisciplinary teams, formulary restriction or preauthorization, prospective audit and feedback, guideline drafting, and monitoring antibiotic use and resistance trends and in different settings, they are associated with better outcomes and lower costs.[57,58]

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

Strengthening AMR preparedness post-COVID-19

The COVID-19 pandemic highlights the pre-existing weaknesses, infection prevention, surveillance and health system resilience, which are closely linked to the AMR issue. In the future, AMR must be integrated with other pandemic preparedness and health security issues, which means to expand on laboratory capacity, data systems, infection prevention and control and supply chain resilience in a way that improves our response to acute outbreaks as well as the chronic AMR crisis.[59,60]

Sustainable funding and research gaps

There is an ongoing need for sustainable ‘push-and-pull’ incentives to support research and development of new antimicrobials, diagnostics, vaccines and other therapies which may not have a large commercial market. As research priorities include improved burden and cost analyses, which also include the study of AMR in community and environment settings, we must also look at improving stewardship practices in resource-poor settings and do more implementation research, which will in turn see better transition from policy to practice.[61,62]

CONCLUSION

Antimicrobial resistance is a slow-moving but major global threat that undermines the practice of modern medicine, jeopardising routine interventions that depend on effective prophylaxis and therapy and increasing the risk of untreatable infections. This growing severity must be addressed through coordinated One Health action at global and national levels, integrating the rational use of antimicrobials, robust infection control and surveillance, innovation and good governance, with particular attention to low- and middle-income countries, which are disproportionately affected. This review brings together current evidence on the global burden of AMR, mechanisms of resistance and the appropriate use of

antibiotics, and can inform antibiotic policies in clinical practice. For countries such as India and other low- and middle-income regions, immediate priorities include strengthening laboratory capacity, surveillance networks and antibiotic stewardship programmes. Only sustained involvement of healthcare professionals such as clinicians, pharmacists and veterinarians, together with policy-makers and society, will reduce the progression of AMR and help maintain the effectiveness of present and upcoming antimicrobial drugs.

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