



Antimicrobial Resistance: Global Burden, Molecular Mechanisms, Emerging Therapeutic Strategies and Future Perspectives

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ABSTRACT :

AMR is now one of the greatest threats to global health, undermining the ability to prevent and treat infectious diseases, and is threatening many advances in medicine. Antimicrobial resistance (AMR) is the ability of microorganisms to survive after previously being sensitive to antimicrobial agents. While resistance is a natural evolutionary process, the use of inappropriate and excessive antimicrobials in humans, animals, agriculture and the environment has contributed to the emergence and spread of antimicrobial resistance.

The spread of bacterial AMR poses a special concern because resistance to the bacteria is linked to treatment failure, longer hospital stays, higher costs, disability, and death. According to a global analysis, in 2021 bacterial AMR was responsible for 4.71 million deaths, of which around 1.14 million were directly attributed to the disease. Without effective interventions, there will be a significant increase in the burden. AMR may have multiple molecular mechanisms such as, but not limited to, enzymatic antimicrobial inactivation, alteration/protection of antimicrobial target, decreased uptake/permeability, active efflux, metabolic adaptation, biofilm formation, and horizontal transfer of resistance determinants.

Alongside traditional antibiotic research, novel methods for antimicrobial drug discovery and development are gaining momentum, such as bacteriophage therapy, antimicrobial peptides, Cas9-based antimicrobial gene therapy, nanotechnology based antimicrobials, anti-biofilm agents, quorum-sensing inhibitors, monoclonal antibodies, microbiome-based therapies, host-directed therapies, and artificial intelligence (AI) assisted drug discovery. But better control of AMR will take more than new drugs. The importance of rapid diagnostics, antimicrobial stewardship, vaccination, genomic surveillance, environmental monitoring, infection prevention, equitable access to healthcare and a well-coordinated. The review covers the global burden of AMR, key molecular mechanisms of antimicrobial resistance, new therapeutic approaches, the challenges we face and future perspectives on a coordinated and precision-based response to AMR.

Keywords: Antimicrobial resistance/Antibiotic resistance; Multidrug resistant bacteria; Molecular mechanisms; Bacteriophage therapy; Antimicrobial peptides; CRISPR-Cas; Nanotechnology; Antimicrobial stewardship; One Health.

Introduction

With the discovery of antibiotics, medicine as we know it today changed. When penicillin was introduced and the antibiotic era followed, the death rate due to bacterial infections was greatly lowered and surgery and organ transplantation, cancer chemotherapy, neonatal medicine, and intensive care made significant strides [15,16]. Antibiotics then became a critical part of contemporary medicine, not just for use in treating known infections but also in preventing infections arising from invasive procedures and immune-suppressive treatments. Increasingly though, antimicrobial resistance (AMR) threatens the effectiveness of antimicrobial therapy. AMR refers to the ability of microorganisms, including bacteria, fungi, viruses and parasites, to become resistant to the effect of antimicrobial medicines because they have changed genetically or phenotypically so that they are able to grow when these medicines are used [1].

Microbial resistance is an innate property of evolution, but it has been greatly accelerated by human activities. Over and inappropriate antimicrobial consumption, inadequate infection control, poor hygiene, lack of diagnosis, inappropriate antimicrobial prescriptions, self-medication, and antimicrobial use in food-producing animals are all involved in the selection and spread of resistant organisms [2,3]. The antimicrobial resistance is thus becoming not only a clinical microbiology problem, but also a public health challenge. It is a multi-faceted social, biological, and environmental and public health problem.

A One Health framework is reinforced by the possibility of the circulation of resistant organisms and resistant genes in humans, animals, food systems, wastewater, soil and other compartments of the environment [17,18]. AMR is a major threat to global health as it impacts on the treatment of infections and the potential for severe illness and mortality, and is recognized by the World Health Organization (WHO) as such [1]. The size of the problem is large. The Global Burden of Disease analysis estimated that in 2021, 1.14 million people died directly as a result of bacterial resistance, with 4.71 million deaths being attributed to bacterial AMR overall [4]. Importantly, the epidemiology of AMR is evolving from one age to another and from one country or region to another. Although there has been a drop in AMR-associated mortality in children under the age of 5, there has been a significant

rise in mortality among older adults [4]. If no effective intervention takes place, forecast models project that deaths directly caused by AMR could reach around 1.91 million per year by 2050, and deaths due to bacterial AMR could be as high as 8.22 million per year [4]. The therapeutic problem is exacerbated by the lack of adequate development of novel truly unique antibacterial agents. At the end of 2023 WHO reported 97 antibacterial products being in clinical development, comprising 57 traditional antibiotics and 40 non-traditional agents, but the pipeline is still not enough to meet the most critical resistant pathogens [19].

Global burden of Antimicrobial resistance

2.1 Mortality and morbidity

Bacterial AMR is a major problem globally, and has grown significantly in recent decades. The Global Burden of Disease study estimated that, in 2021, 4.71 million deaths were caused by AMR due to bacteria, with about 1.14 million deaths being directly caused by resistance [4]. These estimates clearly illustrate that resistant bacterial infections contribute significantly to death worldwide, today. It is not equally shared. The variations between the regions are due to differences in antimicrobial use, healthcare access, vaccination rates, diagnostic availability, infection prevention, sanitation, socio-economic factors, and availability of effective antimicrobial treatment [4,21]. Some regions have especially significant needs, such as South Asia, which has high infectious disease burden and exposure to antimicrobials, healthcare disparities, and a small number of laboratories. AMR is also a significant cause of morbidity. Resistant infections can make effective treatment more difficult and slow, increase hospital stay, require intensive care support and invasive procedures, and costs the healthcare system more [3,22]. In addition, AMR can make procedures relying on successful infection prevention or treatment, such as major surgery, transplantations, chemotherapy, and intensive-care medicine, unsafe [23].

2.2 Major bacterial pathogens

Few bacterial pathogens have a disproportionate burden of antimicrobial resistance and are relatively limited in number. Main organisms of concern are *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Salmonella* spp., *Shigella* spp., and *Neisseria gonorrhoeae* [4,20].

Methicillin-resistant *S. aureus* (MRSA) is still a significant pathogen in both the healthcare-associated (HA-MRSA) and community-associated (CA-MRSA) settings. The high-level resistance of MRSA to β -lactam antibiotics is especially linked to the acquisition of *mecA* or *mecC*, which encodes an altered penicillin-binding protein that has decreased affinity for β -lactam antibiotics [5]. Another important issue is the presence of carbapenem-resistant Enterobacterales. *K. pneumoniae* and *E. coli* can gain the ability to produce extended-spectrum β -lactamases (ESKAPE), AmpC enzymes, carbapenemases and other resistance mechanisms that significantly limit therapeutic choices [5,6]. The presence of carbapenem-resistant *A. baumannii* is especially concerning in intensive-care settings due to its ability to persist in the environment, form biofilms and combine several resistance mechanisms [20]. WHO 2024 Bacterial Priority Pathogens List has been created to prioritize research, development and public-health interventions by placing resistant bacterial pathogens into three groups – critical, high and medium priority. Among the 15 families included in the list are 24 pathogens that continue to be clinically important, focusing on resistant Gram-negative organisms, drug-resistant *M. tuberculosis*, *Salmonella*, *Shigella*, *P. aeruginosa*, *S. aureus*, and more [20].

Drivers of Antimicrobial Resistance

One of the greatest selective pressures that have led to the evolution of resistance is exposure to antimicrobials. When antimicrobial levels kill susceptible organisms while leaving resistant organisms alive, the population of resistant organisms can increase and become predominant [2,6].

Major drivers include:

1. Inappropriate prescribing
2. Excessive use of general antibiotics
3. Self-medication
4. Giving the wrong dose or the wrong length of time.
5. Inadequate microbiological diagnosis
6. Poor infection-control practices
7. Poor sanitation and hygiene.
8. The use of antimicrobials in livestock and aquaculture (Livestock & Aquaculture).
9. Environmental contamination
10. The movement of people to and from other countries. Cross-border travel and migration.
11. Weak surveillance systems [2,3,17].

The importance of antimicrobial use in animals lies in the fact that resistant bacteria and resistance determinants can be transferred from one animal population to another, from human beings to animals, food to animals, and from animals to the environment [17]. Therefore, antimicrobial use should be considered in the context of the wider ecology, not just a health care concern. Microbial resistance mechanisms at the molecular level. There are three types of bacterial resistance: intrinsic, acquired, and adaptive. Intrinsic resistance exists naturally within a bacterial species while acquired resistance occurs due to resistance genes or mutations. Transient phenotypic changes occurring in response to environmental conditions or antimicrobial exposure are adaptive resistance [5,6].

4. Molecular mechanism of antimicrobial resistance

4.1 Enzymatic inactivation

Enzymatic modification or destruction of antimicrobial molecules is one of the most important mechanisms, which include the hydrolysis of the β -lactam ring of penicillins, cephalosporins, monobactams, and, in some instances, carbapenems [5,6]. Extended-spectrum β -lactamases (ESBL), AmpC β -lactamases and carbapenemases are important groups of enzymes. Aminoglycosides also can be modified enzymatically by acetylation, phosphorylation or adenylation, which decreases the interaction with the bacterial ribosome [6]. Enzymatic degradation or modification, is thus an important mechanism allowing bacteria to neutralize antimicrobial agents prior to their reaching their intracellular targets.

4.2 Modification of antimicrobial targets

The first step is to modify what the antimicrobial is targeting. The first is to alter the target of the antimicrobial. Resistance can develop when the bacteria to which an antimicrobial drug has been directed is structurally changed. Variations in penicillin-binding proteins may result in reduced binding to the β -lactam and mutations in DNA gyrase and topoisomerase IV may lead to decreased susceptibility to fluoroquinolones [5,6]. Changes in the ribosome targets may also contribute to resistance to macrolides, aminoglycosides, tetracyclines and other protein-synthesis inhibitors. Target protection proteins may also disrupt the interaction between the antimicrobial and the target, but do not directly affect the target [5].

4.3 Reduced permeability

The antimicrobial activity is in part determined by the ability of a drug to gain access to its intracellular or membrane-associated target. Antimicrobial levels in the cell may thus be decreased when the permeability of the cell's membranes changes. In Gram-negative bacteria, changes or loss of outer membrane porins can lead to less uptake of antimicrobial agents [5,6] making this mechanism relevant.

4.4 Active efflux

In order to keep the intracellular concentration of antimicrobial compounds below the therapeutic level, efflux pumps actively expel them from the bacterial cell. There are several efflux families, such as resistance-nodulation-division, ATP-binding cassette, major facilitator, small multidrug resistance, and multidrug and toxic compound extrusion families [5]. Efflux-mediated resistance can be mediated by several structurally unrelated classes of antimicrobial agents and thus can play a role in multidrug resistance.

4.5 Horizontal gene transfer

Bacterial resistance genes can easily spread horizontally among bacteria. There are two main mechanisms, conjugation, transformation and transduction [6]. Resistance determinants can be acquired and transferred by plasmids, transposons, integrons, insertion sequences and bacteriophages. The significance of horizontal gene transfer is that it can enable bacteria to gain resistance more quickly than spontaneous mutation can. The frequency of the transfer of resistance determinants is therefore a significant factor in the widespread of MDROs.

4.6 Biofilm-associated resistance

Biofilms are microbial communities that grow within a matrix of secreted extracellular polymeric substances. Biofilms can exhibit resistance to antimicrobial agents due to impaired penetration of the antimicrobial agents, altered antimicrobial metabolism, heterogeneity of the micro-environment, stress response, and presence of persistent antimicrobial agents [24]. Biofilm associated resistance is especially important in chronic wounds, medical implants, urinary catheters, chronic respiratory infections, and in prosthetic joint infections [24]. The ability to treat biofilms often requires the use of multiple treatment methods as opposed to standard antibiotic therapy, due to the multiple physiological and structural mechanisms.

5. Emerging Therapeutic Strategies

With the rise of multi drug resistant organism there has been a surge in research on new therapeutic strategies to overcome these pathogens beyond the realm of traditional antibiotics.

5.1 Bacteriophage therapy

Bacteriophages are viruses that invade bacteria and, after replication, can cause the destruction of the bacteria. They are able to identify certain bacterial receptors, giving them the potential to treat the illness according to the pathogen [7]. The benefits of phage therapy are several-fold: it can be specific to a particular bacterium, it does not disrupt commensal bacteria and it may be possible to create cocktails of phages to treat a variety of bacteria. The use of phage-derived enzymes, like endolysins, is also being explored for their antibacterial effects [7]. Some of the limitations, however, are the restricted host range, development of phage resistance, immune neutralization, pharmacokinetic limitations, manufacturing standardization, and regulatory issues [7]. Thus, in the future, engineered phages, phage cocktails, phage-derived enzymes and phage-Antibiotic combinations will be the technology focus.

5.2 Antimicrobial peptides

Antimicrobial peptides (AMPs) are peptides that are found in nature or created synthetically that have antibacterial activity. Numerous AMPs interact with microbial membranes which lead to disruption of the membrane, pore formation, or changes in membrane integrity [8]. AMPs are multimodal antimicrobial agents that may also modulate host immune function [8] and whose action is not so dependent on specific intracellular targets as are many conventional antibiotics. These properties make them good candidates for resistant infections. However, these factors of proteolytic instability, toxicity, poor pharmacokinetics, manufacturing cost and the inability to achieve sufficient concentrations at infection sites make clinical translation difficult [8,25]. Some of these limitations can be addressed by rational peptide engineering and nanotechnology based delivery systems.

5.3 CRISPR-Cas-based antibacterial therapy

The CRISPR-Cas systems are of interest as precision antimicrobial tools as they could specifically target the DNA sequence of bacteria [9]. CRISPR-based strategies could be used to target key bacterial genes, virulence factors, or antimicrobial-resistance genes. One very appealing idea is the ability to select for and eliminate resistance determinants from bacterial populations, which may restore susceptibility to traditional antibiotics. Delivery, however, is a significant issue as the CRISPR components need to be delivered to the target bacterial population and efficiently into the bacterial cells [9]. These could be delivered as bacteriophages, conjugative plasmids, nanoparticles, or engineered bacterial vectors. To achieve future success, not only the CRISPR systems need to be improved, but safe and efficient bacterial delivery systems as well.

5.4 Nanotechnology-based antimicrobial therapy

Nanotechnology offers opportunities to enhance the delivery of antimicrobials, as well as create new antimicrobial activity that is not observed with traditional drugs. The use of nanomaterials can lead to higher concentrations of drugs at the infection site, better penetration of biofilms, controlled release of drugs at the infection site, and greater activity of existing antimicrobial drugs [10]. The materials that have been investigated are silver, gold, zinc oxide, copper-based nanoparticles, lipid nanoparticles, polymeric nanoparticles, dendrimers and nanocomposites [10]. Nanomaterials can cause damage to the membranes of bacteria, produce ROS, disrupt the intracellular processes, or improve the delivery of antimicrobials. However, other factors such as toxicity, biodistribution, environmental persistence, manufacturing reproducibility, and long-term safety are important hurdles to clinical translation [10].

5.5 Anti-biofilm therapies

Biofilms are an important reservoir of persistent antimicrobial tolerance. Therapeutic strategies are thus increasingly targeted to disrupt the biofilm matrix, and bacterial communication, not only the killing of planktonic bacteria [24]. Some of the possible approaches involve the degradation of EPS, inhibition of quorum sensing, biofilm-dispersal agents, antimicrobial coatings, surface modification of medical devices, DNase-based methods, phage-derived enzymes, and combination therapy [24]. Biofilm formation is a multi-interacting pathway, and multitarget approach may be more effective than single-agent approach.

5.6 Quorum-sensing inhibitors

Bacteria use quorum sensing to regulate gene expression in relation to the cell density. This communication system is involved in virulence factor production, biofilm formation, motility, secretion systems and more. Quorum-sensing inhibitors could, therefore, act as anti-virulence agents and not as direct bactericidal agents. The possible strategies are synthetic inhibitors, receptor antagonist, quorum-quenching enzymes and naturally occurring compounds. They could be less competitive in terms of selective pressure in comparison to traditional bactericidal treatment, yet the difficulty and species-specific quorum sensing networks are still a problem. An understanding of monoclonal antibodies and immunotherapeutic approaches. Knowledge of monoclonal antibodies and immunotherapeutic approaches. These can be microbial toxins, surface antigens, capsules, adhesion molecules or other structures associated with microbial virulence. Mechanisms that might be involved are toxin neutralisation, blocking of bacterial adhesion, increased opsonisation and immune-mediated clearance. These could be especially helpful in infections where traditional antimicrobial treatment is inadequate, or in susceptible patient groups. Combination therapy with monoclonal antibodies and antibiotics might offer further therapeutic advantages.

5.7 Microbiome-based therapies

A broad-spectrum antibiotic can alter the normal microbiome and provide an ecological environment which allows resistant organisms to colonize. Therefore, restoring the microbiome-mediated “colonization resistance” is becoming a new approach to control AMR [26]. Possible interventions are probiotics, defined microbial consortia, fecal microbiota transplantation, bacteriocins, engineered commensal bacteria, and microbiome-derived metabolites. The key hurdle is the need to create standardized, reproducible and safe microbiome therapeutics.

5.8 Host-directed therapy

Host-directed therapies involve altering host responses and not directly targeting pathogens in hopes of improving pathogen clearance or decreasing tissue damage. Innate immunity, inflammatory pathways, macrophage activity, autophagy, iron metabolism and epithelial barrier function are possible targets. These approaches might be especially beneficial in the context of pathogens resistant to a number of antimicrobial agents. But immune activation at inappropriate levels can result in tissue damage, so therapeutic modulation needs to find a balance between pathogen clearance and immunopathology.

5.9 Artificial intelligence and antimicrobial discovery

Increasingly, artificial intelligence (AI) and machine learning are being used in the discovery of antimicrobials. These technologies can help to search through vast amounts of chemical, genomic, proteomic and biological data to find compounds that may have antibacterial properties. In a pioneering study, deep learning was shown to be capable of discovering a novel class of structurally unrelated antibacterial agents, called halicins, a large chemical library [11]. These can help to shorten virtual screening, molecular optimization, toxicity prediction, discovery of new targets, prediction of antimicrobial resistance, and the discovery of antimicrobial combinations, among others. But, experimental testing of computational predictions will be needed in microbiological, pharmacological, toxicological and clinical studies. AI is thus not a substitute for experimental research but a tool to accelerate discovery.

6. Combination Antimicrobial Therapy

Use of combination therapy is increasingly relevant in the treatment of infections due to multidrug-resistant organisms. A combination of agents using different mechanisms may provide greater killing ability and a lower chance of resistance occurring to a combination of agents at the same time. These combinations may include antibiotic–antibiotic combinations, antibiotic with β -lactamase inhibitory agents, antibiotic–phage combinations, antibiotic–AMP combinations, antibiotic–nanoparticle combinations and antibiotic–anti-biofilm combinations. But combination therapy may also cause toxicity, drug interactions, antagonism, and inordinate antimicrobial exposure. Rational combinations should thus be based on susceptibility testing, pharmacodynamic considerations, pathogen specific factors, and patient consideration.

Antimicrobial Stewardship

New therapeutic agents can not replace responsible use of anti-microbials. The overarching goal of antimicrobial stewardship is to use antimicrobial therapy that is the right antibiotic, right dose, right route, right time, and right duration with the least exposure. WHO AWaRe classifies antibiotics as Access, Watch and Reserve and gives guidance on how to use the antibiotics optimally [27]. Some of the other interventions that can be part of stewardship programs include prospective audit and feedback, antimicrobial restriction, antimicrobial guidelines, dose optimization, IV-to-oral conversion, diagnostic stewardship, and monitoring of antimicrobial use. The stewardship of the future is going to become ever more data-driven with the integration of electronic health records, rapid diagnostics, local resistance patterns, pharmacokinetic and pharmacodynamic data and predictive algorithms.

Surveillance and Genomic Epidemiology

WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) was created to enhance collection and analysis of AMR and antimicrobial-use data in a standardized way [28]. The traditional surveillance system that relies on antimicrobial susceptibility testing and includes antimicrobial consumption, clinical outcomes, healthcare-associated infection data, environmental surveillance, and information from the animal sector can be strengthened. Whole genome sequencing can be used for identification of resistance determinants, investigations of outbreaks, determination of independent emergence from transmission and detailed epidemiological information. Genomic surveillance in tandem with wastewater surveillance could be an early-warning tool for communities' resistance patterns.

9. One Health Approach

AMR is fundamentally entangled between people, animals, plants and ecosystems. Exposure of livestock, poultry, aquaculture and veterinary products to antibiotics can lead to the evolution of resistant organisms which could then be spread through food, animal contact, wastewater, soil, and other environmental channels [17,18]. A coordinated intervention is therefore needed across human medicine, veterinary medicine, agriculture, environment, food system and health and public health, for a One Health approach. Key components include: ☐ responsible antimicrobial use; ☐ infection prevention;

□vaccination; □environmental monitoring; □antimicrobial stewardship; □surveillance across sectors; □responsible agricultural practices; □improved sanitation; □public education; and □coordinated national and international policy.

Current Challenges

Although scientists have come a long way in their progress, there are still some obstacles in the way of effective control of AMR. A serious difficulty that needs to be overcome in the future. Emergence of resistance - precision and combination therapies Lack of antibiotic innovation New drug-discovery platforms Targeted anti-biofilm approaches: Biofilm associated persistence Engineered phages and phage cocktails Phage host specificity Safe bacterial delivery systems - CRISPR delivery barriers Toxicity of nanoparticles Safety studies over a long term Delayed diagnosis Rapid point of care diagnosis Disruption of gut microbiome/Microbiome-sparing interventions Weak surveillance Integrated genomic and integrated One health surveillance To ensure good stewardship of antimicrobials, strong stewardship programs are in place. Limited economic incentives for antibiotic development Sustainable antibiotic-development models Global inequality Equitable access to diagnostics and effective treatment It is a significant challenge to create the antibacterial pipeline. At the end of 2023, WHO had documented 97 antibacterial agents in clinical development, and highlighted the fact that the current pipeline is still not sufficient in terms of quantity or type to meet the extent and complexity of the AMR challenge [19].

Future Perspectives

10.1 Precision antimicrobial therapy

Precision antimicrobial therapy will be the way of the future in AMR management. By rapid identification of pathogen and resistance determinant, clinicians may be able to choose therapy based on that instead of a lot of empirical broad-spectrum therapy. In the future, molecular diagnostics, genomic sequencing, proteomics, metagenomics and Artificial Intelligence could allow for the identification and prediction of pathogens and resistance in hours, not days. Genomic and Environmental Surveillance.

10.2 Genomic and environmental surveillance

Whole genome sequencing can offer detailed information on resistance genes, resistance pathways. Population-level resistance to an emerging pathogen may be discovered earlier by implementing genomic surveillance alongside wastewater monitoring. This monitoring should be combined with information on antimicrobial consumption and monitoring through animal and environmental surveillance to build a holistic early warning system for AMR.

10.3 Vaccination as an AMR-control strategy

Vaccination contributes to AMR control in an indirect way, through protecting people from getting infected and the need for antimicrobial treatment. This limitation in exposure to antimicrobial provides less opportunity for the emergence and spread of resistant organisms if infection incidence is reduced. Hence, enhancing vaccination programmes is an important part of AMR prevention.

10.5 Novel antibiotic development

New antibiotics will continue to be needed especially in the treatment of life-threatening infections from very resistant organisms. But the old-fashioned approach to antibiotic discovery is not going to solve the AMR crisis. WHO recently highlighted the importance of new agents and new non-traditional modes of action against priority pathogens [19]. Therefore, potential drug-development strategies ought to be focused on novel mechanisms, pathogen-specific agents, resistance-modifying agents, products derived from phages, antimicrobial peptides, agents against virulence, microbiome-based agents and rational combinations. Integrated Future Strategy for AMR Control What should be included in a sustainable, AMR-control framework is the use of a multi-intervention approach instead of relying on a single 'next generation antibiotic'.

11. Conclusion

AMR is a biological, clinical, environmental and social challenge that is complex and continually evolving. Super bugs and the rise of multidrug-resistant organisms are increasingly making traditional antimicrobial treatments ineffective, and could potentially jeopardize significant advances in modern medicine. Bacterial AMR is already a significant cause of death worldwide, and is expected to be a significant cause of death in the future if interventions are not used effectively [4]. Similarly, the molecular mechanisms of resistance are complex, including the ability to inactivate antimicrobial enzymes, modify targets, reduce permeability, actively pump antimicrobials out of cells, acquire of new genes, metabolic adaptation and tolerance in biofilm. [5,6] Thus, drugs that target conventional antibiotic targets are not enough for the future therapeutic development.

However, any one intervention will not be enough. Innovative therapeutics, coupled to fast diagnostics, antimicrobial stewardship, vaccination, infection prevention, genomic surveillance, environmental monitoring and One Health policies, will be key to the future of AMR management. Access to effective medicines and diagnostics, investment in antimicrobial research and development, responsible antimicrobial use, and cooperation between all parts of the world will be crucial. So the best approach to the future is probably not the identification of one "super antibiotic". Rather, it will be a precision-AMR ecosystem that combines surveillance, rapid diagnosis, targeted therapy, stewardship, prevention, and One Health interventions to ensure the continued effectiveness of existing and future antimicrobials.

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