Antimicrobial resistance: a concise update

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Antimicrobial resistance (AMR) is a serious threat to global public health, with approximately 5 million deaths associated with bacterial AMR in 2019. Tackling AMR requires a multifaceted and cohesive approach that ranges from increased understanding of mechanisms and drivers at the individual and population levels, AMR surveillance, antimicrobial stewardship, improved infection prevention and control measures, and strengthened global policies and funding to development of novel antimicrobial therapeutic strategies. In this rapidly advancing field, this Review provides a concise update on AMR, encompassing epidemiology, evolution, underlying mechanisms (primarily those related to last-line or newer generation of antibiotics), infection prevention and control measures, access to antibiotics, antimicrobial stewardship, AMR surveillance, and emerging non-antibiotic therapeutic approaches. The Review also discusses the potential roles of artificial intelligence in addressing AMR, including antimicrobial susceptibility testing, AMR surveillance, antimicrobial stewardship, diagnosis, and antimicrobial drug discovery and development. This Review highlights the urgent need for addressing the global effects of AMR and for rapid advancement of relevant technology in this dynamic field.

Introduction

Antimicrobial resistance (AMR), particularly bacterial AMR, has become a crucial global health threat, jeopardising the efficacy of treatment and prevention of infections. With roughly 5 million deaths associated with bacterial AMR in 2019,[1] and this number projected to increase substantially by 2050 if left unaddressed,[2] urgent action is imperative. For example, the COVID-19 pandemic intensified antibiotic usage and accelerated the development of pathogen resistance,[3] and a multistate outbreak of extensively carbapenem-resistant *Pseudomonas aeruginosa* in the USA linked to multidose artificial tears resulted in severe ocular and systemic infections, with consequent fatalities.[4] The global emergence of AMR against diverse carbapenemases in multiple bacterial species, associated with high mortality and potential biofilm formation, further reinforces the unmet clinical need for action on AMR.[5–7]

Several high-quality AMR-related reviews have been published previously, but most reviews have covered specific areas of AMR such as the burden, risks, and mechanisms of resistance.[1,3,8,9] Recognising the global effects and rapid advancement in this field, we aimed to provide a concise update on bacterial AMR, encompassing the epidemiology, mechanisms of resistance, emerging non-antibiotic therapeutic approaches, and potential roles of artificial intelligence.

Epidemiology and global effects

AMR is a leading cause of mortality that contributes to about 9% of all global deaths.[1] Approximately 13·7 million infection-related deaths were reported in 2019,[10] with AMR-related infections directly contributing to an estimated 1·27 million deaths and indirectly to 4·95 million deaths. The incidences of AMR-associated deaths ranged from 28·0 (Australasia) to 114·8 (western sub-Saharan Africa) per 100 000 people.[1] Substantial geographical variations in AMR gene abundance and diversity were similarly shown by metagenomics analyses of urban sewage.[11] The effects of AMR-related morbidity or mortality are particularly severe in low-income and middle-income countries (LMICs), aggravating extreme poverty. If left unaddressed, LMICs will experience an estimated loss of greater than 5% of gross domestic product by 2050 due to loss of income from indirect costs of care, and the global annual gross domestic product will decline by an estimated 3·8%, resulting in a global loss of US$100 trillion.[2] AMR will also lead to a substantial increase in health-care expenditures due to the cost of prolonged hospital admission, intensive investigations or treatments, disability, and death, a figure that has been estimated to cost $4.6 billion in 2017 in the USA.

The 2022 Global Burden of Disease study identified *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *P aeruginosa* as the six leading causes (73%) of AMR-associated deaths in 2019.[1] These pathogens are part of the 2024 WHO bacterial priority pathogens list (appendix pp 1–2) and overlap with a distinct group of pathogens, ESKAPEE, encompassing *Enterococcus* spp, *S aureus*, *K pneumoniae*, *A baumannii*, *P aeruginosa*, *Enterobacter* spp, and *E coli*, notoriously known to cause drug-resistant nosocomial infections. These pathogens can survive or thrive in health-care environments due to their extensive repertoire of intrinsic or acquired resistance mechanisms and were estimated to cause greater than 330 000 AMR-attributable deaths in 2019.[12] However, these figures might be confounded by the data scarcity in LMICs (with no data from 19 countries), little distinction between community-acquired and nosocomial infections, lack of universal guidelines or protocols for antibiotic susceptibility testing, and case-selection bias (eg, testing only performed in non-responsive cases, leading to overestimation of AMR), highlighting the need for future improvements.[1] In addition, another important WHO critical priority bacterium, *Mycobacterium tuberculosis*, which causes drug-resistant tuberculosis, caused around 1·3 million global deaths in 2022.[13]

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See Online for appendix

Initially observed in high-income countries mainly due to antibiotic overuse or misuse, AMR has rapidly emerged in LMICs as well from 2011 to 2021, primarily attributed to the profound increase in antibiotic usage and increased detection through surveillance programmes.[14] Most AMR infections, including urinary tract infections, sexually transmitted infections (especially those caused by *Neisseria gonorrhoeae*), typhoid fever, and *S pneumoniae*-related infections, are acquired in the community. Community-acquired urinary tract infections, commonly caused by the ESKAPEE pathogens, affected 404·6 million people globally and caused greater than 200 000 deaths in 2019.[15] Compared with those in high-income countries, patients in LMICs face a considerably higher risk of developing nosocomial infections, with urinary tract infections and surgical-site infections being most prevalent.[14] AMR poses substantial health threats to the young (<5 years), the old (>65 years), and weak or immunocompromised patients (eg, those with cancer or diabetes), for whom the emergence of drug-resistant infections is accelerated by the use of prophylactic antibiotics and need for extended antibiotic treatments.[16] Approximately 214 000 neonatal deaths have been attributed to AMR per year globally, particularly in LMICs.[17] AMR also threatens the effectiveness of antibiotics after surgeries (eg, organ transplantations), thereby exacerbating treatment failure and mortality.

Socioeconomic issues play a crucial role in AMR. Regions with little access to clean water, sanitation facilities, and effective antibiotics, in addition to weak health infrastructures account for greater than 90% of AMR-related deaths.[14] In LMICs, the scarcity of basic diagnostic testing capacity contributes to antibiotic misuse or overuse. Studies in sub-Saharan Africa and Asia reported widespread empirical use of antibiotics for febrile illnesses, even when unnecessary.[18] The inadequate resources and surveillance facilities for AMR in LMICs hinder the development of effective antimicrobial interventions. Based on the widespread distribution of AMR genes, Viet Nam, India, and Brazil are potential hot spots for the evolution of new AMR mechanisms.[11]

Globalisation, human mobility, tourism, and climate change can influence the dissemination of AMR. Phylogeographic[19] and genomic[20] studies have provided evidence for the global spread of extensively drug-resistant *Salmonella* Typhi through travel or migration, as also noted for quinolone-resistant *Shigella*, extended-spectrum β-lactamase-producing Enterobacterales, and meticillin-resistant *S aureus*,[21] underlining the importance of safe travel practices, vaccinations, and food safety. Many infectious diseases are climate-sensitive; carbapenem-resistant *P aeruginosa*, *Salmonella*, and *Vibrio cholerae*, for example, are substantially associated with warm season and temperature changes.[22]

Agricultural practices are most likely to influence the distribution of AMR genes,[2,23,24] although not in all cases, as some studies showed limited transmission of AMR between clinical and non-clinical isolates (present in animal, food chain, and environmental settings).[25,26] Antibiotics are used extensively in livestock for disease prevention and treatment, surpassing global human use.[2] In 2017, antimicrobial use in animals was estimated to account for 73% of all antimicrobials used globally, with annual agricultural antibiotic consumption projected to increase by 67%, from 63 151 tonnes in 2010 to 105 596 tonnes by 2030.[22,27] A recent review, based on data extrapolated from 229 countries, highlighted China as the top hot spot for antimicrobial use in food-producing animals, followed by Brazil, India, the USA, and Australia; these five countries were responsible for 58% of global antimicrobial use.[28] Antibiotic use in food production promotes the development of reservoirs of AMR bacteria and genes that can be transmitted to humans through zoonotic means, including direct infection or transmission of AMR bacteria and indirectly through colonisation of the human gut, providing opportunities for horizontal gene transfer from AMR bacteria to gut commensals.[24] However, clinically relevant AMR genes were also observed in wild animals despite no prior contact with antibiotics,[29] emphasising the importance of a One Health approach in understanding the effect of the AMR genes on agricultural and human ecosystems.

Mechanisms of AMR

Following the discovery of penicillin in 1928, 20 novel structural classes of antibiotics were developed between 1930 and 1960 (table 1). However, stagnation in the discovery or development of new antimicrobial classes since the 1980s has led to over-reliance on the existing antibiotics. Multifaceted resistance mechanisms evidenced by bacteria, including reduced membrane permeability, the use of efflux pumps, enzyme modification or degradation of antibiotics, modification of antibiotic targets, and adaptive mechanisms such as biofilm formation, affect the efficacy of nearly all known antibiotics (figure 1 and table 1). Although the timing of developing resistance might vary among different antibiotic-bacteria combinations, most AMR typically occurs within 0–6 months after antibiotic exposure, underlining the formidable challenge of AMR.[30] The mechanisms of AMR have been discussed in comprehensive reviews.[8,12,31,32]

AMR in the context of next-generation and last-line antibiotics

Since 2010, 29 antibiotics have received marketing authorisation; most of these are modifications to existing classes such as carbapenems, aminoglycosides, and macrolides. Despite efforts to circumvent resistance mechanisms through structural alterations, cross-resistance between old and new antibiotics within the same drug classes typically occurs due to the numerous resistance genes in the resistomes,[33] which restrict the efficacy of the new compounds against specific multidrug-resistant pathogens.[34] Furthermore, colistimethate, often regarded as a last-resort antibiotic for treating infections caused by multidrug-resistant Gram-negative bacteria has been threatened by the

	Target site	Examples of AMR-related genes or mutations
Aminoglycosides	30S ribosomal unit	*aac*, *aad*, and *aph*: encode enzymes that modify aminoglycoside to acetylate (*aac*), adenylate (*aad*), or phosphorylate aminoglycoside –OH or –NH_2 groups (*aph*), reducing the binding of aminoglycoside to the ribosome binding site
β-lactams	Cell wall	*bla*: encodes β-lactamase, which cleaves the amide bond in the β-lactam ring *mecA,B,C,D*: encode PBP-2a, which has similar functions as the intrinsic PBP-2, but with a substantially lower binding affinity for β-lactam antibiotics
Fluoroquinolones and quinolones	DNA gyrase, topoisomerase IV, and cell wall	*parC,E* (or *grlA,B*): encode ParC and ParE subunits of DNA topoisomerase IV; mutations inhibit binding of quinolones *gyrA,B*, *parC,E*, *qnr*: mutations prevent binding of quinolones to DNA gyrase *sdrM*, *sepA*, *lmrS*, *qepA*, *norA,B,C*: encode efflux pumps that extrude fluoroquinolones
Fosfomycin	Cell wall	*fosA,B,X*: produces glutathione S-transferase, which catalyses the conjugation of glutathione to carbon-1 of fosfomycin
Fusidic acid	Ribosome EF-G	*fusB*: binding of fusidic acid resistance protein to drug target EF-G in the ribosome enables translation in the presence of fusidic acid
Glycopeptides	Cell wall	*vanA*, *vanH*, *vanX*: reprogram peptidoglycan precursor biosynthesis to reduce the affinity of cellular targets for glycopeptides (eg, vancomycin)
Lincosamides	50S ribosomal unit	*cfr*, *erm*: encode 23S rRNA methyltransferase, which restores bacterial protein biosynthesis *lsa*, *sal*, *vga*, *vml*: protect ribosomes from inhibition by lincosamide
Lipopeptides	Cell wall	*gdpD*: glycerolphosphodiesterase mutations reduce daptomycin binding *mprF*: enhances lysinylation of phosphatidylglycerol, causing an increased net positive charge on the cell wall and increased cell wall thickness *lacF*: increases cell wall thickness
Macrolides	50S ribosomal unit	*erm*: encodes 23S rRNA methyltransferase, which restores bacterial protein biosynthesis *mef*: encodes efflux pump *mel*: encodes ribosomal protection protein
Oxazolidinones	50S ribosomal unit	*cfr*: encodes 23S rRNA methyltransferase, which restores bacterial protein biosynthesis *optrA*, *poxtA*: encodes ABC-F proteins that protect bacteria from the inhibitory effect of oxazolidinones
Phenicols	50S ribosomal unit and cell wall	*cat*: encodes chloramphenicol acetyltransferase enzyme, which chemically modifies phenicols *cfr*: encodes 23S rRNA methyltransferase to block the inhibition of bacterial protein biosynthesis *cmL*, *floR*: encode drug efflux pumps
Polymyxins	Cell membrane	*crrB*, *mcr*, *mgrB*, *pmrA,B,D*: mediate lipopolysaccharide modification to block binding and self-promoted uptake
Trimethoprim	DHFR	*dfrA*: mutation prevents trimethoprim binding *dfrG*: causes frameshift deletion of thymine leading to non-functional $DHFR_{dfrG}$ *folA*: decreases the affinity of DHFR for trimethoprim
Rifamycin	RNA polymerase	*rpoB*: reduces the affinity of antibiotics for the β-subunit of RNA polymerase
Streptogramins	50S ribosomal unit	*cfr*: encodes 23S rRNA methyltransferase, which restores bacterial protein biosynthesis
Sulphonamides	Dihydropteroate synthase	*folP*: decreases the affinity of dihydropteroate synthase for sulphonamides *sul*: encodes forms of dihydropteroate synthase that are not inhibited by sulphonamides
Tetracyclines	30S ribosomal unit	*tetA,B,C,D*: mediate tetracycline efflux *tetMQP*: ribosomal protection
Multiple antibiotics*	Multiple targets	*MexAB-OprM*, *MexXY*, *MexCD-OprJ*, *MexEF-OprN*: RND-based tripartite multidrug efflux pump systems that catalyse the extrusion of their specific substrates from the periplasm through the outer membrane *AcrAB-TolC*: an RND-based tripartite multidrug efflux pump system located at the outer membrane of Gram-negative bacteria *OmpC*, *OmpF*, *OmpK*, *PIB*: major outer membrane porin proteins; loss of these porins inhibits the entry of many different classes of antibiotics (eg, β-lactams, aminoglycosides fluoroquinolones, and others) *msrE*: ABC-F proteins lack the transmembrane domain characteristic of transporters, provide ribosomal protection by interacting with the ribosome and displacing the bound drug

ABC-F=ATP-binding cassette F. AMR=antimicrobial resistance. DHFR=dihydrofolate reductase. EF-G=elongation factor G. PBP=penicillin-binding protein. RND=resistance-nodulation-division. *Some AMR-related genes and proteins can have effects on more than one class of antibiotics.

Table 1: **Summary of major classes of antibiotics, AMR-related genes and proteins, and effects (the list is not exhaustive)**

emergence of plasmid-mediated *mcr*, whereas tigecycline, another last-resort antibiotic for treating infections caused by carbapenem-resistant Gram-negative bacteria, has been threatened by the emergence of *tet(X)*.[35–37] Therefore, new antibacterials that act through novel modes of action are urgently needed.

Teixobactin, a new member of the lipid-II-binding antibiotics, has been widely reported to be a major game changer.[38] However, despite the chemical novelty and broad-spectrum antimicrobial activity of teixobactin, its mechanism of action (ie, disruption of cell wall biosynthesis) is shared by several other drugs, including ramoplanin, nisin, and antimicrobial peptides. To date, teixobactin has not entered clinical trials. A review of anti-Gram-negative agents in clinical development revealed the scarcity of novel chemotypes among compounds in phase 2 and phase 3 clinical trials.[39] Two chemically novel bacterial topoisomerase II inhibitors, zoliflodacin and gepotidacin, stood out.[40] As the target of these inhibitors is conserved in bacteria, they have potent broad-spectrum antibacterial activity,[40] but they might also induce possible cross-resistance with fluoroquinolones due to the shared target.[41] Durlobactam, or ETX2514, is one of the few anti-infectives identified to date with a novel chemical structure and has received US Food and Drug Administration (FDA) approval, in combination with sulbactam (a generic β-lactamase inhibitor),[42,43] for treating infections caused by multidrug-resistant *A baumannii*, a WHO-listed

critical pathogen. Durlobactam is a rationally designed diazabicyclooctane β-lactamase inhibitor with potent activity against various β-lactamase classes and penicillin-binding proteins. Despite its novel chemical structure, durlobactam does not inhibit class B metallo-β-lactamases.[43] Although metallo-β-lactamases are currently less common in *Acinetobacter* spp than other carbapenemases,[44] their existence in the natural population suggests that durlobactam will face resistance in the near future. Additionally, bacterial outer membrane vesicles can serve as versatile tools to donate AMR genes (eg, carbapenem resistance genes)[45] or overcome antibiotics.[46]

Despite advancements in high-throughput screening methods and target-based antibacterial drug discovery, most successes pertain to Gram-positive bacilli,[47] thereby highlighting the enormous challenges posed by intrinsic resistance due to the permeability barrier of Gram-negative bacteria. Efforts have been devoted to improving the understanding of the physicochemical properties governing permeability and export via efflux pumps,[48,49] leading to the use of novel compound libraries and whole-cell bacterial assays. These advancements have yielded recent discovery successes, such as zosurabalpin, a novel LptB2FGC complex inhibitor identified through the screening of about 45 000 tethered macrocyclic peptides.[50] Similarly, the selection of compounds with an increased likelihood of intracellular accumulation in *E coli* identified high-quality starting points for lead optimisation using a high-throughput phenotypic screening assay with clinically relevant multidrug-resistant strains.[51] These efforts, alongside improved methodologies, novel compound libraries, and artificial intelligence, illustrate the potential for innovative screening approaches to uncover new antibiotic classes for tackling AMR.

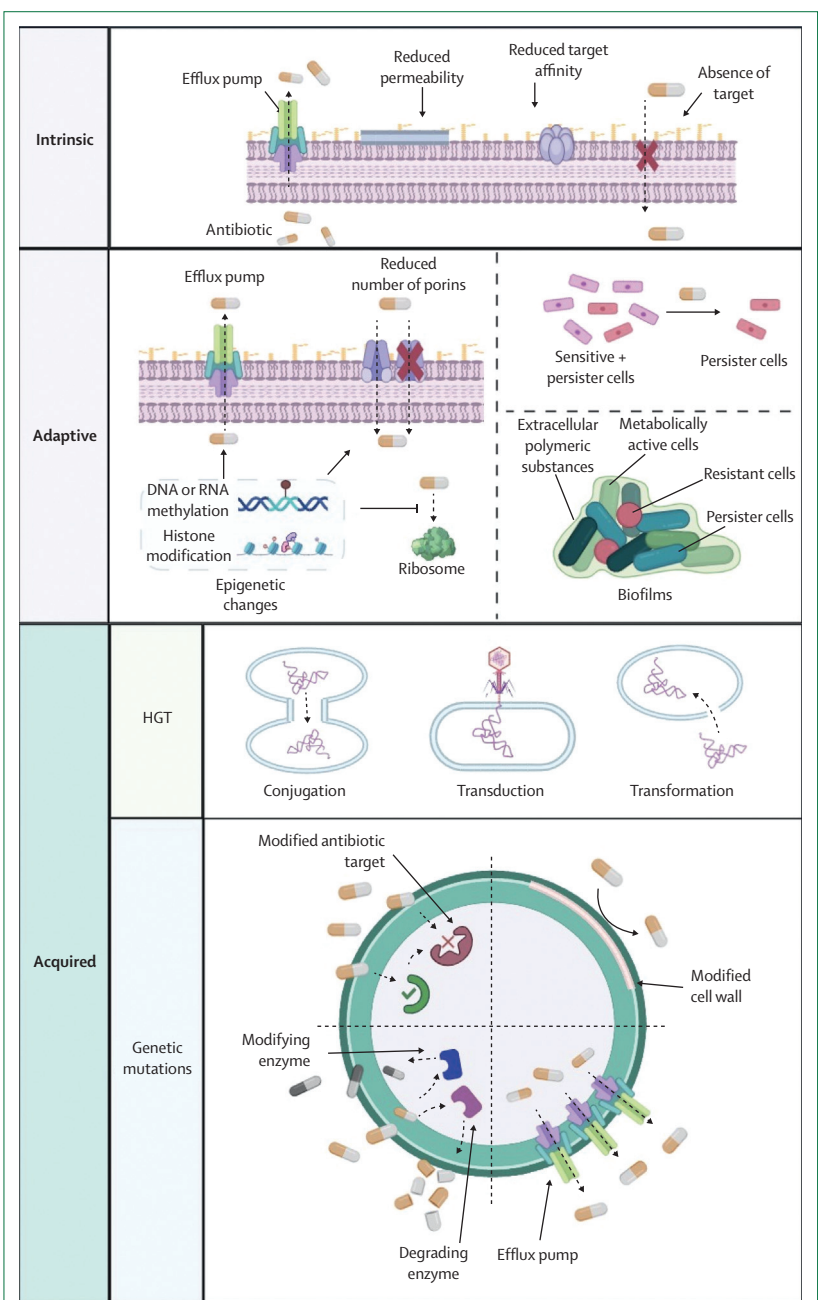

Figure 1: **Mechanisms of AMR**
The schematics present the intrinsic, adaptive, and acquired mechanisms of AMR. (Top panel) Intrinsic resistance reflects inherent bacterial survival properties, including the utilisation of diverse efflux pumps, reduced permeability (eg, outer membrane of Gram-negative bacteria), chromosomally encoded enzymes (eg, β-lactamases), and target modification. (Second panel) Adaptive mechanisms include the use of efflux pump, reduced number of porins, epigenetic changes, the presence of persister cells, and biofilm formation. Epigenetic changes can contribute to adaptive resistance through increased efflux pumps, reduced membrane permeability, and inhibition or prevention of antibiotic binding to target sites. Antibiotic-tolerant bacterial persister cells, which form part of the subpopulations of bacteria or biofilms, or both, can adaptively survive (but not proliferate) in the presence of antibiotics or stressors without genetic mutation. Biofilms, the quintessential adaptive bacterial growth state, enhance the survival of embedded bacteria through mechanical shielding, immune evasion, quorum sensing, the presence of highly diverse microbial communities (which survive or adapt to harsh environments such as scarce nutrients, altered pH, and low oxygen), and genetic transfer among subpopulations. Biofilm-embedded bacteria confer substantial resistance (by 10–1000-fold) to conventional antibiotics. Acquired mechanisms can occur through HGT (third panel) and genetic mutation (bottom panel); (A) Modification of outer membrane compositions of Gram-negative bacteria (eg, lipopolysaccharide modification or porin alteration or downregulation) can affect antibiotic permeability or activity. (B) Energy-dependent efflux pumps are ubiquitous membrane-associated channel machineries that have the ability to pump out antibiotics and toxic substances, thus improving bacterial survival; these pumps operate intrinsically but can also be induced adaptively (by stresses or antibiotics), dysregulated by mutations, or introduced through HGT. (C) Specific enzymes can modify antibiotics through phosphorylation, acetylation, adenylation, glycosylation, oxidation, or hydroxylation, impeding antibiotic binding to their targets. Degradative enzymes, including extended-spectrum β-lactamases, can hydrolytically cleave the β-lactam ring of penicillins or cephalosporins, leading to β-lactam and multidrug resistance. (D) Modification of antibiotic target sites can prevent binding to or allow replacement or bypass of the original drug target. Figure created with BioRender.com. AMR=antimicrobial resistance. HGT=horizontal gene transfer.

Strategies to mitigate AMR

To combat AMR, WHO recently established a global action plan with five components, calling for a multifaceted, coordinated effort from local, national, and global stakeholders and regulatory bodies. Aligned with the global action plan, 178 countries, including China (a major global antibiotic consumer), have implemented national action plans to curb AMR,[52,53] although only about 25% are effectively implementing the national plans.[15] The ultimate goals are to minimise or prevent AMR development, reduce its effects on human and animal health and the global economy, and increase the longevity of the currently available therapies.

Infection prevention and control, antibiotic access, and antimicrobial stewardship

Infection prevention and control programmes are the cornerstone in combating AMR, particularly in LMICs. A recent analysis estimated that ensuring universal access to water, sanitation, and hygiene and vaccines, could prevent greater than 337 000 AMR-associated deaths annually, from direct prevention of drug-resistant infections and reduction in antibiotic consumption.[54]

Vaccines are effective against AMR, both directly and indirectly.[55] Prevention of bacterial infections via vaccination obviates the need for first-line and second-line antibiotics, thereby reducing the emergence of drug-resistant isolates and the need for hospital admission (which could promote the community-to-hospital spread of AMR). Achieving sufficient vaccination coverage to establish herd immunity can also effectively disrupt the circulation of resistant strains, as documented for pneumococcal conjugate and *Haemophilus influenzae* vaccines. In addition, antiviral vaccines reduce the incidence of viral illnesses and minimise unnecessary or inappropriate antibiotic use in viral infections by 13–64%.[56] Vaccine resistance is rarer than antibiotic resistance due to the differences in the usage and purposes of vaccines. Vaccines are administered prophylactically before infection exposure, thus preventing microbial growth and AMR development. Some vaccines that target multiple epitopes could minimise the selective pressures that might otherwise lead to AMR development.

Improving sustainable and equitable access to effective antibiotics, particularly in LMICs, is key to achieving the 10-20-30 global target by 2030: 10% reduction in AMR-attributable deaths, 20% reduction in inappropriate antibiotic use in humans, and 30% reduction in inappropriate antibiotic use in animals.[57] The WHO Access, Watch, Reserve framework advocates the need to allow for universal and affordable Access antibiotics with narrow-spectrum and low risk for AMR, Watch antibiotics for more severe infections, and Reserve antibiotics as last-resort antibiotics for severe multidrug-resistant infections.[58] The key approaches for achieving these goals include reduced antibiotic development costs, increased availability of generic formulations of previously patented antibiotics, accelerated antibiotic access (eg, the SECURE platform), and policies incentivising antibiotic development.

In addition to ensuring antibiotic access, inappropriate use or demands for antibiotics contributing to AMR should also not be overlooked.[59] A recent systematic review highlighted a staggering prevalence (63·4%) of non-prescription antibiotic dispensing in community pharmacies worldwide, particularly in LMICs, with no notable improvement from 2003 to 2023.[60] This occurrence is mainly driven by the strong demand and scarcity of relevant knowledge or awareness in the patients, inaccessible or costly alternative health-care services, personal incentives of the prescribers, and weak antimicrobial stewardship. These issues highlight the need for targeted strategies or interventions in these areas, including improved education or awareness of patients and prescribers, better patient-doctor or patient-prescriber communication, and strengthened antimicrobial stewardship or policies in communities and hospitals.[61] Strengthening hospital-based programmes, such as improving access to second-line antibiotics, practising antimicrobial stewardship, and implementing local antimicrobial guidelines on the basis of local resistance patterns, serve as effective strategies for tackling nosocomial infections.

For more on the **Community Program for Wise Use of Antibiotics** see https://dobugsneeddrugs.org/

Strengthening AMR surveillance and diagnostics

In 2015, WHO launched the Global Antimicrobial Resistance and Use Surveillance System, the first global collaborative initiative for standardising AMR surveillance through the collection, analysis, interpretation, and sharing of data, which currently has 127 participating jurisdictions.[62] Although AMR surveillance sites increased globally from 729 in 2017 to 24 803 in 2021, data on AMR surveillance are not comprehensive, particularly in LMICs. Data heterogeneity among different countries is a well recognised challenge in existing AMR surveillance systems,[1] since this issue hinders effective comparisons and interpretation of disease prevalence, antibiotic usage, and pathogen phenotypes or genotypes. There is also a worldwide scarcity of comprehensive animal AMR surveillance systems due to restricted resources, the absence of legal frameworks, and inadequate access to animal AMR data.

AMR surveillance is a key cornerstone for antimicrobial stewardship, which focuses on promoting evidence-based prescribing, optimising clinical outcomes, minimising drug resistance, and reducing health-care costs without compromising on the quality of care. AMR surveillance data can help to select for the use of the most effective (and narrow-spectrum) antibiotics, guide the empirical antimicrobial protocols, reduce inappropriate prescribing (eg, using ineffective antibiotics for drug-resistant bacteria), and preserve last-resort antibiotics for specific drug-resistant infections.

Timely and accurate diagnosis of the infection is essential for reducing antibiotic misuse or overuse. Diagnostic uncertainty in presumed self-limiting or viral infections can lead to unnecessary antibiotic prescribing.[59] High-throughput molecular diagnostics, including whole-genome sequencing, have increasingly been deployed for

rapid point-of-care microbial testing or detection, AMR investigation, surveillance, and outbreaks over the past decade.[63,64] In particular, whole-genome sequencing enables comprehensive and rapid analysis of an organism's entire genome, providing the highest possible resolution for discriminating a pathogen's capabilities or traits. Nevertheless, this technology requires substantial infrastructure, expertise, and investment, which restricts its accessibility or utility in LMICs, where AMR is most prevalent. There is an urgent need for low-cost and rapid genomic technologies applied locally to translate the benefits of genomic research to global health-care systems. Whole-genome sequencing has the potential to rapidly predict antimicrobial susceptibility and reveal transmission routes from a single assay, although this approach requires further development and validation.[65,66]

Emerging non-antibiotic antimicrobial therapies

In 2022, a WHO report indicated that the clinical pipeline contained 80 new antimicrobial drugs (46 traditional and 34 non-traditional), with 34 agents in phase 1 trials, 29 in phase 2 trials, 14 in phase 3 trials, and three under regulatory evaluation.[67] 28 (61%) of the 46 traditional antibiotics targeted WHO priority pathogens. Details of the currently available antimicrobial therapies (table 2) and their mechanism(s) of action (figure 2) and strengths or weaknesses (figure 3) are summarised.

Antibodies: Human monoclonal antibodies have mainly been used to treat cancer and autoimmune disease, with proven success in the treatment of COVID-19 of late. Palivizumab, the first human monoclonal antibody shown to be effective against infectious diseases, was approved in 1998 by the FDA for preventing respiratory syncytial viral infection in high-risk infants.[73] Subsequently, in 2016, obiltoxaximab was approved for treating inhalational anthrax (in combination with antibiotics). These developments highlight the growing potential of human monoclonal antibodies to serve as antimicrobial therapies.

Human monoclonal antibodies exert rapid and sustained antimicrobial activity through several potential mechanisms, including enhanced opsonisation for phagocytosis, direct bactericidal activity, complement deposition, antivirulence, and toxin neutralisation.[74] The high specificity of human monoclonal antibodies preserves the host natural microbiota and minimises the selective pressure for cross-resistance. Currently, 14 human monoclonal antibody products are in development for infections caused by the ESKAPEE pathogens and *Clostridioides difficile*. Of note, tosatoxumab (also known as AR-301), specific to *S aureus* α-toxin, completed its first phase 3 trial (NCT03816956) in combination with standard-of-care antibiotics, showing a doubling of antibiotic effectiveness in older individuals (over 65 years old) with *S aureus* ventilator-associated-pneumonia,[75] and TRL1068 against *S aureus* biofilm is entering a phase 2 trial (NCT04763759).

A phase 2 trial was conducted to evaluate the efficacy of suvratoxumab, an α-toxin-targeting human monoclonal antibody, in reducing the incidence of *S aureus* pneumonia.[76] The study did not meet the defined endpoint (ie, altered incidence of infection at 30 days after treatment), although suvratoxumab reduced the duration of hospital stay, mechanical ventilation, and treatment. The MODIFY I and MODIFY II phase 3 trials (NCT01241552 and NCT01513239) successfully showed the efficacy of bezlotoxumab, a TcdB-targeting human monoclonal antibody, in reducing the risk of recurrent *C difficile* infection by around 40%, with more pronounced benefit observed in the higher risk group.[77] The higher risk group was defined as age older than or equal to 65 years, history of *C difficile* infection in the previous 6 months, immunocompromised, severe *C difficile* infection, or positive for a *C difficile* strain (ribotype 027, 078, or 244) associated with poor outcomes of the infection. Other phase 2 clinical trials of bezlotoxumab on *C difficile* infection and inflammatory bowel diseases are underway (NCT05304715 and NCT03829475).

Antibody-antibiotic conjugate: Antibody-antibiotic conjugates, conceptually derived from antibody-drug conjugates, are advanced drugs consisting of monoclonal antibodies that are covalently linked to potent antibiotics.[78] Antibody-antibiotic conjugates are designed to selectively bind to specific antigens and deliver antibiotics directly to the infection site. A single dose of a highly effective antibody-antibiotic conjugate, containing anti-*S aureus* antibodies conjugated to vancomycin, administered 24 h after infection, showed efficacy in eradicating intracellular meticillin-resistant *S aureus*[79] in murine models, by releasing the active antibiotics after internalisation. The effect was considerably better than that observed with twice-daily vancomycin, a current standard antibiotic of choice. This study showcased the potential of antibody-antibiotic conjugates in overcoming the limitations associated with unconjugated antimicrobial agents, including poor pharmacokinetic properties, low therapeutic indexes, and undesired toxicity. Thus, antibody-antibiotic conjugates could eventually be used to address tuberculosis and other challenging infections. In principle, targeting pathogens with highly selective antibodies could transform broad-spectrum antibiotics into pathogen-specific or site-specific antibiotics, minimise the adverse effects of broad-spectrum antibiotics, and reduce indiscriminate killing of commensals.

Antimicrobial peptides: Antimicrobial peptides and antibiofilm peptides, a subset of natural host defence peptides, are small (usually <50 amino acids), cationic, and amphiphilic molecules.[32,80,81] In view of their potent and rapid broad-spectrum antimicrobial activity (even against multidrug-resistant ESKAPEE pathogens), antimicrobial peptides have shown great promise as potential therapy for tackling AMR, with minimal risk of inducing AMR.[32,80,82–85] Some antibiofilm peptides display excellent broad-spectrum activity against biofilms (that cause 65% of infections).[32,83] Their favourable properties are attributed to multitargeting of membrane integrity, cell wall biosynthesis, cytoplasmic membrane, or a combination of these.[82,86] Antimicrobial

	Reference	Year Country	Sample size and characteristics	Treatment regimen	Key findings
New-generation antibiotics					
Sulbactam-durlobactam	NCT03894046	2023 USA	207 adult patients with confirmed *Acinetobacter baumannii–calcoaceticus* nosocomial infection	Four times per day IV dose of 1 g of each drug for 7–14 days	Sulbactam-durlobactam was non-inferior to colistin
Gepotidacin	NCT04010539	2019 USA	620 adult patients (>12 years of age)	Two oral doses of 3 g each	Ongoing phase 3 clinical trial
Zoliflodacin	NCT03959527	2019 USA	1092 adult patients (>12 years of age) with uncomplicated gonorrhoea infection	Single oral dose of 3 g	Ongoing phase 3 clinical trial
Gepotidacin	NCT04020341	2019 USA	1531 paediatric and adult female patients (>12 years of age) with ≥2 clinical signs and symptoms of acute cystitis	Twice per day oral dose of 1·5 g for 5 days	Therapeutic success in 58·5% of patients, cf 43·6% for nitrofurantoin
Zoliflodacin	NCT02257918	2017 USA	141 adult patients with uncomplicated urogenital gonorrhoea	Single oral dose of 2 g or 3 g	Effective for treating urogenital and rectal gonococcal infections, cf ceftriaxone; not as effective for pharyngeal infections
Human monoclonal antibodies					
Obiltoxaximab	NCT03088111	2022 USA	100 patients with suspected or probable or confirmed inhalational anthrax infection	Single IV dose of 16 mg/kg	Ongoing phase 4 clinical trial
Tosatoxumab (AR-301) with standard antibiotic treatment	NCT03816956	2022 Multicountry	174 adult patients with *Staphylococcus aureus* ventilator-associated pneumonia	Single IV dose of 20 mg/kg	Phase 3 clinical trial completed
Suvratoxumab	NCT05331885	2022 France	564 mechanically ventilated adult patients (>12 years of age) at high risk of *S aureus* infection	Single IV dose of 2 g or 5 g	Ongoing phase 3 clinical trial
Bezlotoxumab	NCT05304715	2022 Greece	44 adult patients with *Clostridioides difficile* infection	Single IV dose of 10 mg/kg	Ongoing phase 2 clinical trial
Bezlotoxumab plus FMT cf FMT	NCT03829475	2019 USA	120 adult patients with inflammatory bowel disease due to *C difficile* infection	Single IV dose of 10 mg/kg	Ongoing phase 2 clinical trial
Antimicrobial peptides					
LL-37	NCT04098562	2020 Indonesia	40 adult patients with uncomplicated diabetic foot ulcers	Twice per week topical dose of 0·5 mg/mL for 4 weeks	Completed phase 2 clinical trials, no results available
Omiganan	NCT02849262	2016 Netherlands	24 adult patients with human papillomavirus-induced genital lesions	Once per day topical dose of 2·5% for 12 weeks	Reduced human papillomavirus load at the end of the treatment
Omiganan	NCT02576860	2015 USA	263 adult patients with papulopustular rosacea	Once per day topical dose of ∼0.4 g for 12 weeks	Showed potential anti-inflammatory activity against rosacea
Dalbavancin	NCT01339091 and NCT01431339	2014 USA	1303 adult patients with acute bacterial skin and skin-structure infection	Single IV dose of 1 g on day 1 followed by single IV dose of 500 mg on day 8	Non-inferior to twice per day IV vancomycin followed by oral linezolid for the treatment of acute bacterial skin and skin-structure infection
Orbactiv	NCT01252719	2014 USA	954 adult patients with acute bacterial skin and skin-structure infections	Twice per day IV dose of 1·2 g for 7–10 days	Non-inferior to twice per day vancomycin administered for 7 to 10 days for the treatment of acute bacterial skin and skin-structure infections caused by Gram-positive pathogens
Pexiganan	NCT01590758	2014 USA	189 adult patients with mild infections of diabetic foot ulcers	Twice per day topical dose of 0·8% for 14 days	No substantial difference in clinical or microbiological outcomes
Bacteriophages					
S aureus phage	NCT05177107	2021 USA	126 adult patients (18 to 84 years of age) with *S aureus* diabetic foot osteomyelitis	Unknown	Ongoing phase 2a clinical trial
Pyobacteriophages	NCT03140085	2021 Georgia	113 adult patients undergoing transurethral resection of the prostate with complicated or recurrent urinary tract infection	Intravesical	Success rate of phage therapy was similar to that of the placebo
Pyobacteriophages	NCT04682964	2020 Uzbekistan	128 paediatric patients (3 to 14 years of age) with acute tonsillitis	Nebuliser inhalation	Ongoing phase 3 clinical trial
S aureus phage	NCT03395769	2020 Australia	13 adult patients (>21 years of age) with at least two consecutive days of *S aureus* infection	IV (with antibiotics)	Reduced inflammatory response but unproven benefit, compared with optimal antibiotic therapy
P aeruginosa phage	NCT02116010	2019 France and Belgium	27 adult patients with clinically infected burn wounds	Topical	Clinically relevant reduction in bacterial burden but slower pace than standard of care
Gene therapy					
CRISPR-Cas9	Wan et al (2020)[68]	2020 China	In-vitro study – targeting mobilised colistin resistance (*mcr*-1) gene in *Escherichia coli*	In-vitro transformation	Treatment efficiently desensitised *E coli* to colistin

(Table 2 continues on next page)

	Reference	Year Country	Sample size and characteristics	Treatment regimen	Key findings
(Continued from previous page)					
CRISPR	Hamilton et al (2019)[69]	2019 Canada	In-vitro study – testing with an IncP RK2 conjugative plasmid to deliver specific functional sequences from donor *E coli to* recipient *Salmonella enterica* cells	In-vitro transformation	Single or multiplexed single-guide RNAs targeting non-essential genes resulted in higher killing efficacy of *S enterica* than the essential genes
CRISPR-Cas9	Yosef et al (2015)[70]	2015 Israel	In-vitro study – testing with temperate phages to deliver the CRISPR-Cas system into the genome of antibiotic-resistant bacteria	Phage delivery	CRISPR-Cas9 reversed antibiotic resistance and eliminated the transfer of resistance between strains
CRISPR-Cas9	Bikard et al (2014)[71]	2014 France and USA	In-vivo study – testing in a mouse skin *S aureus* colonisation model	Topical application of phagemid to the infected skin area	CRISPR-Cas9 killed virulent *S aureus* and immunised avirulent staphylococci to prevent the spread of plasmid-borne resistance genes
CRISPR-Cas9 (RGN) targeting *eae* gene	Citorik et al (2014)[72]	2014 USA	In-vivo study – testing in a *Galleria mellonella* larvae preclinical model with enterohaemorrhagic *E coli* infection	Phagemids administered behind the proleg of the larvae	RGN treatment improved the survival of *G mellonella* substantially

The ClinicalTrials.gov IDs (preceded by NCT) are provided for trials that are registered. All adult studies were with patients older than 18 years, unless indicated otherwise. FMT=faecal microbiota transfer. IV=intravenous. RGN=RNA-guided nucleases.

Table 2: **Summary of the latest clinical trials for new-generation antibiotics, human monoclonal antibodies, bacteriophages, antimicrobial peptides, and gene therapy**

peptides also have immunomodulatory, wound healing, and a host of other properties.[80,87]

To date, roughly 20 000 natural or synthetic antimicrobial peptides have been discovered. Those with FDA approval, including gramicidin and polymyxins, are traditional antimicrobial peptide-like drugs.[88] Clinical translation of antimicrobial peptides has been challenged by several factors, including susceptibility to proteolysis, low oral bioavailability, cost, and potential toxicity. Furthermore, to date, antimicrobial peptides have not shown superiority over conventional antibiotics in phase 2 or phase 3 clinical trials. Therefore, antimicrobial peptides are most likely more suited for topical administration rather than for systemic administration, for example, in treating biofilm infections.[35] Iseganan oral rinse showed a reduction in microbial load after the first day of treatment in phase 3 clinical trials, but did not show superiority over existing therapy.[89] In contrast, phase 3 trials of topical omiganan showed anti-inflammatory activity against rosacea (NCT02576847, NCT02576860, NCT01784133, and NCT02547441) and prophylactic activity in catheter colonisation and associated infection (NCT00608959).

Antimicrobial peptide-antibiotic combination therapy serves as another attractive strategy that can enhance the overall antimicrobial activity and reduce the dose-dependent toxicity of antimicrobial peptides and antibiotics.[83,86] There is growing interest in utilising peptidomimetic technology, artificial intelligence-assisted peptide design, and advanced drug-delivery systems, including nanoparticles, hydrogels, and DNA-based or RNA-based delivery systems, to enhance the efficacy, safety, and stability of antimicrobial peptides.[90–93]

Bacteriophages: Bacteriophages (phages) are viruses that infect bacteria, and are incredibly abundant in the biosphere.[94] Despite their discovery as early as in 1915, any potential therapeutic significance of phages was overshadowed by the development of antibiotics. With the rise of AMR, phages have regained attention as an alternative to antibiotics. Although phage resistance is well known, phages have several potential advantages in combating AMR.[9,94] Phages target specific bacteria, but leave commensal flora undisturbed, reducing the risk of cross-resistance. The self-amplifying characteristic of phages promotes bacterial lysis and is self-limited in the absence of the target bacteria. Some phages contain polysaccharide depolymerases that can degrade biofilms, aiding in bacterial eradication. Phages can also synergise with antibiotics.[94]

A systematic review highlighted the potential of bacteriophages in treating conditions such as pneumonia, sepsis, meningitis, wound infections, and corneal infections, caused by multidrug-resistant ESKAPEE pathogens.[95] Bacterial eradication was achieved in most (87%) studies, with good safety (7% side-effects) and tolerability. Side-effects were generally self-limiting upon treatment discontinuation. The real-world effectiveness and safety of personalised bacteriophages in treating drug-resistant ESKAPEE infections (primarily through an intravenous route) have been reported in a study by Green and colleagues; 58% of the 12 treated patients presented a favourable clinical response.[96] Another study consisting of 100 cases highlighted the effectiveness and safety of a personalised bacteriophage for treating drug-resistant infection, with 61% of cases achieving eradication of infection.[97] Eradication was 70% more likely with the use of concomitant antibiotics.

Nevertheless, phages are hard to purify and can invoke an immune response. Their specificity is a potential drawback as the causative infectious agent should first be identified before treatment. Phage resistance is well known and can require the use of phage cocktail or consortia, which use several distinct phages.[98,99] Genetically modified bacteriophages can also have enhanced efficacy and reduced resistance development.[99] Another evolutionary solution is phage training by preadaptation to their targeted bacterial hosts in the laboratory before use in therapy,[100] thereby

enhancing their ability to suppress bacterial growth and delay the development of resistance.

Despite their potential, to date, phage-based treatments (under Article 37 of the Declaration of Helsinki) have not translated into positive patient outcomes in individual patients in randomised controlled trials. Personalised treatment requires identifying the active phages, which is expensive and time-consuming. The scarcity of research funding and definitive guidelines or regulations for commercialising phages, high standard of good manufacturing practices, and complex pharmacokinetics or pharmacodynamics present further hurdles for translating phage therapy to clinical use.[101]

Gene therapy: Bacteria use multiple mechanisms to resist phages, including the CRISPR immune system. The discovery of CRISPR has led to various novel genetic technologies, particularly genome-editing with the CRISPR-Cas9 nuclease system.[102] Reprogramming Cas9 nucleases introduces irreversible chromosomal lesions in bacteria, causing cell death.[71] This observation led to the development of Cas9 nucleases as sequence-specific antimicrobial agents, permitting selective killing of one or more bacterial species in a heterogeneous population. Promising preclinical results revealed the destruction of antibiotic-resistant, virulent *S aureus*.[71] This strategy could potentially enable selective decolonisation of antibiotic-resistant bacteria, without disrupting non-targeted microbiota. Thus, owing to its well-established antimicrobial capabilities, CRISPR-Cas9 is positioned as a promising alternative to small-molecule antibiotics. However, further work is required to refine delivery methods, purity, scalability, and host range, to enable widespread application of gene therapy. Alternatively, correction of the underlying host defects that predispose towards clinically recalcitrant infections (eg, cystic fibrosis) offers a promising approach for gene therapy.

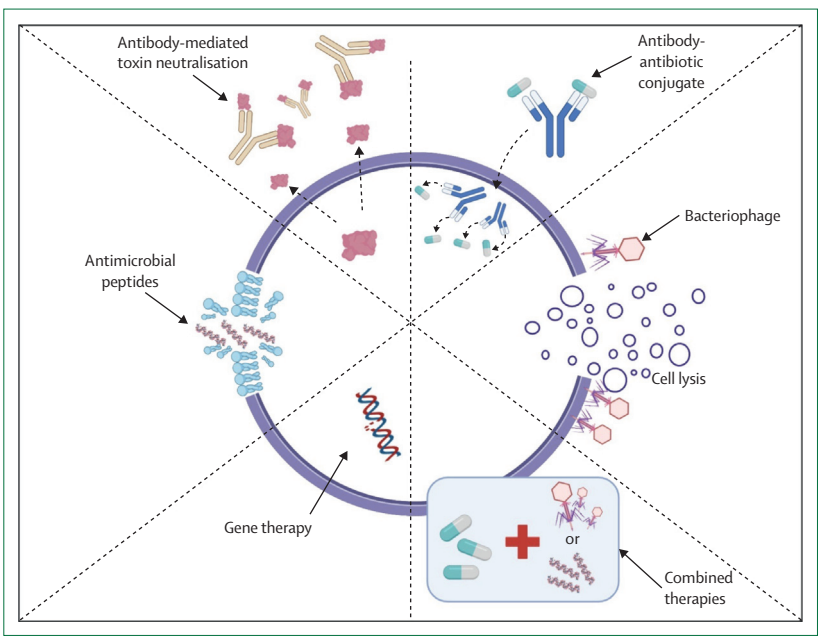

Figure 2: **Emerging therapies for tackling AMR**
Presented are a range of emerging therapies (and their main mechanisms of action) for combating AMR, including human monoclonal antibodies, antibody-antibiotic conjugates, bacteriophages, antimicrobial peptides, combined therapies, and gene therapy. Human monoclonal antibodies exert their antimicrobial activity through enhanced opsonisation for phagocytosis, direct bactericidal activity, complement deposition, antivirulence, and toxin neutralisation. Antibody-antibiotic conjugates are composed of monoclonal antibodies that are covalently linked to potent antibiotics, which facilitate selective binding to specific antigens and direct delivery of antibiotics to the infection site. Antimicrobial peptides, also known as host defence peptides, are equipped with multifaceted antimicrobial modes of action including membrane permeabilisation (the primary action of most cationic antimicrobial peptides), inhibition of cell wall biosynthesis, and targeting of the cytoplasmic membrane. Bacteriophages (or phages) are viruses that can infect bacteria, and their self-amplifying (replication) characteristics can cause bacterial lysis. Gene therapy based on Cas9 nucleases can cause irreversible sequence-specific chromosomal damage to bacteria, causing cell death. Combined therapies, consisting of conventional antibiotics and antimicrobial peptides or bacteriophages, can also serve as an attractive antimicrobial strategy in view of the potential synergy of their components. Figure created with BioRender.com. AMR=antimicrobial resistance.

Potential roles of artificial intelligence

Due to the advancements in artificial intelligence-driven technologies, increased computational power and resources, and availability of big data (including electronic health record and omics data), artificial intelligence is emerging as a powerful tool for tackling infectious diseases and addressing AMR, ranging from antibiotic susceptibility testing, AMR surveillance, antimicrobial stewardship, and diagnosis, to antimicrobial drug discovery or development.[103–106] Artificial intelligence can process or analyse extensive data using computers and machines, through either manual feature engineering (ie, machine learning) or representation learning, such as deep neural networks of human brains (ie, deep learning), and generate new information (ie, generative artificial intelligence).

Traditional phenotypic antibiotic susceptibility testing relies on bacterial growth metrics and usually requires 24–48 h (or longer for slow-growing bacteria such as *Mycobacterium tuberculosis*), which delays the use of optimal antibiotic treatments. Machine learning is increasingly being used to analyse whole-genome sequencing data for rapid antibiotic susceptibility prediction and AMR surveillance, reducing the substantial demand for the bioinformatics resources or expertise required for whole-genome sequencing analysis.[107] This approach offers great promise for large-scale AMR surveillance programmes, particularly in LMICs. Sturm and colleagues[108] reported a machine learning-powered nanomotion platform that can rapidly perform growth-independent phenotypic susceptibility testing (by measuring bacterial vibration) within 2–4 h, with excellent accuracy (90–99%). Highly accurate machine learning models, based on antibiotic susceptibility using electronic health record data, have been successfully developed to guide the use of specific (and narrow-spectrum) antibiotics, effectively reducing the use of second-line antibiotics (by around 70%) and inappropriate antibiotics (by around 20%), as compared with those observed in clinician-prescribed treatments, thereby promoting antimicrobial stewardship.[109] Deep learning has also enabled automated and rapid imaging-based medical diagnostics for various infectious diseases, such as tuberculosis and infectious keratitis.[110,111]

Antimicrobial therapies	Microbial activity	Stability	Action	Cost	Toxicity	Risk of AMR
Human monoclonal antibody	✓ High specificity ✓ Minimal disruption to host natural microbiota	× Can be unstable owing to its proteinous nature	✓ Rapid action	× High cost	× Potential immunogenicity and late-onset toxicity	✓ Low risk of AMR
Antibody-antibiotic conjugate	✓ High specificity × Ineffective against microbes lacking suitable surface antigens	✓ Long half-life with good stability	✓ High pharmacokinetics with quick release of antibiotics once internalised	× High cost	✓ Low toxicity and low off-target effects	✓ Low risk of AMR
Antimicrobial peptides	✓ Broad spectrum of antimicrobial activity ✓ High bactericidal activity	✓ Good water solubility × Short half-life with potentially low stability in circulation	✓ Rapid action	✓ Low synthetic cost	× Potential cytotoxicity or haemolytic activity	✓ Low risk of AMR
Bacteriophages	✓ High specificity ✓ Bactericidal effect ✓ Minimal disruption to host natural microbiota × Narrow spectrum, not suitable as empirical formula × Not accessible to intracellular pathogens	✓ Good stability in humans and at low temperatures	✓ Establish the phage dose automatically by self-replicating; therefore, only one dose might be needed	× High cost for personalised phage therapy	✓ Low toxicity	× Some risk of AMR
Gene therapy	✓ High specificity ✓ Can resensitise bacteria to antibiotics that they were previously resistant to × Residual resistant bacteria remain in the population	× Requires buffering agent, surfactant, antioxidant, and other stabilisers to provide stability	× Unpredictable effect on complex microbial community	× High cost	× Potential off-target gene mutation and adverse immune reaction	× Risk of resistance through mutation

Figure 3: **Summary of the strengths and weaknesses of various emerging non-antibiotic approaches for tackling AMR**
AMR=antimicrobial resistance.

Furthermore, the vast chemical space offers exciting opportunities for artificial intelligence-assisted antimicrobial drug discovery and development, due to its capability for rapid large-scale structure-activity relationship analyses and prediction.[103,106] For instance, a genetic artificial intelligence algorithm was leveraged to design guavanin-2, a molecule that demonstrated potent anti-infective efficacy in a preclinical animal model, illustrating that compounds with significant anti-infective potential could be designed on the computer.[91] Guavanin-2 also exhibited a novel and intriguing mechanism of bacterial killing through membrane hyperpolarization, an insight that was not programmed into the algorithm, revealing an emergent biological property. Additionally, algorithms have been used to rapidly mine entire proteomes (eg, the human proteome), leading to the discovery of thousands of potential antimicrobials, many of which exhibited in vivo antimicrobial activity.[112] This work demonstrated that entire proteomes could be mined for the discovery of new antibiotics. Machine learning or deep learning-assisted proteome mining (eg, the new artificial intelligence model APEX) has been applied to extinct organisms, launching the emerging area of molecular de-extinction,[104,113] which has led to the discovery of several promising antibiotics with potent in-vivo efficacy, including neanderthalin, mammuthusin, mylodonin, elephasin, megalocerin, and hydrodamin. A deep learning approach also yielded abaucin, a compound with strong in-vivo efficacy against *A baumannii*.[114] Machine learning has been used to discover nearly 1 million antibiotics in the global microbiome, encompassing 63 410 metagenomes and 87 920 microbial genomes. Several of these, including lachnospirin-1 and enterococcin-1, proved effective in a preclinical mouse model.[115,116] Overall, these artificial intelligence-driven efforts have dramatically accelerated antibiotic discovery, reducing the process from years to hours.

The main limitation when applying artificial intelligence to small molecules is that the identified compounds might not be chemically synthesisable, but the exciting prospect is that newer computational models can handle multiple outputs, enabling toxicity, pharmacology, and solubility to be modelled alongside activity. A generative artificial intelligence model, named SyntheMol, developed to design easily synthesisable compounds from a chemical space of roughly 30 billion molecules, has successfully created six structurally novel molecules with potent activity against *A baumannii*.[117]

Conclusions

AMR represents a crucial global health threat that is associated with high morbidity and mortality, prolonged hospital

Search strategy and selection criteria

Electronic databases, including MEDLINE (from January, 1950, to June, 2024), Embase (from January, 1980, to June, 2024), Google Scholar, and governmental or regulatory websites, were searched for relevant articles or reports related to antimicrobial resistance. Keywords such as "antimicrobial resistance", "antibiotic resistance", "drug resistance", "antimicrobial stewardship", "ESKAPE", "ESKAPEE", "antimicrobial therapy", "antibiotic", "antibody", "bacteriophage", "antimicrobial peptide", "host defence peptide", "gene therapy", and "vaccine" were used. The final search was updated on June 30, 2024. The included references were selected on the basis of their importance and relevance for this Review.

admission, and increased health-care costs. Numerous factors contribute to the rapid emergence of AMR and antibiotic failure, including the widespread use of antibiotics, scarcity of alternatives, socioeconomic circumstances, medical and agricultural practices, tourism, and globalisation. Addressing AMR requires sustainable and collaborative efforts, which include improving local and international policies and education on antibiotic usage, strengthening surveillance systems, preventing AMR-related infections and transmission, and developing new technologies and alternative antimicrobial therapies. Fostering of collaborative and sustainable research efforts to effectively mitigate the threat of AMR and safeguard the future of modern medicine, global health, and economy is crucial.

Contributors

CSH and DSJT conceptualised and designed the study. CSH, CTHW, and DSJT performed the literature review, data collection, writing of the initial manuscript, and creation of tables and figures. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to the data interpretation. TTA, RL, JSM, SR, AM, BK, SJP, CFN, and REWH critically reviewed the manuscript. All authors approved the final version of the manuscript. DSJT acts as the guarantor of this work.

Declaration of interests

CFN provides consulting services to Invaio Sciences and is a member of the Scientific Advisory Boards of Nowture SL, Peptidus, and Phare Bio. CFN is also on the advisory board of the Peptide Drug Hunting Consortium. REWH is an inventor who holds many patents on antimicrobial and antibiofilm peptides that have been assigned to The University of British Columbia and licensed to ABT Innovations, in which REWH has an ownership position and is the CEO. All other authors declare no competing interests.

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