Contemporary Disquiet in Antimicrobial Resistance and Human Health

Bilal Aslam[1], Gull Naz[1], Ayesha Sarwar[1], Sara Mahmood[1,*], Musrat Shaheen[1], Hassan Ali[1] and Nayab Batool[1]

[1]Institute of Microbiology, Government College University Faisalabad
*Corresponding author: saramahmood@gcuf.edu.pk

Abstract

AMR (antimicrobial resistance) is one of the most considerable threats and a substantial risk for the public health as antibiotics prescribed mostly in human medicines. However, they are also used as therapeutic agent for the treatment of infections in animals and as preventive agent for the growth of infection in herds and also used as a growth promoter in healthy livestock. Misuse and overuse of these drugs is the major cause of AMR in microbes. Pathogenic microbes have many machineries to face dangers around them includes efflux pumps, which remove the drugs outside from the bacterial cell, inactivation of antibiotics by bacterial enzymes, that destroy or modify drug structure, modification in target site by spontaneous mutation, preventing the drugs inside bacterial cells through porin channels which are the factors involved in the emergence of AMR. Recently researchers are working on new strategies to effectively combat AMR challenge such as phyto-chemicals and bacteriophages to overcome the threat to global health.

Keywords: AMR, Antibiotics, Phyto-chemicals, Bacteriophages, Global health

Cite this Article as: Aslam B, Naz G, Sarwar A, Mahmood S, Shaheen M, Ali H and Batool N, 2025. Contemporary disquiet in antimicrobial resistance and human health. In: Zaman MA, Farooqi SH and Khan AMA (eds), Holistic Health and Antimicrobial Resistance: A Zoonotic Perspective. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 27-34. https://doi.org/10.47278/book.HH/2025.38

A Publication of Unique Scientific Publishers

Chapter No: 25-277

Received: 08-Jan-2025
Revised: 21-Feb-2025
Accepted: 18-March-2025

Introduction

Antibiotic resistance has deep evolutionary origins, and the "resistome" antibiotic resistance gene collection represents a complex and rapidly evolving global challenge. Several reasons contribute to the worldwide spread of antibiotic resistance such as population surges, increased international mobility, excessive antibiotic use in medicine and agriculture, environmental selection pressure, poor sanitation, wildlife transmission, and inadequate sewage systems (Marshall & Levy, 2011; Singer et al., 2016). Antibiotic therapy remains a cornerstone of modern medicine in combating infections. However, the "golden age" of antibiotics (1930s-1960s) saw a surge in antibiotic discovery (Nathan & Cars, 2014). Unfortunately, the rise of drug-resistant superbugs leaves scientists struggling to avoid this growing threat. The persistent lack of novel antibiotics, coupled with the widespread misuse of current ones, continues to fuel antibiotic resistance (Aslam et al., 2018).

Antimicrobial resistance (AMR) threatens the interconnected health of humans, animals, and the environment, One Health (Organization, 2022). Since AMR can spread between humans and animals, it also poses a critical zoonotic risk, highlighting the interconnected nature of these health domains (Dafale et al., 2020). The urgent threat of multidrug-resistant (MDR) 'superbugs' demands immediate global action. These bacteria exist in various environments, including humans, animals, and the environment itself, leading to a complex interplay of resistance gene transmission. The global AMR crisis is fueled by the overuse of antibiotics in medicine and agriculture, coupled with poor sanitation and waste management. These conditions create genetic pressures that encourage MDR infections in communities. The global consumption of antimicrobials in livestock, particularly in cattle, poultry, and swine, is a significant concern. Projections indicate a substantial increase in antibiotic use in the world's most populous countries by 2030, which could have severe economic and public health implications (Davies & Davies, 2010; Van Boeckel et al., 2015).

Major global health organizations, including the WHO, WEF, STOP TB Partnership, UNAIDS, Roll Back Malaria, UN Security Council, UN General Assembly, FAO, UNDP, CDC, and IDSA, have issued urgent calls to action to combat the growing threat of antibiotic resistance (Hoffman et al., 2015). In response to this escalating issue, the World Health Assembly commissioned the WHO to draft a global action plan. President Obama issued Executive Order 13676 to create a National Action Plan for antibiotic resistance, increase research funding, and establish the Presidential Advisory Council on Combating Antibiotic Resistance (PACCARB) (Landers & Kavanagh, 2016).

Development of AMR

Bacteria naturally adapt to the selective pressure that antibiotics exert by developing antibiotic resistance. Clinically, bacteria are vulnerable to a newly developed antibiotic, but with prolonged usage, they develop resistance against antibiotics. Evolutionarily, bacteria respond to antibiotics by genetic mutations or acquiring resistant genes from external DNA sources through horizontal gene transfer (HGT). Genetic mutations that alter antibiotic targets, transport mechanisms, and regulatory systems are the driving forces behind antibiotic resistance. The HGT accelerates the global spread of antibiotic resistance, often originating from environmental or commensal bacteria. This highlights the importance of environmental reservoirs of antibiotic resistance genes. These microorganisms must possess their resistance genes to protect themselves against the antibiotics they produce, preventing self-destruction (Davies & Davies, 2010; Koch et al., 2021). Bacteria that exhibit antibiotic resistance may possess genes derived from intrinsic, acquired, or adaptive sources (Table 1) (Lee, 2019).

Table 1: Resistance types and their description.

Resistance Types	Description	Reference
Intrinsic resistance	Bacteria inherit genes that encode intrinsic resistance mechanisms. This resistance is not acquired through genetic mutations or horizontal gene transfer but is encoded within the bacterium's genome. This is often mediated by efflux pumps and reduced cell permeability. These mechanisms allow the bacterium to expel antibiotics or actively limit their entry into the cell.	(Cox & Wright, 2013; Martinez, 2014)
Acquired resistance	Antibiotic resistance can arise through unprompted genetic change or acquired resistant genes via horizontal gene transfer (HGT) mechanisms such as conjugation, transformation, and transduction. Conjugative plasmids are the most common means of horizontal gene transfer (HGT) for antibiotic resistance genes.	(Holmes et al., 2016; Munita & Arias, 2016)
Adaptive resistance	Bacterial phenotype that evolves in response to environmental pressures like exposure to sub-inhibitory antibiotic concentrations or variations in growth factors, nutrients, stress, pH, and ion concentrations. This phenomenon can occur in both human and animal hosts. While the biological mechanisms underlying adaptive resistance remain unclear, several factors may contribute to its development, such as high mutation rates, biofilm formation, population dynamics, and efflux pump activity.	(Fernández & Hancock, 2012; Rizi et al., 2018)

Superbugs and Super-resistance

The excessive use of antibiotics has contributed to the development of multidrug resistance (MDR) in numerous bacterial pathogens. The term "superbug" denotes microbial strains with devastating consequences and multiple mutations conferring heightened levels of antibiotic resistance, making them a critical focus in research. The therapeutic options for MDR are limited, leading to prolonged and more expensive hospital care. Furthermore, certain superresistant strains demonstrate elevated virulence and enhanced transmissibility, underscoring the role of antibiotic resistance as a functional virulence factor (Frieden, 2013). The deadly and multidrug-resistant *Mycobacterium tuberculosis* is a worldwide problem that affects both developed and underdeveloped countries (Sotgiu et al., 2009; Shah et al., 2007;). Other deadly, multidrug-resistant pathogens include *Clostridium difficile*, *Haemophilus influenzae*, *Campylobacter jejuni*, *Klebsiella spp*., *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Staphylococcus aureus,* and *Escherichia coli*. Notably, certain strains, the highly resistant and transmissible MRSA pose a severe threat (Kaur et al., 2014).

Both humans and animals are susceptible to infections caused by *Salmonella enterica, Escherichia coli,* and *Klebsiella pneumoniae*. The extensive usage of β-lactam antibiotics and their associated antibiotic-resistance enzymes has been a major factor in the escalation of AMR. A variety of genetic mechanisms, including mutations and horizontal gene transfer, have resulted in the emergence of multiple β-lactamase classes (Bergšpica et al., 2020). The HGT processes have been identified as the principal mechanism for the dissemination of β-lactam antibiotic resistance genes, occurring in community and hospital environments. *Pseudomonas aeruginosa* has become a critical nosocomial pathogen, especially in burn wound infections associated with hospital-acquired diseases. The alarming rise of antibiotic resistance mechanisms has occurred in parallel with the introduction of novel antibiotic derivatives, such as β-lactams and aminoglycosides, thus limiting the potential for effective therapeutic options. *Staphylococcus aureus*, often referred to as a "superbug," is commonly found in the nasal passages of approximately 75% of individuals and can cause painful skin infections, such as boils. Deadly MDR-TB continues to plague hospitals worldwide. The discovery of methicillin in 1959 was considered a breakthrough against penicillinase-producing bacteria, yet the emergence of MRSA within three years demonstrated its inability to provide lasting protection, challenging the concept of a permanent cure (Koch et al., 2021).

Staphylococcus aureus is a significant gram-positive superbug with increasing antibiotic resistance. This bacterium is commonly carried in the nasal passages of about 30% of the population and is a frequent cause of skin infections like boils. Although *S. aureus* does not have the same historical prominence as *Mycobacterium tuberculosis*, it has recently become a major threat, causing serious hospital-acquired infections. After penicillin's discovery, *S. aureus* infections were thought to be controllable, but resistance soon developed. The 1959 introduction of methicillin, the first designer antibiotic to combat penicillinase-producing strains, initially seemed promising. However, the rapid emergence of MRSA within just three years precipitated the development of additional multi-drug-resistant strains. MRSA, once confined to healthcare settings, has now developed a significant community-acquired pathogen, with increased virulence and transmissibility. Community-acquired MRSA (CA-MRSA) shares many characteristics with MRSA but carries distinct mec gene clusters and new virulence genes, like the Panton-Valentine leukocidin gene (Enright et al., 2002; DeLeo & Chambers, 2009).

Superbugs are ubiquitous in the environment, with a significant impact on public health, particularly in resource-limited settings. *Vibrio cholerae* is a notable example of a pathogenic superbug (Ahmad et al., 2018).

Antibiotic Resistance Mechanisms

Antimicrobial agents and bacteria exist in a dynamic ecological relationship, driving bacteria to evolve strategies to counteract the toxic effects of antibiotic agents. Antibiotics act on four primary bacterial targets: the functioning and permeability of the cell membrane, the ribosome system for protein synthesis, and the enzymatic activities involved in nucleic acid production, and the structural integrity of the cell wall. Bacteria have developed resistance mechanisms to mitigate these effects, such as decreasing membrane permeability to limit drug entry, mutating or chemically modifying antibiotic targets, producing enzymes that inactivate antibiotics, and efflux pumps help cells by pushing drugs out, making them less effective.

Limiting Drug Uptake

The Gram-negative bacterial outer membrane, constituted largely of lipopolysaccharide highly acylated glycolipid contributes to intrinsic resistance by forming a selective permeability barrier, thus restricting the entry of antibiotics. One important characteristic of outer membrane proteins, porin-mediated permeability, is altered in various ways and contributes to acquire resistance. Porins determine the influx of antibiotics by facilitating the uptake of hydrophilic antibiotics such as tetracyclines, fluoroquinolones, β-lactams, and chloramphenicol (Choi & Lee, 2019). Alterations in the structure and function of porin proteins, resulting from genetic mutations, can contribute to the development of antibiotic resistance. Such mutations reduce porin-mediated permeability and contribute significantly to resistance, especially when paired with other potent mechanisms like enzymes that break down antibiotics or active efflux pumps. This synergistic interaction results in markedly higher resistance levels (Ghai & Ghai, 2018). A significant mechanism of antimicrobial resistance is biofilm formation, observed in bacteria including *Enterococcus faecalis, Staphylococcus epidermidis,* and *Pseudomonas aeruginosa*. Biofilms formed as aggregates of microbial groups encased in an intuitive network, adhering to surfaces. Additionally, biofilms may prevent the establishment of bactericidal antibiotic concentrations throughout their structure (Van Acker et al., 2014; Uruén et al., 2020).

Drug Target Modification

Mutations in bacterial chromosomal genes encoding antibiotic targets may introduce changes in the structure of the target molecule. Although slight, this can drastically alter the tight binding interactions between the antimicrobial drug and its specific molecular target, allowing resistance (Kapoor et al., 2017). Both gram-positive and gram-negative bacteria can develop resistance to fluoroquinolones, probably because of genetic variations particularly in the DNA gyrase's quinolone resistance-determining area (topoisomerases II and IV) (Ashley et al., 2017). Bacteria like *Streptomyces spp.*, which naturally produce aminoglycosides, have developed inherent resistance to their antibiotic products (Laws et al., 2019). Among these, enzymatic inactivation represents the predominant mechanism of aminoglycoside resistance. Resistance to protein synthesis inhibitors macrolides, tetracyclines, chloramphenicol, and aminoglycosides is often driven by modifications to the 30S or 50S ribosomal subunits (Anandabaskar, 2021). Aminoglycosides selectively bind to the 30S subunit, interfering with protein synthesis, whereas macrolides, lincosamides, and chloramphenicol target the 50S subunit (Haider et al., 2022).

The methylation process is one alternative mechanism of target modification that is known for its high efficiency in conferring antibiotic resistance. Erm methylases, a family of methyltransferases, alter the 23S rRNA target location to prevent streptogramin B, lincosamides, and macrolides from accessing it. Additionally, in many bacterial species, resistance to certain antibiotics has been linked to methylation of the *cfr* gene, which codes for a methyltransferase (Saha & Sarkar, 2021). The acquisition of *mecA* or *mecC* genes is typically associated with the development of β-lactam resistance in *Staphylococcus* species. These genes impact the effectiveness of β-lactam antibiotics by encoding different penicillin-binding proteins that have low affinity for them (Wendlandt et al., 2015; Foster, 2017).

Drug Inactivation

Bacteria's ability to neutralize antibiotics is a significant contributor to drug resistance and occurs through two primary mechanisms: either the addition of a chemical group to the antibiotic molecule or its breakdown (Noor et al., 2021). Structural features of antibiotics, such as hydroxyl and amide groups, are particularly prone to modification through hydrolysis. These antibiotics lose their effectiveness when β-lactamases cause dissociation of the β-lactam ring, produced by *Enterobacterales*. These β-lactamases, which were previously classified as cephalosporinases and penicillinases, stop penicillin-binding proteins (PBPs) from interacting with them. The blaZ gene, which codes for the β-lactamase enzyme, is the cause of Staphylococcus aureus's resistance to penicillin. By preventing peptidoglycan cross-linking, β-lactam antibiotics interfere with the formation of cell walls and cause cell death (Sharma et al., 2024). It was recently discovered that some bacterial species have an enzyme encoded by the *tetX* gene that hydrolyzes tetracycline. One frequently seen process of drug inactivation is involved in the chemical alteration of pharmaceuticals by acetyl, phosphoryl, and adenyl transfer. Phosphorylation and adenylation primarily target aminoglycosides, while acetylation targets a broader range of antibiotics (Nikaido & Pagès, 2012; Blair et al., 2015).

Active Drug Efflux

The cytoplasmic membrane contains activated efflux pumps that allow bacteria to regulate the intracellular concentration of antibiotics and other antibacterial substances. Antibiotics are transported out of the bacterial cell via efflux pumps, resulting in a low intracellular concentration of the drugs that prevents them from reaching their target. *Escherichia coli* was found to have the first plasmid-encoded efflux pump in 1980, which showed the ability to efflux tetracycline. Since efflux pumps have been demonstrated to be essential to bacterial physiology, pathogenicity, and metabolism before the use of antibiotics, it seems unlikely that their main function is to extrude drugs. Additionally, efflux pumps may naturally release poisonous compounds like bile to aid bacteria in surviving, invading, and colonizing their host. MexAB-OprM, BmrA, and NorA extrude a range of structurally distinct antibacterial substances (Zack et al., 2024). RND (Resistance-Nodulation-Division Family), SMR (Small Multidrug Resistance Family), ABC (ATP-Binding Cassette), MFS (Major Facilitator Superfamily), MATE (Multidrug and Toxic Compound Extrusion Family), and DMT (Drug/Metabolite Transporter Family) are the six families of bacterial efflux pumps that are primarily responsible for multidrug resistance. Although the majority are chromosomally encoded, mobile genetic elements frequently encode substrate-specific pumps (such as those for macrolides, tetracyclines, and chloramphenicol) (Poole, 2005; Blair et al., 2014).

Misuse of Antibiotics

Sir Alexander Fleming warned in 1945 about the potential misuse of antibiotics, predicting that overuse would lead to resistance. Increasing resistance is largely due to the overuse of antibiotics in modern medicine. Through epidemiological surveys, substantial correlations were documented between consumption levels and the establishment of resistant bacteria. Bacterial resistance genes may be transmitted vertically from parent cells or acquired horizontally from genetically unrelated organisms via mobile genetic elements like plasmids, a process known as horizontal gene transfer, or HGT. HGT enables the exchange of resistance traits across bacterial species.

Additionally, spontaneous mutations can generate resistance. Antibiotics exert selective pressure, removing susceptible strains and allowing resistant bacteria to dominate through natural selection. Despite decades of warnings, global antibiotic overprescription continues to drive resistance (Nature, 2013; Read & Woods, 2014; Spellberg & Gilbert, 2014).

Global surveys reveal significant misconceptions about antibiotics, particularly among less-educated populations, with many believing they can combat viral infections similar to ubiquitous cold and seasonal flu. Furthermore, antibiotics are frequently administered, especially in developing countries with inadequate diagnostic facilities. Easy access to over-the-counter antibiotics is fueling a global crisis of drug-resistant superbugs. The absence of antibiotic stewardship policies and standardized treatment guidelines amplifies this problem, especially in developing nations. The volume of antibiotics prescribed in the United States highlights the urgent need for strategies to reduce their use. An analysis of the IMS Health Midas database, which utilizes sales data from retail and hospital pharmacies to estimate antibiotic consumption, indicated that in 2010, 22.0 standard units of antibiotics (defined as one dose, such as a pill, capsule, or ampoule) were prescribed per capita (Van Boeckel et al., 2014; Chokshi et al., 2019; Aldeyab et al., 2020).

AMR Sources and Transmission Routes

The assessment and expansion of drug resistance are shaped by multiple factors, including human activities and environmental conditions. Humans, animals, water, and the environment can all harbor antimicrobial resistance genes. These genes can spread between and within these reservoirs, fueling antibiotic resistance. Wastewater treatment plants and agricultural practices, including using animal manure as fertilizer and administering antibiotics to livestock, are significant sources of antimicrobial resistance (Hashmi, 2020). In community settings, a significant pathway remains the fecal-oral route, often associated with inadequate sanitation, especially relevant for resistant *Enterobacteriaceae*. Additionally, sexual contact plays a pivotal role in disseminating resistant *Neisseria gonorrhoeae*, particularly among high-risk core groups. MRSA is a model case within healthcare settings, with transmission linked to extended hospital stays and healthcare workers' hand contamination. In recent years, AMR *Enterobacteriaceae* colonization within the human microbiota has escalated dramatically, with over half the population in some regions carrying ESβL-producing strains. Additionally, the global spread of carbapenem resistance driven by mechanisms such as NDM, KPC, and OXA-48 presents a growing concern (Holmes *et al.,* 2016).

An Escalating Risk for Global Public Health

Antimicrobial resistance (AMR) is a critical threat that has greatly increased morbidity and mortality rates. This issue arises largely due to the overuse and inappropriate application of antibiotics, particularly in less developed regions. As a hidden global epidemic threatening global public health, the incidence and dissemination of antimicrobial-resistant bacterial illnesses have increased unexpectedly in the twenty-first century, necessitating urgent intervention. Any country can have antibiotic resistance, and people of any age or gender can be affected. Given its current state, drug-resistant infections are one of the biggest threats to people's health, safe food, and a sustainable future (Salam et al., 2023).

Antimicrobial-resistant diseases were predicted to account for 1.27 million deaths in 2019, In contrast, over 5 million deaths were reported due to diseases caused by antibiotic resistance, according to important research released in January 2022. The impact of AMR on human health can be therapeutic and preventive. Direct therapeutic implications include treatment failures and increased complications. In contrast, preventive implications can be observed in treatment options compromised for immunosuppressive conditions like cancer chemotherapy, complex surgical procedures like transplantation, and invasive procedures like catheterization or intubation (Founou et al., 2017). In 2014, the Government of Canada launched a national strategy to combat antimicrobial resistance (AMR), involving multiple agencies and worldwide parameters to prevent, control, and execute an international Action Plan on AMR (Kasimanickam et al., 2021).

The COVID-19 pandemic has heightened public health concerns, including the rise of antimicrobial resistance (AMR), due to the widespread and often unwarranted use of antibiotics, such as azithromycin, to cure COVID-19 (Ansari et al., 2021). This has contributed to the increasing prevalence of antimicrobial-resistant pathogens, as evidenced by the fact that 72% of hospitalized COVID-19 patients were prescribed broad-spectrum antibiotics, even though the incidence of bacterial or fungal infections was low (Sulis et al., 2022). This raises significant concerns about the effectiveness of antimicrobial stewardship protocols. Furthermore, the detection of *mcr-1*, a gene associated with colistin resistance, in humans, animals, and food across more than 30 countries highlights the growing global challenge of AMR (George, 2018).

How to Control AMR

Antimicrobial resistance (AMR) significantly threatened human, animal, and environmental health. Animals can serve as reservoirs for multidrug-resistant (MDR) pathogens, which can be transmitted through direct contact or consumption of contaminated food products. Addressing AMR requires a coordinated, multisectoral approach involving healthcare, agriculture, finance, trade, education, and non-governmental organizations at national and international levels. This collaboration should encompass both horizontal integration across sectors within a country and vertical integration between different levels of governance, regionally and globally (Salam et al., 2023).

Researchers have recently identified novel strategies to address AMR in addition to existing therapies including bacteriophages, combination therapy, systems for delivering medications, and physicochemical approaches. The RNA interference and CRISPR-Cas system are two notable examples. The RNA is employed to establish highly sensitive antimicrobial assays to evaluate the mode of action and assess the required stringency for specific targets (Dillac et al., 2024). To mitigate the emergence of resistance, regulatory bodies and stakeholders should prioritize the development of novel antibiotics and restrict their use to critical situations. Furthermore, innovative approaches to antibiotic stewardship, such as optimizing storage conditions, are crucial to preserving their efficacy (Dillac et al., 2024).

Nanotechnology provides a promising platform for developing innovative treatments. Nanoparticle-based vaccines have been studied in both pre-clinical and clinical trials to prevent bacterial infections. Nanomaterials can also be engineered to deliver several antigens and adjuvants at the same time, which is particularly essential for controlling the quality and duration of immune responses (Organization, 2019). Antimicrobial resistance (AMR), as well as the morbidity and mortality caused by antibiotic-resistant bacterial infections, is not a

novel concern. However, AMR has been established at an alarming rate, with the emergence of pathogens that exhibit resistance to not just one, but multiple classes of antibiotics. Vaccines as interventions to reduce AMR have historically been under-recognized, yet their beneficial impact in reducing AMR has been well-documented (Jansen & Anderson, 2018). The key strategies to address antimicrobial resistance (AMR) are listed in Fig. 1.

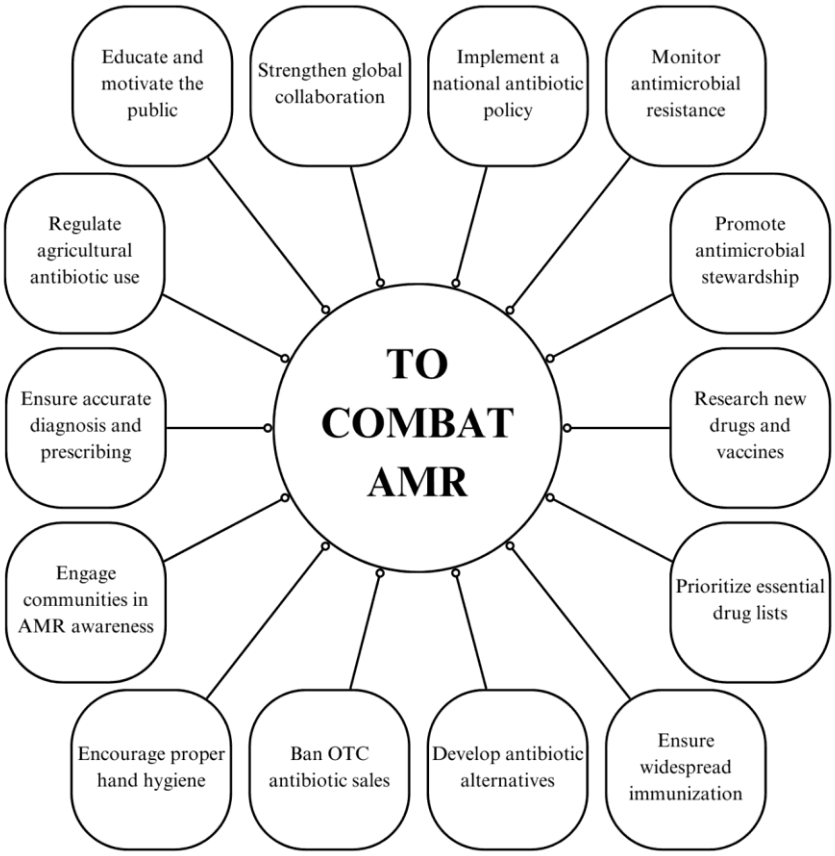

Fig. 1: Key strategies to address antimicrobial resistance (AMR). (Canva)

Alternatives to Antibiotics

Natural resources, particularly plants, are increasingly being explored as potential alternatives to conventional antibiotics (Naz et al., 2024). Still, the antimicrobial potency of many phytochemicals, such as polyphenols, alkaloids, and flavonoids, remains unexplored. Furthermore, the translation of these laboratory discoveries into clinical practice presents a significant challenge. Recent technological advancements in fields like biotechnology, genetic engineering, and synthetic chemistry have opened new avenues for innovative therapeutic development, offering hope to cope with the present AMR dilemma. Scientists are exploring the natural phenomenon of microbial chemical warfare to develop novel ways of developing antibiotics that kill disease-causing bacteria. Moreover, insights into the microbial competition, where the bacteria, viruses, and molds each produce defensive chemicals to outcompete each other, is shaping new strategies to develop alternatives to antibiotics, hence hope in tackling the growing menace of AMR (Othman et al., 2019; Amaning Danquah et al., 2022). Different product categories, as listed below in table 2, are considered as an alternative to the antibiotics used for the treatment of bacterial infections.

Table 2: Different product categories are considered as an alternative to the antibiotics used for the treatment of bacterial infections.

Targeted Bacteria	Product Name	Product Type	Company	References
Clostridium difficile	Bezlotoxumab	Antibodies	Merck	(Johnson & Gerding, 2019)
	NVB302	Antimicrobial peptides	Novacta Biosystems	(Crowther et al., 2013)
	RBX2660	Probiotics	Rebiotix	(Blair, 2023)
Pseudomonas aeruginosa	MEDI3902	Antibodies	MedImmune	(Hebert et al., 2020)
	Murepavadin	Antimicrobial peptides	Roche	(Martin-Loeches et al., 2018)
	AmpliPhage-001	Bacteriophages	AmpliPhi Biosciences	(Camara, 2015)
Escherichia coli	ExPEC4V	Vaccine	Janssen Pharmaceuticals	(Huttner & Gambillara, 2018)
	Colicins	Bacteriocins	University of Oxford	(Lazdunski et al., 1998)
Staphylococcus aureus	CF-301	Lysins	ContraFect	(Schuch et al., 2017)
	MEDI4893	Antibodies	MedImmune	(Wang et al., 2022)
Mycobacterium tuberculosis	RUTI	Therapeutic vaccine	Archivel Farma	(Cardona & Amat, 2006)
	VPM1002	Vaccine	Serum Institute of India	(Nayak, 2021)

Conclusion

A comprehensive and multifaceted approach is required to effectively combat the growing challenge of antimicrobial resistance. First, increasing knowledge, ensuring consistent, and accurate data collection are crucial to understanding the extent of the issue, as inadequate information has hindered predictions and solutions. The development of new diagnostic tools has to be promoted on international, multidisciplinary levels with consideration for the "one health" approach, that deals with human, animal, and environmental health. Alternatives to antibiotics, such as probiotics and bacteriophages, hold significant promise, especially in resource-limited settings, for reducing AMR's burden. Public awareness campaigns, along with screening and treatment for person-to-person transmission, are essential in reducing its spread. By integrating these measures, AMR can be managed effectively, reducing its threat to global health.

References

Ahmad, S., Raza, S., Uddin, R., & Azam, S. S. (2018). Comparative subtractive proteomics based ranking for antibiotic targets against the dirtiest superbug: Acinetobacter baumannii. *Journal of Molecular Graphics and Modelling*, *82*, 74-92.

Aldeyab, M., López-Lozano, J.-M., & Gould, I. M. (2020). Global antibiotics use and resistance. *Global Pharmaceutical Policy*, 331-344.

Amaning Danquah, C., Minkah, P. A. B., Osei Duah Junior, I., Amankwah, K. B., & Somuah, S. O. (2022). Antimicrobial compounds from microorganisms. *Antibiotics*, *11*(3), 285.

Anandabaskar, N. (2021). Protein synthesis inhibitors. *Introduction to Basics of Pharmacology and Toxicology: Volume 2: Essentials of Systemic Pharmacology: From Principles to Practice*, 835-868.

Ansari, S., Hays, J. P., Kemp, A., Okechukwu, R., Murugaiyan, J., Ekwanzala, M. D., Ruiz Alvarez, M. J., Paul-Satyaseela, M., Iwu, C. D., & Balleste-Delpierre, C. (2021). The potential impact of the COVID-19 pandemic on global antimicrobial and biocide resistance: an AMR Insights global perspective. *JAC-antimicrobial resistance*, *3*(2), dlab038.

Ashley, R. E., Dittmore, A., McPherson, S. A., Turnbough Jr, C. L., Neuman, K. C., & Osheroff, N. (2017). Activities of gyrase and topoisomerase IV on positively supercoiled DNA. *Nucleic Acids Research*, *45*(16), 9611-9624.

Aslam, B., Wang, W., Arshad, M. I., Khurshid, M., Muzammil, S., Rasool, M. H., Nisar, M. A., Alvi, R. F., Aslam, M. A., & Qamar, M. U. (2018). Antibiotic resistance: a rundown of a global crisis. *Infection and Drug Resistance*, 1645-1658.

Bergšpica, I., Kaprou, G., Alexa, E. A., Prieto, M., & Alvarez-Ordóñez, A. (2020). Extended spectrum β-lactamase (ESBL) producing Escherichia coli in pigs and pork meat in the European Union. *Antibiotics*, *9*(10), 678.

Blair, H. A. (2023). RBX2660 (REBYOTA®) in preventing recurrence of Clostridioides difficile infection: a profile of its use in the USA. *Drugs & Therapy Perspectives*, *39*(10), 331-338.

Blair, J. M., Richmond, G. E., & Piddock, L. J. (2014). Multidrug efflux pumps in Gram-negative bacteria and their role in antibiotic resistance. *Future Microbiology*, *9*(10), 1165-1177.

Blair, J. M., Webber, M. A., Baylay, A. J., Ogbolu, D. O., & Piddock, L. J. (2015). Molecular mechanisms of antibiotic resistance. *Nature Reviews Microbiology*, *13*(1), 42-51.

Camara, B. (2015). Actualités dans la prise en charge de l'infection respiratoire par Pseudomonas aeruginosa et les thérapeutiques inhalées. *Revue des Maladies Respiratoires Actualités*, *7*(5), 573-577.

Cardona, P., & Amat, I. (2006). Origin and development of RUTI, a new therapeutic vaccine against Mycobacterium tuberculosis infection. *Archivos de Bronconeumología ((English Edition))*, *42*(1), 25-32.

Choi, U., & Lee, C. R. (2019). Distinct Roles of Outer Membrane Porins in Antibiotic Resistance and Membrane Integrity in Escherichia coli. *Front Microbiol*, *10*, 953. https://doi.org/10.3389/fmicb.2019.00953

Chokshi, A., Sifri, Z., Cennimo, D., & Horng, H. (2019). Global contributors to antibiotic resistance. *Journal of Global Infectious Diseases*, *11*(1), 36-42.

Cox, G., & Wright, G. D. (2013). Intrinsic antibiotic resistance: mechanisms, origins, challenges and solutions. *Int J Med Microbiol*, *303*(6-7), 287-292. https://doi.org/10.1016/j.ijmm.2013.02.009

Crowther, G. S., Baines, S. D., Todhunter, S. L., Freeman, J., Chilton, C. H., & Wilcox, M. H. (2013). Evaluation of NVB302 versus vancomycin activity in an in vitro human gut model of Clostridium difficile infection. *Journal Antimicrob Chemother*, *68*(1), 168-176. https://doi.org/10.1093/jac/dks359

Dafale, N. A., Srivastava, S., & Purohit, H. J. (2020). Zoonosis: an emerging link to antibiotic resistance under "one health approach". *Indian Journal of Microbiology*, *60*, 139-152.

Davies, J., & Davies, D. (2010). Origins and evolution of antibiotic resistance. *Microbiology and Molecular Biology Reviews*, *74*(3), 417-433.

DeLeo, F. R., & Chambers, H. F. (2009). Reemergence of antibiotic-resistant Staphylococcus aureus in the genomics era. *The Journal of Clinical Investigation*, *119*(9), 2464-2474.

Dillac, L., Christie, W., van Dalen, D., & Adiningrat, R. P. P. (2024). New approaches to combat Antimicrobial Resistance (AMR)? hal-04575519, version 1. http://dx.doi.org/10.5281/zenodo.14030122

Enright, M. C., Robinson, D. A., Randle, G., Feil, E. J., Grundmann, H., & Spratt, B. G. (2002). The evolutionary history of methicillin-resistant Staphylococcus aureus (MRSA). *Proceedings of the National Academy of Sciences*, *99*(11), 7687-7692.

Fernández, L., & Hancock, R. E. (2012). Adaptive and mutational resistance: role of porins and efflux pumps in drug resistance. *Clinical Microbiology Reviews*, *25*(4), 661-681.

Foster, T. J. (2017). Antibiotic resistance in Staphylococcus aureus. Current status and future prospects. *FEMS Microbiology Reviews*, *41*(3), 430-449.

Founou, R. C., Founou, L. L., & Essack, S. Y. (2017). Clinical and economic impact of antibiotic resistance in developing countries: A systematic review and meta-analysis. *PloS one*, *12*(12), e0189621.

Frieden, T. (2013). Antibiotic resistance threats in the United States. *Centers Dis Control Prev*, *114*.
George, A. (2018). Antimicrobial resistance, trade, food safety and security. In (Vol. 5, pp. 6-8): Elsevier.
Ghai, I., & Ghai, S. (2018). Understanding antibiotic resistance via outer membrane permeability. *Infect Drug Resist*, *11*, 523-530. https://doi.org/10.2147/idr.S156995
Gross, M. (2013). Antibiotics in crisis. *Current Biology*, *23*(24), R1063-1065. https://doi.org/10.1016/j.cub.2013.11.057
Haider, A., Ikram, M., & Rafiq, A. (2022). Antimicrobials; drug resistance. In *Green nanomaterials as potential antimicrobials* (pp. 109-124). Springer.
Hashmi, M. Z. (2020). *Antibiotics and antimicrobial resistance genes: Environmental occurrence and treatment technologies*. Springer Nature. 1-19. ISBN 978-3-030-40422-2 (eBook). https://doi.org/10.1007/978-3-030-40422-2
Hebert, W., DiGiandomenico, A., & Zegans, M. (2020). Multifunctional monoclonal antibody targeting Pseudomonas aeruginosa keratitis in mice. *Vaccines*, *8*(4), 638.
Hoffman, S. J., Caleo, G. M., Daulaire, N., Elbe, S., Matsoso, P., Mossialos, E., Rizvi, Z., & Røttingen, J. A. (2015). Strategies for achieving global collective action on antimicrobial resistance. *Bull World Health Organ*, *93*(12), 867-876. https://doi.org/10.2471/blt.15.153171
Holmes, A. H., Moore, L. S., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., Guerin, P. J., & Piddock, L. J. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet*, *387*(10014), 176-187. https://doi.org/10.1016/s0140-6736(15)00473-0
Huttner, A., & Gambillara, V. (2018). The development and early clinical testing of the ExPEC4V conjugate vaccine against uropathogenic Escherichia coli. *Clinical Microbiology and Infection*, *24*(10), 1046-1050.
Jansen, K. U., & Anderson, A. S. (2018). The role of vaccines in fighting antimicrobial resistance (AMR). *Human vaccines & Immunotherapeutics*, *14*(9), 2142-2149.
Johnson, S., & Gerding, D. N. (2019). Bezlotoxumab. *Clinical infectious diseases*, *68*(4), 699-704.
Kapoor, G., Saigal, S., & Elongavan, A. (2017). Action and resistance mechanisms of antibiotics: A guide for clinicians. *Journal of Anaesthesiology Clinical Pharmacology*, *33*(3), 300-305.
Kasimanickam, V., Kasimanickam, M., & Kasimanickam, R. (2021). Antibiotics use in food animal production: escalation of antimicrobial resistance: where are we now in combating AMR? *Medical Sciences*, *9*(1), 14.
Kaur, N., Prasad, R., & Varma, A. (2014). Prevalence and antibiotic susceptibility pattern of methicillin resistant Staphylococcus aureus in tertiary care hospitals.
Koch, N., Islam, N. F., Sonowal, S., Prasad, R., & Sarma, H. (2021). Environmental antibiotics and resistance genes as emerging contaminants: methods of detection and bioremediation. *Current Research in Microbial Sciences*, *2*, 100027.
Landers, T., & Kavanagh, K. T. (2016). Is the Presidential Advisory Council on Combating Antibiotic Resistance missing opportunities? *Am J Infect Control*, *44*(11), 1356-1359. https://doi.org/10.1016/j.ajic.2016.07.008
Laws, M., Shaaban, A., & Rahman, K. M. (2019). Antibiotic resistance breakers: current approaches and future directions. *FEMS Microbiology Reviews*, *43*(5), 490-516.
Lazdunski, C. J., Bouveret, E., Rigal, A., Journet, L., Lloubès, R., & Bénédetti, H. l. n. (1998). Colicin import into Escherichia coli cells. *Journal of Bacteriology*, *180*(19), 4993-5002.
Lee, J. H. (2019). Perspectives towards antibiotic resistance: from molecules to population. *Journal Microbiol*, *57*(3), 181-184. https://doi.org/10.1007/s12275-019-0718-8
Marshall, B. M., & Levy, S. B. (2011). Food animals and antimicrobials: impacts on human health. *Clinical Microbiology Reviews*, *24*(4), 718-733.
Martin-Loeches, I., Dale, G. E., & Torres, A. (2018). Murepavadin: a new antibiotic class in the pipeline. *Expert Review of Anti-infective Therapy*, *16*(4), 259-268.
Martinez, J. L. (2014). General principles of antibiotic resistance in bacteria. *Drug Discovery Today: Technologies*, *11*, 33-39. https://doi.org/https://doi.org/10.1016/j.ddtec.2014.02.001
Munita, J. M., & Arias, C. A. (2016). Mechanisms of Antibiotic Resistance. *Microbiol Spectr*, *4*(2), 481-511. https://doi.org/10.1128/microbiolspec.VMBF-0016-2015
Nathan, C., & Cars, O. (2014). Antibiotic resistance—problems, progress, and prospects. *New England Journal of Medicine*, *371*(19), 1761-1763.
Nature, E. (2013). The antibiotic alarm. *Nature*, *495*(7440), 141.
Nayak, S. (2021). Newer Vaccines for Tuberculosis Prevention. *Pediatric Infectious Disease*, *3*(3), 122.
Naz, G., Sarwar, A., Sultana, S., Sarwar, F., Rasheed, M., Ali, H., Hameed, A., & Zahra, H. (2024). Plant Essential Oils as an Alternative Antimicrobial Therapy. In (pp. 114-122). https://doi.org/10.47278/book.CAM/2024.121
Nikaido, H., & Pagès, J.-M. (2012). Broad-specificity efflux pumps and their role in multidrug resistance of Gram-negative bacteria. *FEMS Microbiology Reviews*, *36*(2), 340-363.
Noor, Z. Z., Rabiu, Z., Sani, M. H. M., Samad, A. F. A., Kamaroddin, M. F. A., Perez, M. F., Dib, J. R., Fatima, H., Sinha, R., & Khare, S. K. (2021). A review of bacterial antibiotic resistance genes and their removal strategies from wastewater. *Current Pollution Reports*, 1-16.
Organization, W. H. (2019). *Turning plans into action for antimicrobial resistance (AMR): working paper 2.0: implementation and coordination*.
Organization, W. H. (2022). *Global antimicrobial resistance and use surveillance system (GLASS) report 2022*. World Health Organization.
Othman, L., Sleiman, A., & Abdel-Massih, R. M. (2019). Antimicrobial activity of polyphenols and alkaloids in middle eastern plants. *Frontiers in Microbiology*, *10*, 911.
Ponzo, E., De Gaetano, S., Midiri, A., Mancuso, G., Giovanna, P., Giuliana, D., Zummo, S., & Biondo, C. (2024). The Antimicrobial Resistance Pandemic Is Here: Implementation Challenges and the Need for the One Health Approach. *Hygiene*, *4*(3), 297-316.

Poole, K. (2005). Efflux-mediated antimicrobial resistance. *Journal of Antimicrobial Chemotherapy*, *56*(1), 20-51.

Read, A. F., & Woods, R. J. (2014). Antibiotic resistance management. *Evolution, medicine, and public health*, *2014*(1), 147.

Rizi, K. S., Ghazvini, K., & Noghondar, M. K. (2018). Adaptive antibiotic resistance: Overview and perspectives. *Journal Infection Disease Ther*, *6*(363), 2332-0877.1000363.

Saha, M., & Sarkar, A. (2021). Review on multiple facets of drug resistance: a rising challenge in the 21st century. *Journal of Xenobiotics*, *11*(4), 197-214.

Salam, M. A., Al-Amin, M. Y., Salam, M. T., Pawar, J. S., Akhter, N., Rabaan, A. A., & Alqumber, M. A. (2023, July). Antimicrobial resistance: a growing serious threat for global public health. In *Healthcare* (Vol. 11, No. 13, p. 1946). MDPI.

Schuch, R., Khan, B. K., Raz, A., Rotolo, J. A., & Wittekind, M. (2017). Bacteriophage lysin CF-301, a potent antistaphylococcal biofilm agent. *Antimicrobial Agents and Chemotherapy*, *61*(7), 10.1128/aac. 02666-02616.

Shah, N. S., Wright, A., Bai, G. H., Barrera, L., Boulahbal, F., Martín-Casabona, N., Drobniewski, F., Gilpin, C., Havelková, M., Lepe, R., Lumb, R., Metchock, B., Portaels, F., Rodrigues, M. F., Rüsch-Gerdes, S., Van Deun, A., Vincent, V., Laserson, K., Wells, C., & Cegielski, J. P. (2007). Worldwide emergence of extensively drug-resistant tuberculosis. *Emerg Infection Disease*, *13*(3), 380-387. https://doi.org/10.3201/eid1303.061400

Sharma, S., Chauhan, A., Ranjan, A., Mathkor, D. M., Haque, S., Ramniwas, S., Tuli, H. S., Jindal, T., & Yadav, V. (2024). Emerging challenges in antimicrobial resistance: implications for pathogenic microorganisms, novel antibiotics, and their impact on sustainability. *Frontiers in Microbiology*, *15*, 1403168.

Singer, A. C., Shaw, H., Rhodes, V., & Hart, A. (2016). Review of antimicrobial resistance in the environment and its relevance to environmental regulators. *Frontiers in Microbiology*, *7*, 1728.

Sotgiu, G., Ferrara, G., Matteelli, A., Richardson, M. D., Centis, R., Ruesch-Gerdes, S., Toungoussova, O., Zellweger, J. P., Spanevello, A., Cirillo, D., Lange, C., & Migliori, G. B. (2009). Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. *Eur Respir J*, *33*(4), 871-881. https://doi.org/10.1183/09031936.00168008

Spellberg, B., & Gilbert, D. N. (2014). The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. *Clinical Infectious Diseases*, *59*(suppl_2), S71-S75.

Sulis, G., Sayood, S., & Gandra, S. (2022). Antimicrobial resistance in low-and middle-income countries: current status and future directions. *Expert Review of Anti-infective Therapy*, *20*(2), 147-160.

Uruén, C., Chopo-Escuin, G., Tommassen, J., Mainar-Jaime, R. C., & Arenas, J. (2020). Biofilms as Promoters of Bacterial Antibiotic Resistance and Tolerance. *Antibiotics (Basel)*, *10*(1). 3. https://doi.org/10.3390/antibiotics10010003

Van Acker, H., Van Dijck, P., & Coenye, T. (2014). Molecular mechanisms of antimicrobial tolerance and resistance in bacterial and fungal biofilms. *Trends in Microbiology*, *22*(6), 326-333. https://doi.org/10.1016/j.tim.2014.02.001

Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., Teillant, A., & Laxminarayan, R. (2015). Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences*, *112*(18), 5649-5654.

Van Boeckel, T. P., Gandra, S., Ashok, A., Caudron, Q., Grenfell, B. T., Levin, S. A., & Laxminarayan, R. (2014). Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *The Lancet Infectious Diseases*, *14*(8), 742-750.

Wang, H., Chen, D., & Lu, H. (2022). Anti-bacterial monoclonal antibodies: next generation therapy against superbugs. *Applied Microbiology and Biotechnology*, *106*(11), 3957-3972.

Wendlandt, S., Shen, J., Kadlec, K., Wang, Y., Li, B., Zhang, W.-J., Feßler, A. T., Wu, C., & Schwarz, S. (2015). Multidrug resistance genes in staphylococci from animals that confer resistance to critically and highly important antimicrobial agents in human medicine. *Trends in Microbiology*, *23*(1), 44-54.

Zack, K. M., Sorenson, T., & Joshi, S. G. (2024). Types and Mechanisms of Efflux Pump Systems and the Potential of Efflux Pump Inhibitors in the Restoration of Antimicrobial Susceptibility, with a Special Reference to Acinetobacter baumannii. *Pathogens*, *13*(3), 197. https://www.mdpi.com/2076-0817/13/3/197