Infection and Drug Resistance

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REVIEW

Methicillin Resistant *Staphylococcus aureus*: Molecular Mechanisms Underlying Drug Resistance Development and Novel Strategies to Combat

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Abstract: Antimicrobial resistance (AMR) represents a major threat to global health. Infection caused by Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the well-recognized global public health problem globally. In some regions, as many as 90% of *S. aureus* infections are reported to be MRSA, which cannot be treated with standard antibiotics. WHO reports indicated that MRSA is circulating in every province worldwide, significantly increasing the risk of death by 64% compared to drug-sensitive forms of the infection which is attributed to its antibiotic resistance. The emergence and spread of antibiotic-resistant MRSA strains have contributed to its increased prevalence in both healthcare and community settings. The resistance of *S. aureus* to methicillin is due to expression of penicillin-binding protein 2a (PBP2a), which renders it impervious to the action of β-lactam antibiotics including methicillin. The other is through the production of beta-lactamases. Although the treatment options for MRSA are limited, there are promising alternatives to antibiotics to combat the infections. Innovative therapeutic strategies with wide range of activity and modes of action are yet to be explored. The review highlights the global challenges posed by MRSA, elucidates the mechanisms underlying its resistance development, and explores mitigation strategies. Furthermore, it focuses on alternative therapies such as bacteriophages, immunotherapy, nanobiotics, and antimicrobial peptides, emphasizing their synergistic effects and efficacy against MRSA. By examining these alternative approaches, this review provides insights into the potential strategies for tackling MRSA infections and combatting the escalating threat of AMR. Ultimately, a multifaceted approach encompassing both conventional and novel interventions is imperative to mitigate the impact of MRSA and ensure a sustainable future for global healthcare.

Keywords: MRSA, AMR, resistome, phage therapy, nanoparticles, antimicrobial peptides, lytic

Introduction

Background of *Staphylococcus aureus*

Staphylococcus aureus belongs to the genus staphylococcus. The bacteria was first identified in 1871 by Von Recklinghausen.[1] Scottish surgeon Ogston later confirmed its role in abscesses and suppurative diseases in 1880. Ogston observed the cocci in grape-like clusters and named it Staphylococcus due to its resemblance to a bunch of grapes. Rosenbach further classified them as *Staphylococcus aureus* and *Staphylococcus albus* in 1884, with the latter later renamed as *Staphylococcus epidermidis*.[2] *S. aureus* is a non-spore-forming, non-motile, gram positive cocci that commonly reside in the skin and upper respiratory system. It is a major component of the body's microbiota and often associated with infections, particularly bacteremia. Pathogenic strains of *S. aureus* can cause several infections, from mild infections to fatal conditions like bloodstream infections and pneumonia.[3] The emergence of strains resistant to antibiotics, especially *S. aureus* resistant to the drug methicillin (MRSA), is a significant global health concern. MRSA poses a substantial threat both in medical settings and community settings, where it spreads rapidly.

MRSA is well known for spreading quickly and infecting people.[4] It can be transmitted through direct contact with infected individuals, contaminated surfaces, or contaminated healthcare settings.[5] This ease of transmission contributes to

Received: 14 September 2023
Accepted: 29 November 2023
Published: 14 December 2023

its rapid spread within communities and healthcare facilities.[6] The bacteria can colonize the skin and mucous membranes of individuals without causing infection. This colonization can lead to a reservoir of MRSA, allowing for its rapid proliferation and subsequent transmission.[7] The resistance of MRSA to multiple antibiotics, including methicillin, makes it difficult to treat and control. This resistance allows MRSA to survive and multiply in the presence of antibiotics, further contributing to its rapid proliferation.[8] MRSA is a common cause of healthcare-associated infections, such as surgical site infections, bloodstream infections, and pneumonia.[9] The close proximity of patients in healthcare settings, compromised immune systems, and invasive medical procedures can facilitate the rapid spread of MRSA within these environments.[10] MRSA can also cause infections in the community, particularly among individuals with close skin-to-skin contact, such as athletes in contact sports or individuals living in crowded conditions. These community-associated infections contribute to the overall burden of MRSA and its rapid proliferation.[11] Most of *S. aureus*-related morbidity and mortality can be attributed to MRSA. The prevalence of antibiotic resistance has made treatment challenging, necessitating the search for effective therapies.[1,12,13]

Antimicrobial Resistance

Although using antibiotics in modern medicine for treating infections caused by bacteria has changed the field, throughout time, the indiscriminate, improper, and frequently abusive use of antibiotics has led bacteria to develop drug resistance. These bacterial strains are resistant to common treatment interventions. Realizing that development of AMR has outpaced the invention of potential antibiotics is disappointing.[14] AMR has been designated by the World Health Organization (WHO) among the leading global health threats.[15] AMR is a condition in which microorganisms proliferate or reproduce in application of medications intended to stop or kill them.[15,16] AMR occurs when microbes adapt to the effects of antimicrobial agent intended to kill or inhibit them. These cause infections to become more difficult to be treated, leading to a higher chance of disease transmission, complicated illness and increased mortality.[17] The significantly rising prevalence of AMR pathogen poses a significant threat to human and animal health, limiting treatment options for bacterial infections, which in turn affects treatment outcome, while decreasing affordability of treatment and increasing mortality.[18] The majority of the world is infested with multidrug-resistant superbugs and bacteria. Antibiotic resistance pathogens significantly raise both morbidity and mortality rates.[19] Antimicrobial resistance is growing quickly and poses a threat to outpace the introduction of new antimicrobials.[20]

AMR is a serious threat to the entire world and is rapidly getting worse.[18] In 2016, AMR was expected to lead over 700,000 annual death, of which 50,000 deaths were occurred in Europe and the United States of America. As implied by O'Neill J, high death rate of 700,000 per year would increase to an extremely worrying 10 million annually.[21] According to the estimation of World Health Organization, if viable alternatives to existing antibiotics are not discovered, by 2050 antimicrobial resistance may result in 10 million deaths per year at a cost of hundred trillion dollars worldwide, with the highest rates of mortality occurring in Africa and South Asia. This would surpass the rates of cancer and heart disease.[22]

As determined by a global survey in 2019, antimicrobial resistance has accounted for 4.95 million deaths, which significantly surpasses O'Neill J prediction of annual deaths due to AMR[21], of which 25% of deaths were attributed by bacterial AMR. Among the surveyed 23 pathogenic bacteria, thoracic and lower respiratory infections, abdominal and bloodstream infections resulted for 79% of the deaths brought by antimicrobial resistant pathogens. The most common bacteria attributed to AMR were ESKAPE pathogen. MRSA resulted in over 100, 000 deaths.[23] The emergence of antibiotic resistance is the main cause of the increased incidence rate of MRSA. MRSA strains are resistant to a wide range of medications, including beta-lactam antibiotics like methicillin. MRSA is more challenging to treat because of its resistance to the effects of common antibiotics. Methicillin and other beta-lactam antibiotics, however, continue to work against MSSA strains.[24] The primary mechanism of antibiotic resistance in *S. aureus* is the acquisition of resistance genes, like the *mecA* gene that confers methicillin resistance. Other mechanisms include the synthesis of efflux pumps, beta-lactamase enzymes, modifications to drug targets, and decreased drug permeability due to modifications in the bacterial cell wall.[25] AMR in *S. aureus* has significant clinical implications. Compared to methicillin-susceptible *S. aureus* (MSSA) infections, MRSA infections are linked to longer hospital stays, treatment failures, and greater death rates. Treatment options are further restricted by the spread of multidrug-resistant MRSA strains, such as vancomycin-resistant MRSA (VRSA) and linezolid-resistant MRSA.[26]

Methicillin Resistant *Staphylococcus aureus* (MRSA)

MRSA is *Staphylococcus aureus* with that possess SCCmec element encoding pbp2a. PBP2a has a low affinity for most of the beta-lactam antibiotics, rendering most of beta lactam antibiotics ineffective in inhibiting the trans-peptidase activity of the enzyme and preventing cell wall synthesis. This mechanism confers resistance to a wide range of beta-lactam antibiotics.[27] The other mechanism is through production of beta lactamase. Some MRSA strains produce beta-lactamase, and they can hydrolyze beta lactam antibiotics, including methicillin.[28] MRSA was originally discovered in 1960, soon after methicillin was made available as a treatment for penicillin-resistant *S. aureus*. MRSA exhibits antibiotic resistance through PBP2a and PBP2c proteins encoded by the *mecA* and *mecC* genes, respectively. The transposable genetic element called staphylococcal chromosomal cassette mec (SCCmec) possesses the *mecA* or *mecC* gene, which code for a penicillin-binding protein (PBP2a). Acquiring the SCCmec makes the bacteria resistant to beta-lactam antibiotics. PBP2a alternative penicillin-binding protein, encoded by the *mecA* gene, is responsible for high-level methicillin resistance.[29]

Although MRSA was discovered shortly after methicillin became readily available, whole-genome sequencing revealed that MRSA emerged of long before the use of methicillin, suggesting that the occurrence of MRSA was not initially fueled by the use of methicillin; instead, utilization of penicillin has driven the selection for *S. aureus* strains possessing the gene that codes for penicillin-binding protein ie *mecA* before the methicillin has developed.[30,31] *MecA*, is not to *Staphylococcus aureus*, it is incorporated from an extra species. It has been suggested that the species *Staphylococcus sciuri* is the source for *MecA*.[32,33] *S. sciuri* is a source for the staphylococci *mecA* gene that leads resistance to the drug methicillin.[34]

MRSA is a serious pathogen that found in both within community and hospitals. Methicillin, works by interfering penicillin-binding protein engaged in crosslinking of peptidoglycan, a trans-peptidase that catalyzes cell-wall cross-linking, *S. aureus* develops resistance to this class of drug by expressing penicillin-binding protein, that carry out the normal tasks for the host being resistant to methicillin treatment.[35]

The expanding development of AMR staphylococci is becoming threat around the world because it leads to critical mortality and morbidity due to their related healthcare or community-acquired infections. MRSA strains first observed in adult patients who visited hospital, having previous history of methicillin usage. MRSA was also isolated from people who appeared to be in good health and who had never visited a hospital or had any other contact with health care facilities. These show that *Staph* and *MRSA* can also cause infection outside of hospitals and medical facilities. Strains of MRSA that present in healthcare setting, in livestock, and community setting are classified as health care, livestock, and community associated, respectively.[36–38]

Health care associated MRSA (HA-MRSA) primarily present in healthcare participants and hospitalized patients.[39] Community-associated MRSA (CA-MRSA) are infections in people with good health with no previous hospitalization and medical procedure. CA-MRSA reported for the first time 1980s among residents of Western Australian villages who had never been hospitalized before.[11] Soon after the strains there have quickly disseminating in a variety of populations all over the world, with outbreaks being reported in various nations.[40] The strains emerged as a serious pathogen in healthcare, and community settings, studies have shown that the health care and community associated MRSA coexist within both community and healthcare settings.[39,41] Livestock associated MRSA (LA-MRSA) was reported in 2005. LA-MRSA is primarily associated with clonal complex (CC) 398, considered a significant pathogen in animal that is also capable of colonizing and infecting humans.[42,43] MRSA is now a major concern for public health worldwide. Research from various parts of the globe consistently show that MRSA is more common than MSSA. For instance, data from more than 200 studies were analyzed in a systematic review and meta-analysis that was published in the Lancet Infectious Diseases in 2018. The study revealed that MRSA was more common than MSSA overall across all regions, including Europe, North America, Asia, and Africa.[44] The emergence of antibiotic resistance is the main cause of the increased incidence rate of MRSA. Methicillin and other beta-lactam antibiotics are among the many medications to which MRSA strains have developed resistance. Because of this resistance, MRSA is more challenging to treat since it can withstand the effects of common antibiotics leading to higher mortality rate than MSSA. On the other hand, methicillin and other beta-lactam antibiotics continue to work on MSSA strains.[45] This resistance allows MRSA to survive and thrive in environments where MSSA strains would be susceptible to treatment, leading to a higher incidence of MRSA infections. MRSA has demonstrated enhanced transmissibility compared to MSSA. The altered cell wall structure and increased

virulence factors in MRSA strains contribute to their ability to persist on surfaces, survive in the environment, and spread between individuals. MRSA can be transmitted through direct contact with infected individuals, contaminated surfaces, or through respiratory droplets.[44] The higher incidence rate of MRSA relative to MSSA can be attributed to its antibiotic resistance, the prevalence of healthcare-associated and community-associated infections, enhanced transmission dynamics, the emergence of livestock-associated strains, and limited treatment options. Addressing these factors requires a multifaceted approach, including improved infection control measures, antibiotic stewardship, and continued research into alternative treatment options.[46]

Mechanisms of AMR Development in *S. aureus*

Antimicrobial resistance development is not a condition that is associated with simple process, rather influenced by numerous elements, including organisms' genetic makeup, environmental factors, and the use of antibiotics. The genetic makeup of an organism is a crucial factor in the AMR. Mutations can lead to structural alteration or protein function which can make the organism less susceptible to drugs. Additionally, certain genetic elements can provide resistance to number of drugs, for example antibiotic resistance genes. Bacterial defenses have evolved aiming to defend themselves from external pressures like antimicrobials. While most bacterial cells in the presence of lethal stress die, persister cells can survive and, continue growth after the perturbing stress is removed. Persisters are group of bacterial cells that possess the ability to survive when exposed to intense stressors, thereby presenting obstacles in the complete eradication of infections.[47] In particular, Staphylococcal bacteria can adopt several phenotypes, like "small colony variations" and development of biofilm, that help the persistent cells. These particular lifestyles help staphylococci become more resilient to antibiotics.[48–51]

S. aureus can develop antibiotic resistance through genetic acquisition or gene mutation. Bacteria with the resistance genes are forced to survive and proliferate, resulting from selective pressure from extensive antibiotic usage.[52] (I) Mutation: spontaneous changes in the bacterial chromosome that cause some bacteria to become resistant to antibiotics. Every time the bacterium divides there is a possibility for mutations to occur. These mutations can appear anywhere in the DNA and are random. External factors like radiation or harmful chemicals can also cause mutations. While some mutations are harmful for the bacteria, others can be advantageous under the right conditions. If a mutation gives a bacterium an advantage in a specific environment it will be selected and persist in the population, then grow faster and reproduce more readily than its neighbors. Some mutations might make the bacterium develop antibiotic resistance. *Staphylococcus aureus* develops fluoroquinolone resistance due to changes in amino acid sequence in specific locations in the topoisomerase IV A subunit, DNA gyrase A and B subunits through efflux mediated by NorA.[53,54] NorAn is a variant of an efflux pump that demonstrates a significant contribution to bacterial multidrug resistance. Efflux pumps are specialized proteins located in the bacterial cell membrane that actively expel various substances, including antibiotics.[55] NorAn, specifically, is commonly found in *Staphylococcus aureus* and plays a defensive role by facilitating the removal of antibiotics from the cell, thereby reducing their efficacy. This efflux pump variant presents a challenging hurdle in the treatment of bacterial infections, as it diminishes the intracellular concentration of antibiotics and contributes to multidrug resistance.[53,54]

(II) Acquisition of foreign DNA through horizontal or vertical gene transfer, also known as "mobile genetic elements" (MGEs). Antibiotic resistance can be either chromosome-maintained or plasmid mediated. Acquired resistance is the process by which a microorganism that was once liable for a particular antibiotic became resistant. Resistance acquisition can come from incorporation of genetic materials from donor bacteria to competent recipient bacteria or incorporation of the intended genetic material from the resistome. Some bacterial genes are contained on mobile genetic elements (MGE) which enhance motility of antimicrobial resistance genes (ARGs), allowing them to disseminate quickly within a bacterial community.[56–58] MGEs, which can spread a range of AMR factors across bacterial genomes: including chromosomal cassettes, plasmids, insertion sequences, integrons, phages, pathogenicity islands, and transposons. Other MGEs integrate into the host DNA, whereas plasmids are often extrachromosomal. The development of drug resistance in staphylococci is facilitated by MGEs. For instance, *S. aureus* gained resistance to vancomycin and methicillin by acquiring VanA operon from enterococci, and chromosomal cassette harboring *mecA* respectively.[25,59]

Bacterial species also have the capacity to withstand the effects of antibiotics through intrinsic resistance, which is found within their genomes. Certain microorganisms are resistant to certain antimicrobial agents. For instance, for antibiotics that target cell wall to exert an effect, the bacteria must possess the cell wall. Natural resistance can either be inherent or induced. The inherent resistance results from an organism's biology, independent of horizontal transmission of genes and selective pressure of antibiotics. Decrease in the outer membrane's permeability and the normal activation of pumping efflux are the two most frequent bacterial mechanisms implicated in intrinsic resistance. Inherent resistance could result from; lack of antibiotic affinity for bacterial target, the antibiotic's inability to enter the bacterium cell, the bacteria may use chromosomally encoded efflux pumps to extrude the medication, or may possess enzymes that are able to degrade the target drug.[25,60–62]

Horizontal gene transfer (HGT), is the exchange of genetic material between bacterial species. HGT is a crucial factor in the dissemination of antimicrobial resistance genes (ARGs) throughout various bacterial populations. This is crucial element in the emergence of new strains of resistant organisms.[63] Various investigations have demonstrated that bacteria from livestock and associated environments contain mobile genetic components harboring ARGs, this poses a potential risk since these resistance characteristics can be transferred between human and animal pathogenic bacteria.[64] Horizontal gene transfer has enabled AMR to expand from nonpathogenic organisms to pathogenic ones, fueling pathogen evolution. It is now widely accepted that all pathogenic bacteria, commensal bacteria, environmental bacteria, phages and MGEs collectively house the resistome (ARGs). The pathogenic bacteria can incorporate the resistance genes from the resistome.[65]

There are three recognized mechanisms by which genetic transfer in bacteria is accomplished: transformation, conjugation, and transduction. Among those conjugations is believed to have the most impact on the propagation of AMR genes. This is because it provides better environmental protection, an effective way of entering the target cell than transformation, and has a wider host range compared to bacteriophage transduction.[66] Antimicrobials work by killing, inhibiting, or neutralizing the microorganism without harming the host cell; by interrupting bacterial cell wall synthesis, interfering with vital process like protein and folate synthesis.[67] Bacterial growth is inhibited, when the antibiotic effectively interacts with its target. To make this interaction happen; the target must be recognized by the antibiotic, and there must be high enough concentration of antibiotic present at the target to effectively impede its function. Therefore, all resistance mechanisms are based on either altering the target or lowering the amount of free antibiotic that can reach the target.[16,19] There are two main mechanisms that bacteria withstand the effects of antibiotics: (i) decreasing the concentration of antibiotic reaching its target or preventing at all. (ii) Modifying the target that antibiotics act on. Decreased permeability of the cell wall, enhancing efflux, altering drug target site, and inactivating the drug are the main molecular mechanisms that bacteria use to alter the drug target or lower the concentration of the antibiotics reaching the target, thereby enhancing resistance.[25,68]

Factors Associated with Resistance Development

Although it is thought that antibiotic resistant genes existed prior to the discovery of antimicrobials, utilization of these antimicrobials has enhanced the development and dissemination of AMR genes in pathogenic bacterial strains.[69] The way antibiotics are used has impact on how quickly and how much resistance develops. It is truly amazing how well bacteria can adapt and change in response to a wide range of selective pressures, including the presence of antimicrobial agents. Although bacteria develop antibiotic resistance through natural selection or through adaptation to perturbing environmental conditions, there are many factors that trigger development of resistance (Figure 1).[70] Inappropriate use of antimicrobials, poor and lack of diagnostics, substandard/falsified medicines, antimicrobial use in agriculture, environmental antimicrobial residues are among the main factors associated with resistance development.[71]

Inappropriate Use of Antimicrobials

Although microorganisms can develop resistance to certain antimicrobial agents naturally, improper utilization of antibiotics has highly influenced the emergence of resistance.[72] Antibiotic misuse and overuse are the primary risk factors for emergence of AMR. Inappropriate use of antibiotics selects resistant bacteria. Resistant microbes can grow even when the antibiotics are present. Inappropriate use of antibiotics can perturb gut microbiota, these make resistant microbes outcompete susceptible microbes and can spread the genetic information encoding resistance. Numerous

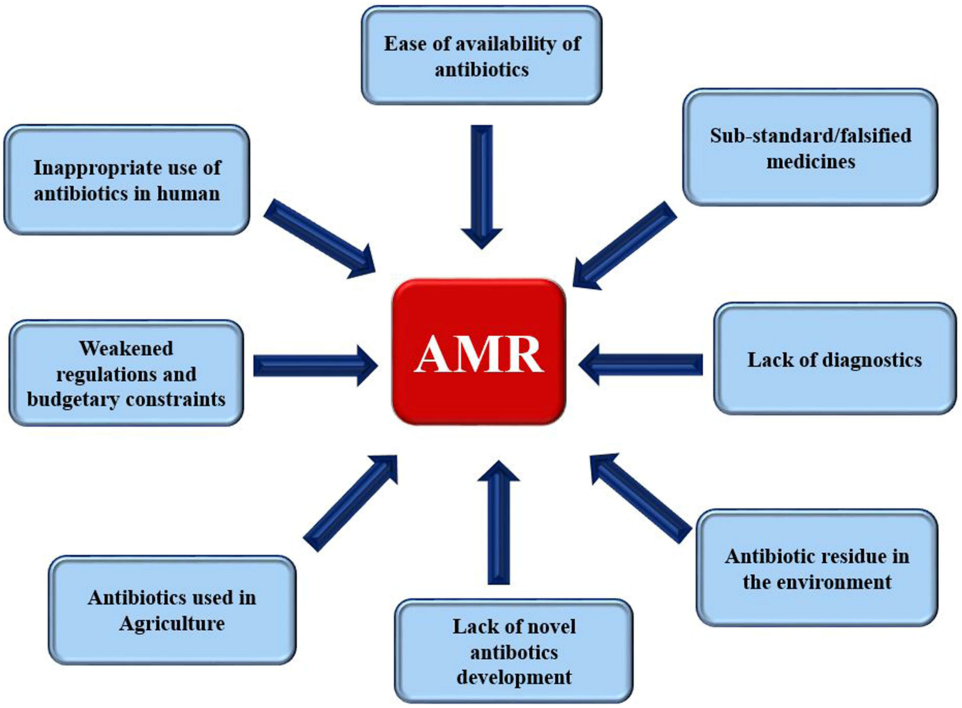

Figure 1 Diagrammatic representation of factors contributing to AMR development.

studies have provided evidence demonstrating a strong connection between the inappropriate use and excessive use of antibiotics and the emergence of resistance in MRSA. For example, a 2017 study published in the Journal of Antimicrobial Chemotherapy examined antibiotic consumption and the prevalence of MRSA in hospitals.[73] The findings revealed a significant correlation between higher antibiotic usage rates and a greater incidence of MRSA infections. This association remained statistically significant even after accounting for factors such as patient characteristics and infection control practices. In another study published in the New England Journal of Medicine in 2018, researchers investigated the impact of antibiotic exposure on MRSA colonization among residents of nursing homes. The results indicated that individuals who had recently received antibiotics were more likely to be colonized with MRSA compared to those who had not been prescribed antibiotics.[74] This suggests that antibiotic mis use increases the risk of MRSA colonization and subsequent infections.

Antibiotic-related changes to the normal flora are selected for highly resistant bacteria. The gut is well known to have a significant role in host health. Reduced microbial diversity and modifications to the functional characteristics of the microbiota pave a way for the emergence and selection of AMR strains. Antibiotic misuse is fairly common practice in both high-income and low-income nations worldwide. In Africa, the most popular prescribed drugs are antibiotics. A survey conducted on factors predicting antibiotic use in five African countries, it found that among the 90% of acutely ill people who sought care outside the home 36% of patients received antibiotics. One in four people who received antibiotics came from an informal dispenser, and more than 30% of people accessed antibiotics without a prescription.[71,75]

The use of antibiotics in excess and in the wrong circumstances in agriculture is a significant public health issue because it serves as a major driver of antibiotic resistance. When antibiotics are used in agriculture, they can create an environment that enhances the growth of AMR bacteria. These resistant bacteria can spread through the air, water, soil, and other sources, leading to the spread of AMR pathogens in humans. Furthermore, in animal when infections are treated with antibiotics, these AMR bacteria can spread to humans from interaction with animals, food, and other sources. As a result, the excessive application of antibiotics in agriculture has a direct impact on human health, leading to increased risk of developing antibiotic-resistant infections. Because antibiotic-resistant bacteria linked to animals can have medical importance ie Humans can get diseases from animals, found widely distributed in the environment through

animal waste, and are simply transmittable to humans through food chains. These could result in complex, incurable, and protracted infections in people, increasing healthcare costs and occasionally even resulting in death.[76]

Sub-Standard or Falsified Medicines

Sub-standard medicines are products that purposefully or fraudulently conceal their origin, identity, or composition. Medical products that are falsely labeled may be lacking the active ingredients, contain incorrect dosage of the appropriate active ingredient, or miss the active ingredient itself.[77] These falsely fabricated medical supplies could be poisonous in nature, containing either lethal doses of the incorrect active ingredient or other harmful toxins.[69] Falsified medicines are manufactured in unsterilized and hazardous conditions by an inexperienced person, and unidentified ingredients and it is more likely those products contaminate with bacteria. Inadequate antibiotics with low concentrations or incorrect dosages can lead to the development of antimicrobial resistance. A study found that low- and middle-income countries' poor antibiotics obtained from unregulated sources had lower levels of active ingredients. This made resistant strains more likely to emerge and raised the risk of treatment failure.[78] Sub-standard medicines are frequently produced in poorly regulated or unregulated manufacturing facilities with inadequate quality control methods. Insufficient quality control led to inconsistent drug composition and dosages in subpar and counterfeit antibiotics found in Southeast Asia and Africa, as per a study by McManus and Naughton, such differences could result in less-than-optimal treatment of infections like MRSA.[79] Falsified antibiotics might have insufficient amounts of their active components, which would cause the body to produce sub-therapeutic concentrations. Bacteria may be subject to selective pressure as a result, which may favor the survival and spread of resistant strains like MRSA. Ayukekbong et al conducted a study that brought attention to the possible role that sub-standard medications play in the spread of MRSA and other forms of antimicrobial resistance in low- and middle-income nations.[80]

Sub-standard antibiotics may lead to sub-inhibitory concentrations of the active pharmaceutical ingredient. In bacteria, low antibiotic concentrations can lead to the development of resistance and result in treatment failure. There may be room for resistance to develop and be selected if the antibiotic concentration is lower than that required to kill or cease bacterial growth.[81,82]

Inefficient Diagnostic Facilities

Diagnostic facilities have crucial role in treatment efficacy and resistance development. They can help identify the presence of drug-resistant bacteria or viruses that may be present in a person or environment. Diagnostic tests can also help to identify the specific type and level of resistance present in a particular organism, which can influence treatment decisions and choices. These help prevent the spread of drug-resistant organisms.[83] Additionally, diagnostic tests can help to identify the genetic components of drug-resistance, which can help inform the creation of novel treatments and strategies to fight AMR pathogens. Diagnostics are crucial in avoiding inappropriate utilization of antibiotics, because it guides medical professionals to choose the most appropriate prescription for a specific condition, thus reducing the likelihood of antibiotic resistance.[52]

The inability to precisely identify the specific pathogen causing an infection leads to prescription of inappropriate or broad-spectrum antibiotics. This leads to unnecessary costs and promotes the emergence of antibiotic resistance. Poor diagnosis leads to inappropriate use of antibiotics. For instance, when antibiotics are taken for a viral infection, the bacteria in our body are attacked. These are bacteria that either help us or are not causing infection. When harmless flora are improperly treated, they may develop antibiotic resistance traits that they can pass on to other bacteria, or it can lead to emergence of potentially harmful bacteria to replace the harmless normal flora.[84] Budgetary constraints restrict how AMR surveillance is prioritized. Mainly, low-income and developing countries lack quick, practical diagnostic equipment for medical professionals to identify the exact cause of infection.[85,86] A significant weapon in fighting AMR is good diagnosis. Treatment effectiveness can be increased by tailoring drug of choice to infection while lowering costs by prescribing antibiotics that are appropriate for the infection.[87] A strong diagnosis can help reduce the development of resistance by ensuring that the correct medications are prescribed and taken as directed. This helps prevent drug-resistant bacteria from developing as a result of misdiagnosis or incorrect medication. Additionally, a firm diagnosis may help identify and remove environmental sources of infection, such as contaminated food or water supplies, which can also increase the emergence of resistance.[52] One tool in the arsenal of antimicrobial stewardship is the ability to differentiate viral and bacterial infections.[88] Good diagnosis figures out

the causative pathogen and its resistance profile. Diagnostics is crucial to mitigate the silent AMR pandemic through enabling for active surveillance of drug resistance and enabling the best utilization of accessible medicines, ensuring the specific and effective application of mediation. Molecular methods are often used in identifying the underlying genetic mechanism(s) for AMR. Thanks to nucleic acid tests, the field of diagnostics has undergone a revolution by allowing medical professionals to recognize pathogens and their AMR genes. NGS, or next-generation sequencing shown to be effective in identifying mutations and locating ARGs. Development of affordable diagnostic tools that can be used in low-resource settings without advanced laboratory equipment is challenging. Adoption of current diagnostics to more accurately diagnose infections could reduce antibiotic misuse and the escalating threat of AMR.[88–90]

Utilization of Antimicrobials in Veterinary Setting

Antimicrobials are not only utilized in medical settings as treatment options for human diseases. They are widely utilized in the production of livestock, where antibiotics can be used to treat animal diseases, as growth enhancer, to increase outcome of feed conversion and disease prevention. With high concern given, the class and modes of action of these drugs used in veterinary practice are close kinship or identical (the same member, perform similar tasks, and behave similarly) to those prescribed to humans.[91] Utilization of antibiotics in agricultural setting has connection with development of AMR in bacteria. When antibiotics are used to treat livestock and poultry, the bacteria in the animals can develop resistance to the drugs. This resistant strain of bacteria can spread to other animals, humans, and the associated environment, paving a way to a greater risk of infection and dissemination of AMR bacteria. Residues of antibiotics present in the surrounding environment can also lead to a greater risk of antibiotic resistance. When antibiotics are used on crops, the residue can enter the environment and can have effect on bacteria population, leading to the development of resistant strains.[76,92]

This can happen when antibiotics are used on animals in factory farms, and then spread to via the food chain to humans. It can also occur when antimicrobials are utilized in treating infections in farm animals allowing resistant bacteria to survive and spread. The use of veterinary medications in animals used for food production can lead to accumulation of antimicrobial residues in items made from animals (milk, meat, honey, and eggs), posing medical risk to the consumers. In addition, utilization of antimicrobials in agricultural setting can enhance the spread of AMR pathogen through water, soil, and air, which can then be passed on to humans.

In northern nations and Africa, frequent misuse of antibiotics happens in farming, fattening up animals for slaughter and preventing disease in unhygienic factory farms.[93–95] The establishment of colistin resistance shows that resistance can be further boosted by using high dosages of antibiotics to treat infections or promote growth. Utilization of avoparcin as growth enhancer has also found to have the same effect. Also, the glycopeptide vancomycin, which is utilized in treating MRSA, has made enterococci resistant to severe infections.[96] Antibiotics used in agriculture to promote growth are already prohibited by the European Union. A multifaceted strategy that incorporates various sectors is required to effectively combat antimicrobial resistance in low- and middle-income nations.[97]

Current Therapeutic Options

Antibiotic Stewardships

This approach focuses on the appropriate and judicious use of antibiotics to minimize the development of resistance. However, inappropriate utilization may lead to resistance development. Using antibiotics only when it is necessary and following guidelines for their optimal use is curtailed in minimizing the likelihood of resistance development.[98] Antibiotics are the mainstay of treatment for *S. aureus* infections. However, the treatment depends on the severity of the infection, the location of the infection, and the antibiotic susceptibility of the bacteria. Commonly used antibiotics for *S. aureus* infections include beta-lactams (such as penicillin and cephalosporins), macrolides (such as erythromycin), tetracyclines (such as doxycycline), and fluoroquinolones (such as ciprofloxacin). However, some strains of *S. aureus* have developed resistance to these drugs, eg, MRSA. Still majority of MRSA infections are treated with appropriate utilization of antibiotics. Most of simple skin and soft tissue infections (SSTIs) that are suspected of having an MRSA infection can be empirically treated with oral antibiotics such as clindamycin, trimethoprim/sulfamethoxazole, and tetracyclines like minocycline or doxycycline.[99] In patients with normal renal function, higher dosages of trimethoprim/sulfamethoxazole (160/800 mg, one tablet three times daily or two tablets

twice daily in adults) are advised.[99,100] More recent medications, like tedizolid and linezolid, as well as delafloxacin, can be utilized as substitute oral regimens if they are accessible and economical.

Combination Therapy

Combination therapy is a type of medical treatment that involves the use of two or more drugs or therapies to achieve a better therapeutic effect than what could be achieved with a single therapy alone. The rationale behind combination therapy is that different drugs or therapies may have different mechanisms of action or targets, and when used together, they can complement each other's effects, enhance efficacy, and reduce side effects.[101] Combination therapy is used in cases where the infection is particularly severe or resistant to a single antibiotic treatment. In some cases, like MRSA infection combining different antibiotics can be more effective against drug-resistant bacteria than using a single antibiotic. This approach can help overcome resistance mechanisms and improve treatment outcomes. The choice of empirical antibiotic therapy for MRSA infections depends on a number of factors, including the patient's profile, drug availability, side effect profile, disease type, and local patterns of *S. aureus* resistance. With other resistance profile screened, alternative antibiotics such as vancomycin, daptomycin, linezolid, and ceftaroline are used to treat MRSA infections.[102] For MRSA infections, Vancomycin is the primary antibiotic used. Vancomycin and other glycopeptides are frequently the antibiotics of choice for treating MRSA infections in various parts of the world.[103] Vancomycin is often considered the drug of choice for severe MRSA infections. It works by inhibiting bacterial cell wall synthesis. However, in some cases, MRSA strains may develop resistance to vancomycin, leading to treatment failure.

In some cases, linezolid or daptomycin may be used as an alternative or in combination with vancomycin.[104] However, the incidence of vancomycin intermediate *S. aureus* (VISA), which is less susceptible to vancomycin than other strains, and vancomycin resistant *S. aureus* (VRSA), which is resistant to vancomycin, is making the treatment ineffective.[105] Linezolid works by inhibiting bacterial protein synthesis. It is effective against MRSA and is often used as an alternative to vancomycin, especially in cases where vancomycin resistance is a concern.[106]

Commonly used combination therapies used to treat MRSA infections include Beta-lactam antibiotics plus aminoglycosides, a combination often used to treat serious MRSA infections such as endocarditis or sepsis. Combination of vancomycin and rifampin or gentamycin is used to treat methicillin-resistant *S. aureus* (MRSA) infections.[107] Although administration of antibiotics is effective in treating MRSA infection, the depletion in microbiota and the emergence of drug resistance are concerns. There is a need for novel therapeutic option to treat this important group of pathogen without perturbing the microbiota.[108]

Surgical Treatment

While antibiotics are commonly used to treat MRSA infections, surgical intervention may also be necessary in certain cases. In some cases, staph infections can involve deep tissue or bone, making it difficult for antibiotics to reach the site of infection.

In such cases, surgical debridement (removal of infected tissue) is being implemented to control the infection. Furthermore, surgical management was found to be particularly beneficial in cases of recurrent or persistent MRSA infections. By removing the source of infection, surgical interventions helped break the cycle of reinfection and contributed to long-term resolution.[109]

MRSA infections can sometimes lead to the formation of abscesses, which are collections of pus that form in tissue. If abscess is large or located in a sensitive area, surgical drainage may be necessary to remove the pus and prevent further spread of infection. The infection can sometimes affect joints, causing septic arthritis. In these cases, surgery may be necessary to drain the joint and remove any infected tissue. Sometimes infection may occur in patients with prosthetic devices, such as joint replacements or pacemakers. In these cases, surgical removal of the device may be necessary to control the infection.[110]

Mitigation Strategies

One Health Approach

AMR cannot be effectively combated without an ecological strategy rooted in "One Health" idea.[111] The aim of one health is obtaining suitable outcomes for health recognizing the interdependence between animal, people and the environment they share (Figure 2). Human population growth and spread into new locations puts people in close contact

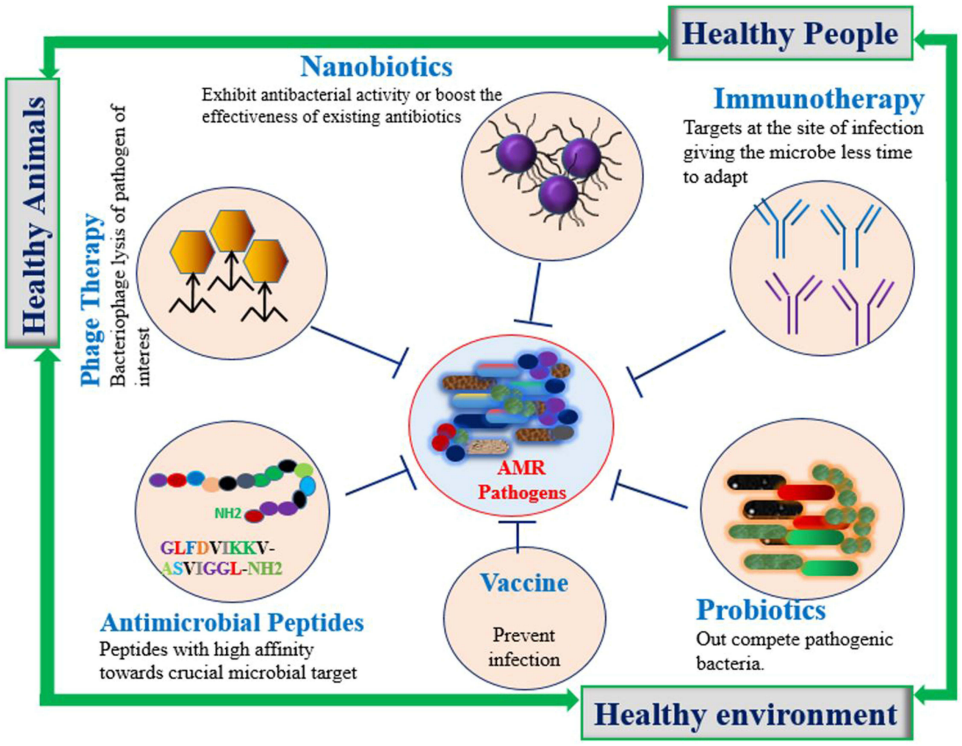

Figure 2 Schematic representation of AMR mitigation under one health perspective, and alternative therapeutic approaches to combat AMR.

with both domestic and wild animals. Land use and climate change disrupt habitats, which creates new possibilities for disease transmission. There are numerous instances where family members of farmer have the same AMR bacteria as their livestock. Resistant bacteria can be common in livestock. Veterinarians who treat livestock are also susceptible to carrying antimicrobial resistant bacteria, the pathogen might then continue to spread in the community.[112] Every animal has bacteria living on their bodies. Antibiotics are frequently used in animal farms to promote growth as well as to treat and prevent infections. Once antibiotic-resistant bacteria have colonized the farm animals, they may then spread to other animals. It is more likely that the bacteria could be introduced to the meat processing or slaughter. Animal manure can contaminate crops that come in contact with. Consuming bacteria-contaminated food can result in an infection. Additionally, genes or bacterial strains that are resistant may be transmitted to the microbiota of the utilizers. The resistant bacteria may later lead to infections, or spread to other individuals.[113] Bacteria may circulate spread through water while drinking or through other mechanisms, such as irrigation, washing, cooking utensils, or hygienic needs. Numerous water sources, including rivers, treatment plants with sewage effluents, and drinking water sources, have been found to contain resistant bacteria. Typhoid fever, cholera, and other bacterial diseases can spread through contaminated water. Resistant bacteria can enter the water in several ways; the significant source is the release of untreated animal and human waste.[114] AMR is a serious issue affecting human, environmental, and animal health worldwide. Since AMR is a complicated issue, it is essential to look at it from several perspectives to tune it in the context of the one health concept. Sixty percent of human pathogens, on average and 75% of emerging illnesses that affect people are zoonotic. Interactions between humans and animals are growing, which increases the danger of zoonotic infections and the establishment of resistant pathogens. WHO recommends utilizing the One Health model to combat antibiotic resistance that integrates health of people, animals, and the environment.[115] The one health approach to the approach takes into account that antimicrobial resistance can arise from utilization of antimicrobial substances in people, animals, and environment they share. Strategies for limiting AMR expansion include the judicious utilization of antimicrobial agents in human and animal health settings, improved hygiene practices, and improved animal husbandry practices.[116] In order to track MRSA and its dynamics of transmission, the One Health approach places a strong emphasis on the integration of environmental, animal, and human surveillance systems. An integrated surveillance system can effectively identify the

sources, transmission routes, and risk factors associated with MRSA infections in humans and animals.[117] WHO has released new recommendations for the use of medically significant antimicrobials in animals used for food production, urging farmers and food producers to avoid routine usage of antimicrobials to promote growth and avoid sickness in wholesome animals. By limiting their usage in animals, this directive aids in protecting the potency of antimicrobials that are crucial for human therapy. One health strategy would aid in the prevention of AMR through awareness campaigns, education on proper antibiotic use, political commitment, and antimicrobial stewardship. Collaboration and communication between the veterinary, environmental, and human health sectors are prioritized in the One Health approach. This collaboration enables the sharing of knowledge, resources, and best practices to prevent and control MRSA.[117]

Novel Therapeutic Strategies

The use of antimicrobials has paved novel way to treat infections successfully, saving the lives of countless patients and improving their health globally. However, our capacity to treat widespread illnesses is in danger due to development and dissemination of antimicrobial resistant pathogens.[118] WHO has implicated the development and dissemination of AMR as an international problem and the significant rise in morbidity and mortality caused by antibiotic-resistant. As AMR increases new, novel, and powerful therapeutic and preventative measures are needed to address the challenges typically linked with the emergence AMR.[14] AMR has remained a threat to public health, of which MRSA has given the highest priority. Due to this novel strategies like bacteriophage therapy, antimicrobial peptides, nanobiotics, combination therapy are being utilized to combat AMR (Figure 2). These strategies offer a benefit over antibiotics in that most of them have constrained inhibition spectra, making them effective for targeted treatment, and allow the selection of medications based on the specific target bacteria without harming commensal bacteria, and preventing collateral harm of microbiota.[13]

Bacteriophage Therapy

Bacteriophages are bacteria infecting viruses. Phage therapy involves utilization of bacteriophages to infections caused by bacteria. There are countless varieties of bacteriophages, from the environment to our guts.[13] There are two types of these viruses: lytic and lysogenic. Given their capacity to result in bacterial lysis, lytic phages have the most promise in medicine in treating bacterial infections. Infectious disease control is seriously challenged by AMR in bacterial pathogens. The globe is significantly seeking for new medicines. The long-considered medicinal use of bacteriophages is supported by a large number of anecdotal stories of its efficacy. The practice of phage-based therapy is a method that has been employed for nearly a century for the treatment of bacterial infections. Phages possess the ability to specifically target and eliminate certain bacterial strains, including those forming biofilms.[119] Biofilms are communities of bacteria surrounded by a protective matrix they produce themselves, making them highly resistant to antibiotics and immune responses. Phages have developed different mechanisms to penetrate and disrupt biofilms, and an important strategy involves the production of depolymerases.[120] Using depolymerase enzymes, bacteriophages can potentially damage the matrix outside the cells of the biofilm. Depolymerases are enzymes produced by phages that can break down the extracellular polymeric substances (EPS) present in the biofilm matrix. EPS generally consists of polysaccharides, proteins, and DNA, which contribute to the structural integrity and protection of the biofilm.[121] Research studies have made advancements in identifying various phage species that show potential against Methicillin-resistant *Staphylococcus aureus* (MRSA) in the context of phage therapy and biofilm eradication.[13] Researchers have successfully isolated and characterized phages that specifically target MRSA in their investigations, eg, phages like MR-10, MR-11, MR-12, and MR-14, which have displayed effectiveness against MRSA strains in laboratory and animal models.[122–124] These phages have demonstrated their ability to selectively attack and destroy MRSA cells, leading to a reduction in their population. A study published in "Antimicrobial Agents and Chemotherapy", researchers assessed the efficacy of a combination of phages, known as a phage cocktail, against MRSA biofilms.[125] The phage cocktail consisted of multiple phages that targeted different MRSA strains. The results revealed that the phage cocktail significantly decreased the biomass of the biofilms and disrupted their structure, thereby increasing the susceptibility of MRSA to antibiotics and facilitating bacterial clearance, showing bacteriophages could be useful agents in curing clinical biofilm infection. Recent therapeutic achievements in case studies using customized phage cocktails have rekindled interest in phage therapy, and numerous clinical trials are underway.[119,126,127]

A recent case study report showed that MRSA infection has been successfully treated with phage therapy, an old man of 72-year who has presented with persistent MRSA infection of a prosthetic joint, successfully recovered after intravenous administration of specific phage.[128] Several phages have demonstrated efficacy in treating MRSA infection (Table 1). Studies have shown that phage therapy's clinical outcomes are enhanced by the immunological modulation that the phage itself causes. PhiMR003 is a MRSA phage, showing significant virulent effect and a broad spectra to clinical isolates of MRSA in vitro. Wounds infected with MRSA strains treated with phiMR003 showed a decrease in number of bacteria, a decrease in inflammation, and a quicker rate of wound healing.[129] Patients typically receive a variety of phages (a "cocktail") that attack bacteria in various ways. Phage cocktail NOV012, prepared from two highly characterized staphylococcus aureus phages (phage P68 and K710) appears safe to use for extended periods to treat sinuses and it could infect and lyse a wide range of *S. aureus* including MRSA. Long-term administration of NOVO12, locally applied to the frontal sinus twice a day for 20 days was regarded as safe, without inducing inflammatory responses or tissue damage with sinus mucosa. NOVO12 is the most promising products, a phage cocktail, administered as a form of gel for topical treatment of MRSA.[130]

Bacteria have evolved phage resistance via a variety of mechanistic methods which function throughout the entire phage life cycle to endure the ongoing phage effect. The "innate" defense mechanisms employed by bacteria against phage predation include preventing adhesion of the phage to the surface receptors of the bacteria (receptors hiding or mutation); preventing phage genome incorporation, Restriction-Modification mediated degradation of phage genome, and utilizing the abortive infection systems. The other system, known as Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) works by incorporating short viral sequences into CRISPR locus of the bacterium to provide sequence-specific adaptive immunity. Consequently, the bacteria are able to identify and clear infections. Phage resistance emerges once per 10^7 host cells which is tenfold lower than that of antibiotics.[134,135] When using phage therapy, particularly to treat MRSA, phage resistance is a crucial factor to take into account. Phage-resistant bacteria, such as MRSA, can evolve defense mechanisms against phage infection, which reduces the efficacy of phage-based therapies.[136] Studies on MRSA have revealed phage resistance. For example, a study published in the journal "Frontiers in Microbiology" examined the evolution of phage resistance in MRSA strains.[137] The researchers looked at the genetic changes that occurred in MRSA when it developed resistance to specific phages. They found that certain genes involved in the phage infection process had phage receptor mutations that promoted resistance. Another investigation into the frequency of phage resistance in clinical isolates of MRSA showed bacteriophage resistance. The investigators examined a set of MRSA strains and evaluated each one's susceptibility to a range of phages. They discovered differences in the MRSA strains' susceptibilities to various phages, suggesting the existence of phage resistance.[136]

Studies have shown that phage resistance can be overcome using phage cocktail or, substituting with other phage. Clinical trial conducted using bacteriophage to treat a patient presented with Netherton syndrome (NS), chronic MRSA skin infection and allergy to multiple groups of antibiotics, found to be effective. By the 7th day of treatment with Pyophage cocktail and Sb-1 phage topically and orally, the infiltrated, hyperemic areas became smaller, the thickness of the yellowish film layer reduced, and mobility improved in the joints and areas of normal skin began to appear. No

Table 1 Summary of Successful Phage Therapy Case Reports Against MRSA

Patient's Sex; Age	Phage Isolate	Type of Infection	Route of Administration	Outcome	Ref
Female; 61	SaWIQ0456AØ1	Refractory MRSA chronic rhinosinusitis	IV and intranasal	Clearance of infection and return to health, negative culture	[131]
Male; 72	phiMR003	Prosthetic joint MRSA infection	Wound site	Decrease in inflammation, and a faster rate of wound closure	[128]
Female; 80	1493 and 1815	Prosthetic joint MRSA infection	Local injection	Eradication of biofilm	[132]
Female; 30	676/F, A3/R, and A5/80	Intestinal	Oral	Eradication of bacteria	[133]

allergic reactions toward the phage preparations were seen. This study also showed that phage resistance can be usually overcome by substituting another phage preparation.[138]

Recent research on animals indicates that mutations in bacteria that increase resistance to phage may have fitness expenses for the bacteria, which might be helpful to the host. In certain situations, the changes made to the bacteria that encourage phage resistance also make them more susceptible to antibiotics, which increase their effectiveness when used in conjunction with the antibiotics to enhance efficacy.[126,139,140] The bacteria may cost for mutations that give them resistance to phages, which could impair their general fitness or capacity to tolerate other stresses. These mutations may change the metabolism or physiology of the bacteria, unintentionally increasing their susceptibility to antibiotics. Stated differently, the modifications that confer resistance against phages could potentially compromise the bacteria's ability to fend off antibiotics.[140] Phage resistance-related mutations may affect the bacterial cell surface receptors or other biological elements that phages use to enter and multiply within their host. These changes may also have an effect on how antibiotics interact with their targets, which could make the bacteria more susceptible to certain antibiotics.[141] Phage resistance mechanisms in MRSA may affect the expression or functionality of efflux pumps, which are responsible for removing antibiotics from bacterial cells. Changes in the efflux pump activity may inadvertently impact the efficacy of antibiotics, thereby the bacteria's susceptibility to them.[13]

Similarly, maintaining anti-viral defense mechanisms such as CRISPR-Cas adaptive immunity and DNA restriction-modification enzymes has a cost.[140,142]

A variety of different phages are required to provide patients with adequate therapeutic options for a variety of infectious diseases. Even though there is no proof that phage particles directly cause toxicity, it found important to research the interaction of phage with mammalian cells. To prevent adverse host reactions, this necessitates that preparations of phages to be free of bacteria, toxins, and other substances. The best methods for identifying bacteriophages continue to be electron microscopy. Bacteriophage genome sequencing is necessary to confirm their lifestyle and to gain a more comprehensive understanding of their biology. Whole-genome sequencing will make it possible to comprehend the role of phage-encoded proteins and biomolecules involved in the lysis and death of bacterial cells.[143]

Antimicrobial Peptides

Antimicrobial peptides are gene-encoded polypeptide sequences which are important components of immune response of most organisms. AMPs are small-sized proteins having role in host immunological defense in most living organisms. Scientists trying to solve the issue of AMR have long been interested in the antibacterial capabilities of AMPs seen in vitro settings. AMPs contain positively charged short chains of amino acids (of 10 t0 50 aa), they are amphiphilic, these properties make them easily adhere to and pierce the bacterial membrane bilayer by "toroidal-pores", "barrel-staves", and "carpets", which cause intracellular leaking.[144] AMPs exhibit broad-spectrum activity against multidrug-resistant (MDR) bacteria and can also break down bacterial biofilms. While AMPs primarily target the cell membrane, they can also interfere with protein folding, break down bacterial cell walls, and stop enzyme activity. Because antibiotic-resistant bacteria have been growing steadily, antibiotics are gradually losing their effectiveness. Because of this, it is imperative to create novel therapeutic strategies to combat MDR bacteria; one such strategy is the use of AMP as an alternative to traditional antibiotics.[145] It has been demonstrated that antimicrobial peptides (AMPs) have strong antimicrobial activity against MRSA. Bacterial cell membranes with a negative charge attract catalytic peptides, or AMPs. They interfere with the bacterial cell's lipid bilayer, causing instability and disruption. The integrity of the bacterial cell membrane may be compromised by the insertion of AMPs due to pore formation or membrane thinning.[146] Once they are inserted into the bacterial cell membrane, AMPs can interfere with ion homeostasis. They have the ability to create pores or channels that let ions like calcium and potassium enter the bacterial cell. This imbalance in ions can cause cell death by interfering with essential cellular functions.[147] AMPs may increase the permeability of the bacterial cell membrane, allowing cell contents to leak out. This includes essential substances such as nucleotides, amino acids, and ATP (adenosine triphosphate). The absence of these necessary components further impairs the viability and function of bacterial cells.[148] Certain AMPs have the ability to target intracellular components by penetrating the bacterial cell membrane. Through their interactions with intracellular proteins, RNA, or DNA, they can impair bacterial growth and replication and interfere with vital cellular functions, for instance LL-37.[149] AMPs have the ability to directly combat

microbes while also influencing the immune system. They have the ability to trigger the release of immune mediators such as chemokines and cytokines, which in turn can enhance the recruitment of immune cells to the infection site and incite an inflammatory response. By doing so, the infection may be eradicated and the host's immune system may be strengthened to combat MRSA.[150]

Studies have shown that the bactericidal action of antimicrobial peptides is by increasing permeability of membrane, creation of asymmetry in membrane lipids, and causing the loss of vital metabolites and other components of the cell, all of which result in death. The peptide can also kill the bacteria by preventing the synthesis of proteins, nucleic acids, and other crucial proteins that have crucial role in the formation of cell wall.[151] Antimicrobial peptides have been utilized to treat wound MRSA infection (Table 2). AMPs can be applied topically to the site of the wound. They can be combined to create dressings, ointments, gels, or creams that are applied directly to the contaminated area. Through this targeted application, the AMPs can directly engage in antimicrobial activity and promote wound healing with the MRSA bacteria that are present in the wound.[152] Apart from their antimicrobial properties, AMPs have also been demonstrated to have immunomodulatory and wound-healing characteristics.[153] AMPs, when used in conjunction with standard antibiotics, can enhance the management of MRSA-infection. The synergistic effects of AMPs and antibiotics can help overcome antibiotic resistance and increase overall treatment efficacy. Combination therapy can eradicate MRSA bacteria, slow-down the spread of new infections, and quicken the healing process of wounds.[154] Researchers have also looked at creating bioengineered AMPs with enhanced stability and antimicrobial activity. These modified AMPs may be more effective against drug-resistant bacteria like MRSA. The characteristics of AMPs, such as their increased stability, toxicity reduction, and specific targeting to MRSA, can be enhanced by the application of bioengineering techniques.[155]

Live Bio-Therapeutics

Live bio-therapeutics is administration of beneficial, nonpathogenic bacteria to out compete pathogenic bacteria and aid in their clearance. Understanding and appreciating the value of human microflora has contributed to the rise in the use of probiotic supplements.[159] Probiotics are crucial bacteria having significant importance to the host, form a symbiotic relationship with the host and when properly ingested.[160] Enhanced epithelial barrier, enhanced intestinal mucosal adhesion, inhibition of microbial attachment and competition in the elimination of pathogenic microorganisms, the generation of antimicrobial agents, and modulation of the immune response are among the main mechanisms by which probiotics work. When the host receives antimicrobial therapy, the microflora gets disrupted, which favors selection of drug-resistant pathogenic bacterial strains like MRSA. In animal studies, probiotics have been shown to modify the gut microbiota, decrease the number of genes that lead to antibiotic resistance, and increase the efficacy of antibiotic treatment. Research has indicated that certain probiotic strains have the ability to inhibit the growth and adhesion of antibiotic-resistant pathogens, such as MRSA.[161] Suggesting probiotics may be useful in reducing the emergence of antibiotic resistance. Probiotics can help maintain a healthy microbial balance and minimize the need for antibiotics by using a variety of mechanisms, including immunomodulation, gut microbiota modulation, production of antimicrobial substances, and competitive exclusion.[162]

Table 2 Summary of Effective AMPS Against MRSA

AMPs	Origin	Amino Acid Sequence	Mechanism of Action on MRSA	Ref.
Cathelicidin LL-37	Human derived Cathelicidin AMPs	LLGDFFRKSKEK-IGKEFKRIVQRIK-DFLRNLVPRTES	Affect quorum detection and gene expression in biofilms to stop growth	[156]
Citropin1.1	*Litoria citropa isolate*	GLFDVIKKVASVIGGL-NH2	Efficient against MRSA. Found to have MIC of 16 g/mL against deep wound, cutaneous lesion MRSA isolate	[157]
Temporin A	*Rana temporaria* isolate (from skin secretion)	FLPLIGRVLSGIL-NH2	Significantly affected both MRSA and MSSA. Exhibit a MIC of 4 g/mL against MRSA of surgical wound isolate	[158]

The probiotics will aid in reestablishing the microflora that has been disturbed, thereby reducing the likelihood of the emergence of resistant variants. Probiotic organisms' have capacity to inhibit the binding of pathogens to host receptors, the production of antimicrobial substances, improve host immune surveillance, and trigger inflammatory responses.[163] *Lactobacillus species, Enterococcus species*, Bacillus species, Streptomyces species, *Saccharomyces cerevisiae, Corynebacterium accolens*, and *Lactococcus lactis* derived Nisin are among the substances used as probiotics.[164] Numerous studies have demonstrated a synergistic effect between probiotics and antimicrobial-based therapy in treating of bacterial and fungal infections.[164] *S. aureus*'s ability to form biofilms could result in a further issue with its phenotype of antibiotic resistance, which could lead to serious and persistent infections as of MRSA. To stop and damage pathogens that are associated with biofilms, efficient antibiofilm agents are needed. Probiotics found to be effective in preventing pathogen biofilm from forming as well as their colonization, and competing for nutrients, demonstrating great role in combating the infection.[8] Use of probiotics reduces AMR genes carried by hospital surface microbiota. A study revealed that the use of probiotic-based hospital sanitization reduce the frequency of AMR genes carried by hospital surface microbiota by up to 99%.[165]

Nanobiotics

Nanobiotics are nanomaterials that exhibit antibacterial activity or boost the effectiveness of existing antibiotics.[15] Nanobiotics have various applications like implantable medical device coatings. NPs are being utilized used as antibacterial agents.[166] Application of nanobiotics in fighting AMR pathogens like MRSA is the emerging paradigm that demonstrates the difficulties that human faced from infections caused by AMR bacteria. Nanobiotics can kill bacteria using a variety of mechanisms.[167] Nanobiotics are nanomaterials that exhibit antibacterial activity or boost the effectiveness of existing antibiotics. Since nanoparticles may specifically target a single bacterial cell, they can boost an antimicrobial agent's potency and prevent the emergence of resistance to it. Some nanoparticles act as antibiotics on their own. There are several nanoparticles that can be used to treat bacterial infection, Silver nanoparticles (Ag NPs) and zinc oxide nanoparticles (ZnO NPs), and gold nanoparticles (Au NPs). Silver nanoparticles (Ag NP) have the most effective antibacterial activity of all nanobiotics.[168,169]

Silver Nano Particles (AgNPs)

Silver nanoparticles are particles of silver produced by nanotechnology with a size between 1 and 100 nm. Since they are nanosized, they have far greater surface area to volume ratios, which considerably improves their broad-spectrum antibacterial activities.[170] AgNPs are used in many different areas because of their special magnetic, optical, electrical, and antibacterial qualities. Silver nanoparticles are becoming more and more popular as a result of their diverse modes of action on bacteria. Including direct AgNPs attachment to the cell wall and changing membrane's structural integrity. AgNPs then penetrate the bacterial cell and cause more damage until the bacterial cell is unable to carry out essential cellular functions (Table 3). The bacterium will be affected by oxidative attack caused by AgNPs' ability to generate Free radicals and reactive oxygen species. Another mechanism of action is through changing essential signaling transduction, required for bacterial replication.[171–173] AMPs and silver nanoparticles are becoming alternative treatments for MRSA infection. Both substances have wide-ranging characteristics that make them good candidates for combating MRSA.

Table 3 AgNPs' Antibacterial Action on MRSA

Properties of the Silver Nanoparticles'	Mechanism of Action	Ref.
Spherical AgNPs with size range of 4.5 to 26 nm	AgNPs displays a 1.2 mg/mL MIC. Reactive oxygen species accumulating disrupt the MRSA membrane and caused cell death.	[175]
Spherical AgNPs with size range of 16–18 nm	At a MIC of 8 g/mL, MRSA growth is inhibited, and AgNPs cause a buildup of reactive oxygen species that causes MRSA to suffer oxidative damage.	[176]
Spheric AgNPs (5–10 nm)	Inhibit MRSA growth at between 11.25 and 45 μg/mL MIC value, dislodge the biofilm formed by MRSA once observed under a scanning electron microscope.	[177]

Although each agent has the ability to have independent antimicrobial effects, combining them can have a higher antimicrobial effect due to their synergistic and complimentary effects.[174]

Opinion and Future Perspectives

The global challenges posed by antimicrobial resistance (AMR) are extensive and multifaceted. In order to successfully stop the spread of these infections, it becomes crucial to possess a thorough understanding of the underlying molecular mechanisms in the development of AMR. Without viable alternatives to existing antibiotics, we are facing a future where the consequences of AMR could be devastating.[22] We must actively seek out alternative treatments or be prepared to witness once curable illnesses leading to preventable fatalities. Excessive antimicrobial utilization in both medical and agricultural settings has contributed to the increasing levels of antibiotics in the environment, causing a range of consequences on microbial ecosystems. Consequently, antibiotic resistance is spreading rapidly worldwide, posing a significant threat to healthcare.

Embracing novel approaches like bacteriophages, probiotics, immunotherapy, nanobiotics, and AMPs, in combination with judicious use of antibiotics, holds promise in controlling antimicrobial resistant and securing a better future for global public health. Understanding the molecular mechanisms of AMR development, including the incorporation of transposable genetic elements and their contribution to the emergence of novel antibiotic-resistant genes, is crucial to comprehending the spread of AMR pathogens, including notorious bacteria like MRSA. Promising approaches, such as the use of bacteriophages and the inhibition of bacterial biofilms, have shown potential in combating MRSA. However, it is imperative to conduct further research to develop novel approach and gain increased knowledge of the molecular mechanisms that leads to AMR development to effectively control the spread of this dangerous pathogen.

Understanding the molecular mechanisms underlying AMR, implementing a One Health approach, and exploring novel therapeutic strategies are key to combatting this crisis. By investing in research, optimizing alternative treatments, and fostering interdisciplinary collaborations, we can pave the way for a future where AMR is effectively controlled, and global public health is safeguarded.

Conclusion

The challenges of antimicrobial resistance (AMR) are vast and complex. To combat the dissemination of these infections, knowing the molecular mechanisms driving AMR development is essential. Without viable alternatives to current antibiotics, estimates indicate that by 2050, AMR could lead to cost of hundred trillion USD globally and result 10 million annually deaths.[22] The message is clear: we must seek alternative treatments or face a future where once curable illnesses become preventable fatalities. The increasing levels of antibiotics in the environment, driven by medical and agricultural demand, have severe consequences on microbial ecosystems, rapidly spreading antibiotic resistance worldwide and posing a genuine threat to healthcare.

To mitigate the threats to health of people, animals, and the environment, a coordinated and interdisciplinary strategy like one health is judged to be mandatory.[178] Employing novel strategies like bacteriophages, probiotics, immunotherapy, nanobiotics, and antimicrobial peptides, alongside responsible antibiotic use, could effectively control the spread of AMR-causing bacteria and ensure a better future for global public health. Understanding the molecular mechanisms of AMR development is key in combating antimicrobial-resistant bacteria, including MRSA. Promising strategies, such as bacteriophages and biofilm inhibition, have shown potential against MRSA. However, further research is needed to develop more effective strategies and deepen our understanding of AMR's molecular mechanisms to control its dangerous spread.

While numerous novel therapeutic strategies have been described, only a few have progressed to advanced clinical trials. Addressing challenges like stability, extraction costs, and cytotoxicity is crucial before employing these alternative therapeutics in medical settings. Nevertheless, increased research efforts are expected to yield effective antibacterial alternatives capable of treating life-threatening infections. Overall, combating AMR requires understanding, interdisciplinary collaboration, and optimized strategies.

Abbreviations

AMR, Antimicrobial Resistance; MRSA, Methicillin-resistant *Staphylococcus aureus*; AMPs, Antimicrobial peptides; ARGs, antimicrobial resistant genes; CA, Community Associated; CDC, Centers for Disease Control and Prevention; EEA, European Economic Era; EU, European Union; HGT, Horizontal Gene Transfer; LPS, Lipopolysaccharide; MGE, Mobile Genetic Element; MIC, Minimum Inhibitory Concentration; MRSA, Methicillin-resistant *Staphylococcus aureus*; NPs, Nanoparticles; WHO, World Health Organization.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Algammal AM, Hetta HF, Elkelish A. Methicillin-Resistant *Staphylococcus aureus* (MRSA): one health perspective approach to the bacterium epidemiology, virulence factors, antibiotic-resistance, and zoonotic impact. *Infect Drug Resist*. 2020;13:3255–3265. doi:10.2147/IDR.S272733
2. Namvar AE, Bastarahang S, Abbasi N, et al. Clinical characteristics of Staphylococcus epidermidis: a systematic review. *GMS Hygiene and Infection Control*. 2014;9(3):Doc23. doi:10.3205/dgkh000243
3. Hindy JR, Quintero-Martinez JA, Lee AT, et al. Incidence trends and epidemiology of *Staphylococcus aureus* bacteremia: a systematic review of population-based studies. *Cureus*. 2022;14(5):e25460. doi:10.7759/cureus.25460.
4. O'Hara LM, Calfee DP, Miller LG, et al. Optimizing contact precautions to curb the spread of antibiotic-resistant bacteria in hospitals: a multicenter cohort study to identify patient characteristics and healthcare personnel interactions associated with transmission of methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis*. 2019;69(Supplement_3):S171–S177. doi:10.1093/cid/ciz621.
5. Weber DJ, Rutala WA. Understanding and preventing transmission of healthcare-associated pathogens due to the contaminated hospital environment. *Infect Control Hosp Epidemiol*. 2013;34(5):449–452. doi:10.1086/670223
6. Popovich KJ, Green SJ, Okamoto K, et al. MRSA transmission in intensive care units: genomic analysis of patients, their environments, and healthcare workers. *Clin Infect Dis*. 2021;72(11):1879–1887. doi:10.1093/cid/ciaa731
7. Al-Kharabsheh R, Ahmad M. Skin and mucous membranes colonisation with *Staphylococcus aureus* or MRSA as a risk factor for surgical site infections in elective Caesarean Section. *J Obstetrics Gynaecol*. 2022;42(5):888–893. doi:10.1080/01443615.2021.1954147
8. Nataraj BH, Mallappa RH. Antibiotic resistance crisis: an update on antagonistic interactions between probiotics and methicillin-resistant *Staphylococcus aureus* (MRSA). *Curr Microbiol*. 2021;78(6):2194–2211. doi:10.1007/s00284-021-02442-8
9. Nelson RE, Slayton RB, Stevens VW, et al. Attributable mortality of healthcare-associated infections due to multidrug-resistant gram-negative bacteria and methicillin-resistant *Staphylococcus aureus*. *Infect Control Hosp Epidemiol*. 2017;38(7):848–856. doi:10.1017/ice.2017.83
10. Lee AS, De Lencastre H, Garau J, et al. Methicillin-resistant *Staphylococcus aureus*. *Nat Rev Dis Primers*. 2018;4(1):1–23. doi:10.1038/s41572-018-0001-z
11. David MZ, Daum RS. Community-associated methicillin-resistant *Staphylococcus aureus*: epidemiology and clinical consequences of an emerging epidemic. *Clin Microbiol Rev*. 2010;23(3):616–687. doi:10.1128/CMR.00081-09
12. Soe PE, Han WW, Sagili KD, Satyanarayana S. High prevalence of methicillin-resistant *Staphylococcus aureus* among healthcare facilities and its related factors in Myanmar (2018–2019). *Trop Med Infect Dis*. 2021;6(2). doi:10.3390/tropicalmed6020070
13. Walsh L, Johnson CN, Hill C, Ross RP. Efficacy of phage- and bacteriocin-based therapies in combatting nosocomial MRSA infections. *Front Mol Biosci*. 2021;8:654038. doi:10.3389/fmolb.2021.654038
14. Chakraborty N, Jha D, Roy I, et al. Nanobiotics against antimicrobial resistance: harnessing the power of nanoscale materials and technologies. *J Nanobiotechnol*. 2022;20(1):375. doi:10.1186/s12951-022-01573-9
15. World Health Organization. Antimicrobial resistance; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance. Accessed December 4, 2023.
16. Matamoros-Recio A, Franco-Gonzalez JF, Forgione RE, Torres-Mozas A, Silipo A, Martín-Santamaría S. Understanding the antibacterial resistance: computational explorations in bacterial membranes. *ACS Omega*. 2021;6(9):6041–6054. doi:10.1021/acsomega.0c05590
17. Abushaheen MA, Alosaimi M, Fatani AJ, et al. Antimicrobial resistance, mechanisms and its clinical significance. *Disease-a-Month*. 2020;66(6):100971. doi:10.1016/j.disamonth.2020.100971
18. Saha M, Sarkar A. Review on multiple facets of drug resistance: a rising challenge in the 21st century. *J Xenobiot*. 2021;11(4):197–214 doi:10.3390/jox11040013.
19. Christaki E, Marcou M, Tofarides A. Antimicrobial resistance in bacteria: mechanisms, evolution, and persistence. *J Mol Evolut*. 2020;88(1):26–40. doi:10.1007/s00239-019-09914-3
20. Morrison L, Zembower TR. Antimicrobial resistance. *Gastrointest Endosc Clin N*. 2020;30(4):619–635. doi:10.1016/j.giec.2020.06.004
21. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations; 2016. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf. Accessed December 4, 2023.
22. Samir S, El-Far A, Okasha H, Mahdy R, Samir F, Nasr S. Isolation and characterization of lytic bacteriophages from sewage at an Egyptian tertiary care hospital against methicillin-resistant *Staphylococcus aureus* clinical isolates. *Saudi J Biol Sci*. 2022;29(5):3097–3106. doi:10.1016/j.sjbs.2022.03.019
23. Murray CJL, Ikuta KS, Sharara F. 2022 Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629–655. doi:10.1016/S0140-6736(21)02724-0
24. Gurung RR, Maharjan P, Chhetri GG. Antibiotic resistance pattern of *Staphylococcus aureus* with reference to MRSA isolates from pediatric patients. *Future Sci OA*. 2020;6(4):Fso464. doi:10.2144/fsoa-2019-0122

25. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS Microbiol*. 2018;4(3):482–501. doi:10.3934/microbiol.2018.3.482
26. Chambers HF, Deleo FR. Waves of resistance: *Staphylococcus aureus* in the antibiotic era. *Nat Rev Microbiol*. 2009;7(9):629–641. doi:10.1038/nrmicro2200
27. Lee AS, de Lencastre H, Garau J, et al. Methicillin-resistant *Staphylococcus aureus*. *Nat Rev Dis Primers*. 2018;4(1):18033. doi:10.1038/nrdp.2018.33
28. Bush K, Bradford PA. Epidemiology of β-lactamase-producing pathogens. *Clin Microbiol Rev*. 2020;33(2):10–128. doi:10.1128/CMR.00047-19
29. Fishovitz J, Hermoso JA, Chang M, Mobashery S. Penicillin-binding protein 2a of methicillin-resistant *Staphylococcus aureus*. *IUBMB Life*. 2014;66(8):572–577. doi:10.1002/iub.1289
30. Harkins CP, Pichon B, Doumith M, et al. Methicillin-resistant *Staphylococcus aureus* emerged long before the introduction of methicillin into clinical practice. *Genome Biol*. 2017;18(1):130. doi:10.1186/s13059-017-1252-9
31. Kuroda M, Ohta T, Uchiyama I, et al. Whole genome sequencing of meticillin-resistant *Staphylococcus aureus*. *Lancet*. 2001;357(9264):1225–1240. doi:10.1016/S0140-6736(00)04403-2
32. Stapleton PD, Taylor PW. Methicillin resistance in *Staphylococcus aureus*: mechanisms and modulation. *Sci Prog*. 2002;85(Pt 1):57–72. doi:10.3184/003685002783238870
33. Wu SW, de Lencastre H, Tomasz A. Recruitment of the *mecA* gene homologue of *Staphylococcus sciuri* into a resistance determinant and expression of the resistant phenotype in Staphylococcus aureus. *J Bacteriol*. 2001;183(8):2417–2424. doi:10.1128/JB.183.8.2417-2424.2001
34. Zeman M, Mašlaňová I, Indráková A, et al. *Staphylococcus sciuri* bacteriophages double-convert for staphylokinase and phospholipase, mediate interspecies plasmid transduction, and package *mecA* gene. *Sci Rep*. 2017;7(1):46319. doi:10.1038/srep46319
35. Larsen J, Raisen CL, Ba X, et al. Emergence of methicillin resistance predates the clinical use of antibiotics. *Nature*. 2022;602(7895):135–141. doi:10.1038/s41586-021-04265-w
36. Raygada JL, Levine DP. Methicillin-resistant *Staphylococcus aureus*: a growing risk in the hospital and in the community. *Am Health Drug Benefits*. 2009;2(2):86–95.
37. Zhu F, Zhuang H, Ji S, et al. Household transmission of community-associated methicillin-resistant *Staphylococcus aureus*. *Front Public Health*. 2021;9:658638. doi:10.3389/fpubh.2021.658638
38. Anjum MF, Marco-Jimenez F, Duncan D, Marín C, Smith RP, Evans SJ. Livestock-associated methicillin-resistant *Staphylococcus aureus* from animals and animal products in the UK. *Front Microbiol*. 2019;10:2136. doi:10.3389/fmicb.2019.02136
39. Parvez MAK, Ferdous RN, Rahman MS, Islam S. Healthcare-associated (HA) and community-associated (CA) methicillin resistant *Staphylococcus aureus* (MRSA) in Bangladesh - Source, diagnosis and treatment. *J Genet Eng Biotechnol*. 2018;16(2):473–478. doi:10.1016/j.jgeb.2018.05.004
40. Uehara Y, Sasaki T, Baba T, et al. Regional outbreak of community-associated methicillin-resistant *Staphylococcus aureus* ST834 in Japanese children. *BMC Infect Dis*. 2019;19(1):35. doi:10.1186/s12879-018-3646-z
41. Kateete D, Bwanga F, Seni J, et al. CA-MRSA and HA-MRSA coexist in community and hospital settings in Uganda. *Antimicrob Resist Infect Contr*. 2019;8(1). doi:10.1186/s13756-019-0551-1
42. Cuny C, Köck R, Witte W. Livestock associated MRSA (LA-MRSA) and its relevance for humans in Germany. *Int J Med Microbiol*. 2013;303(6–7):331–337. doi:10.1016/j.ijmm.2013.02.010
43. Chroboczek T, Boisset S, Rasigade JP, et al. Clonal complex 398 methicillin susceptible *Staphylococcus aureus*: a frequent unspecialized human pathogen with specific phenotypic and genotypic characteristics. *PLoS One*. 2013;8(11):e68462. doi:10.1371/journal.pone.0068462
44. Hasanpour AH, Sepidarkish M, Mollalo A, et al. The global prevalence of methicillin-resistant *Staphylococcus aureus* colonization in residents of elderly care centers: a systematic review and meta-analysis. *Antimicrob Resist Infect Control*. 2023;12(1):4. doi:10.1186/s13756-023-01210-6
45. Ali Alghamdi B, Al-Johani I, Al-Shamrani JM, et al. Antimicrobial resistance in methicillin-resistant *Staphylococcus aureus*. *Saudi J Biol Sci*. 2023;30(4):103604. doi:10.1016/j.sjbs.2023.103604
46. Turner NA, Sharma-Kuinkel BK, Maskarinec SA, et al. Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research. *Nat Rev Microbiol*. 2019;17(4):203–218. doi:10.1038/s41579-018-0147-4
47. Lewis K. Persister cells. *Ann Rev Microbiol*. 2010;64(1):357–372. doi:10.1146/annurev.micro.112408.134306
48. Loss G, Simões PM, Valour F, et al. *Staphylococcus aureus* Small Colony Variants (SCVs): news from a chronic prosthetic joint infection. *Front Cell Infect Microbiol*. 2019;9:363. doi:10.3389/fcimb.2019.00363
49. Bowler P, Murphy C, Wolcott R. Biofilm exacerbates antibiotic resistance: is this a current oversight in antimicrobial stewardship? *Antimicrob Resist Infect Control*. 2020;9(1):162. doi:10.1186/s13756-020-00830-6
50. Hernando-Amado S, Coque TM, Baquero F, Martínez JL. Defining and combating antibiotic resistance from One Health and Global Health perspectives. *Nat Microbiol*. 2019;4(9):1432–1442. doi:10.1038/s41564-019-0503-9
51. Dashtbani-Roozbehani A, Brown MH. Efflux pump mediated antimicrobial resistance by staphylococci in health-related environments: challenges and the quest for inhibition. *Antibiotics*. 2021;10(12). doi:10.3390/antibiotics10121502
52. Machowska A, Stålsby Lundborg C. Drivers of irrational use of antibiotics in Europe. *Int J Environ Res Public Health*. 2019;16(1):27. doi:10.3390/ijerph16010027
53. Hashem RA, Yassin AS, Zedan HH, Amin MA. Fluoroquinolone resistant mechanisms in methicillin-resistant S*taphylococcus aureus* clinical isolates in Cairo, Egypt. *J Infect Dev Ctries*. 2013;7(11):796–803. doi:10.3855/jidc.3105
54. Kaatz GW, Seo SM. Mechanisms of fluoroquinolone resistance in genetically related strains of *Staphylococcus aureus*. *Antimicrob Agents Chemother*. 1997;41(12):2733–2737. doi:10.1128/AAC.41.12.2733
55. Staats G, Mc Carlie S, Van der Walt B, Bragg R. The linkage between antibiotic and disinfectant resistance. In: *Antimicrobial Research and One Health in Africa*. Springer; 2023:241–274.
56. Johansson MHK, Bortolaia V, Tansirichaiya S, Aarestrup FM, Roberts AP, Petersen TN. Detection of mobile genetic elements associated with antibiotic resistance in *Salmonella enterica* using a newly developed web tool: mobileElementFinder. *J Antimicrob Chemother*. 2020;76(1):101–109. doi:10.1093/jac/dkaa390
57. Partridge SR, Kwong SM, Firth N, Jensen SO. Mobile genetic elements associated with antimicrobial resistance. *Clin Microbiol Rev*. 2018;31(4). doi:10.1128/CMR.00088-17

58. Khedkar S, Smyshlyaev G, Letunic I, et al. Landscape of mobile genetic elements and their antibiotic resistance cargo in prokaryotic genomes. *Nucleic Acids Res*. 2022;50(6):3155–3168. doi:10.1093/nar/gkac163
59. Malachowa N, DeLeo FR. Mobile genetic elements of *Staphylococcus aureus*. *Cell Mol Life Sci*. 2010;67(18):3057–3071. doi:10.1007/s00018-010-0389-4
60. Martinez JL. General principles of antibiotic resistance in bacteria. *Drug Discov Today Technol*. 2014;11:33–39. doi:10.1016/j.ddtec.2014.02.001
61. Davidovich NV, Kukalevskaya NN, Bashilova EN, Bazhukova TA. [General principles of antibiotic resistance evolution in bacteria (review of literature)]. лсновные принципы антибиот эволюцииикорезистентност у бактерий (обзор литературы). Клиническая лабораторная диагностика. *Klinicheskaia laboratornaia diagnostika*. 2020;65(6):387–393. Russian. doi:10.18821/0869-2084-2020-65-6-387-393
62. Martínez JL, Baquero F, Bouza E, Gutiérrez-Fuentes JA, Coque TM. Ecology and evolution of chromosomal gene transfer between environmental microorganisms and pathogens. *Microbiol Spectr*. 2018;6(1). doi:10.1128/microbiolspec.MTBP-0006-2016
63. Sun D, Jeannot K, Xiao Y, Knapp CW. Editorial: horizontal gene transfer mediated bacterial antibiotic resistance. *Front Microbiol*. 2019;10:1933. doi:10.3389/fmicb.2019.01933
64. Vinayamohan PG, Pellissery AJ, Venkitanarayanan K. Role of horizontal gene transfer in the dissemination of antimicrobial resistance in food animal production. *Curr Opin Food Sci*. 2022;47:100882. doi:10.1016/j.cofs.2022.100882
65. von Wintersdorff CJ, Penders J, van Niekerk JM, et al. Dissemination of antimicrobial resistance in microbial ecosystems through horizontal gene transfer. *Front Microbiol*. 2016;7:173. doi:10.3389/fmicb.2016.00173
66. Norman A, Hansen LH, Sørensen SJ. Conjugative plasmids: vessels of the communal gene pool. *Philos Trans R Soc London Ser B*. 2019;364(1527):2275–2289. doi:10.1098/rstb.2009.0037
67. Eyler RF, Shvets K. Clinical pharmacology of antibiotics. *Clin J Am Soc Nephrol*. 2019;14(7):1080–1090. doi:10.2215/CJN.08140718
68. Zhu Y, Huang WE, Yang Q. Clinical perspective of antimicrobial resistance in bacteria. *Infect Drug Resist*. 2022;15:735–746. doi:10.2147/IDR.S345574
69. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Global Health*. 2015;109(7):309–318. doi:10.1179/2047773215Y.0000000030
70. Sweileh WM. Global research publications on irrational use of antimicrobials: call for more research to contain antimicrobial resistance. *Globalizat Health*. 2021;17(1):94. doi:10.1186/s12992-021-00754-9
71. Xavier SP, Victor A, Cumaquela G, Vasco MD, Rodrigues OAS. Inappropriate use of antibiotics and its predictors in pediatric patients admitted at the Central Hospital of Nampula, Mozambique. *Antimicrob Resist Infect Contr*. 2022;11(1):79. doi:10.1186/s13756-022-01115-w
72. Burnham C-AD, Leeds J, Nordmann P, O'Grady J, Patel J. Diagnosing antimicrobial resistance. *Nat Rev Microbiol*. 2017;15(11):697–703. doi:10.1038/nrmicro.2017.103
73. Andreatos N, Shehadeh F, Pliakos EE, Mylonakis E. The impact of antibiotic prescription rates on the incidence of MRSA bloodstream infections: a county-level, US-wide analysis. *Int J Antimicrob Agents*. 2018;52(2):195–200. doi:10.1016/j.ijantimicag.2018.04.003
74. Jernigan JA, Hatfield KM, Wolford H, et al. Multidrug-resistant bacterial infections in US hospitalized patients, 2012–2017. *N Engl J Med*. 2020;382(14):1309–1319. doi:10.1056/NEJMoa1914433
75. Ghana M. Policy on antimicrobial use and resistance; 2017. Available from: https://www.moh.gov.gh/wp-content/uploads/2018/04/AMR-POLICY-A5_09.03.2018-Signed.pdf. Accessed December 4, 2023.
76. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic use in agriculture and its consequential resistance in environmental sources. *Potential Public Health Implic*. 2018;23(4):795. doi:10.3390/molecules23040795.
77. World Health Organization. World Health Organization (WHO): substandard and falsified medical products; 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products. Accessed December 4, 2023.
78. Zabala GA, Bellingham K, Vidhamaly V, et al. Substandard and falsified antibiotics: neglected drivers of antimicrobial resistance? *BMJ Global Health*. 2022;7(8):e008587. doi:10.1136/bmjgh-2022-008587
79. McManus D, Naughton BD. A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: a focus on context, prevalence, and quality. *BMJ Global Health*. 2020;5(8). doi:10.1136/bmjgh-2020-002393
80. Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. *Antimicrob Resist Infect Control*. 2017;6(1):47. doi:10.1186/s13756-017-0208-x
81. Ferry T, Leboucher G, Fevre C, et al. Salvage debridement, antibiotics and implant retention ("DAIR") with local injection of a selected cocktail of bacteriophages: is it an option for an elderly patient with relapsing Staphylococcus aureus prosthetic-joint infection? *Open Forum Infect Dis*. 2018;5(11). doi:10.1093/ofid/ofy269
82. Gullberg E, Cao S, Berg OG, et al. Selection of resistant bacteria at very low antibiotic concentrations. *PLoS Pathog*. 2011;7(7):e1002158. doi:10.1371/journal.ppat.1002158
83. Shanmugakani RK, Srinivasan B, Glesby MJ, et al. Current state of the art in rapid diagnostics for antimicrobial resistance. *Lab Chip*. 2020;20(15):2607–2625. doi:10.1039/D0LC00034E
84. Trevas D, Caliendo AM, Hanson K, Levy J, Ginocchio CC; America ftIDSo. Diagnostic tests can stem the threat of antimicrobial resistance: infectious disease professionals can help. *Clin Infect Dis*. 2020;72(11):e893–e900. doi:10.1093/cid/ciaa1527
85. Pokharel S, Raut S, Adhikari B. Tackling antimicrobial resistance in low-income and middle-income countries. *BMJ Global Health*. 2019;4(6):e002104. doi:10.1136/bmjgh-2019-002104
86. Sartelli M, C. Hardcastle T. Antibiotic use in low and middle-income countries and the challenges of antimicrobial resistance in surgery. *Antibiotics*. 2020;9(8):497. doi:10.3390/antibiotics9080497
87. McAdams D, Wollein Waldetoft K, Tedijanto C, Lipsitch M, Brown SP. Resistance diagnostics as a public health tool to combat antibiotic resistance: a model-based evaluation. *PLoS Biol*. 2019;17(5):e3000250. doi:10.1371/journal.pbio.3000250
88. Cohen A, Bont L, Engelhard D, et al. A multifaceted 'omics' approach for addressing the challenge of antimicrobial resistance. *Future Microbiol*. 2015;10(3):365–376. doi:10.2217/fmb.14.127
89. Anjum MF, Zankari E, Hasman H. Molecular methods for detection of antimicrobial resistance. *Microbiol Spectr*. 2017;5(6). doi:10.1128/microbiolspec.ARBA-0011-2017

90. Vasala A, Hytönen VP, Laitinen OH. Modern tools for rapid diagnostics of antimicrobial resistance. *Front Cell Infect Microbiol*. 2020;10:308. doi:10.3389/fcimb.2020.00308
91. Islam KS, Shiraj-Um-Mahmuda S, Hazzaz-Bin-Kabir M. Antibiotic usage patterns in selected broiler farms of Bangladesh and their public health implications. *J Public Health Dev Ctries*. 2016;2(3):276–284.
92. Economou V, Gousia P. Agriculture and food animals as a source of antimicrobial-resistant bacteria. *Infect Drug Resist*. 2015;8:49–61. doi:10.2147/IDR.S55778
93. Levy SB. Antibiotic resistance: an ecological imbalance. Paper presented at: Ciba Foundation Symposium 207-Antibiotic Resistance: Origins, Evolution, Selection and Spread: Antibiotic Resistance: Origins, Evolution, Selection and Spread: Ciba Foundation Symposium; 2007.
94. Ben Y, Fu C, Hu M, Liu L, Wong MH, Zheng C. Human health risk assessment of antibiotic resistance associated with antibiotic residues in the environment: a review. *Environ Res*. 2019;169:483–493. doi:10.1016/j.envres.2018.11.040
95. Manyi-Loh C, Mamphweli S, Meyer E, Okoh A. Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications. *Molecules*. 2018;23(4):795. doi:10.3390/molecules23040795
96. Gharaibeh MH, Shatnawi SQ. An overview of colistin resistance, mobilized colistin resistance genes dissemination, global responses, and the alternatives to colistin: a review. *Vet World*. 2019;12(11):1735–1746. doi:10.14202/vetworld.2019.1735-1746
97. Kyprianou M. Ban on antibiotics as growth promoters in animal feed enters into effect; 2005. Available from: https://ec.europa.eu/commission/presscorner/detail/en/IP_05_1687. Accessed December 4, 2023.
98. Cox JA, Vlieghe E, Mendelson M, et al. Antibiotic stewardship in low-and middle-income countries: the same but different? *Clin Microbiol Infect*. 2017;23(11):812–818. doi:10.1016/j.cmi.2017.07.010
99. Kavanagh KT, Abusalem S, Calderon LE. View point: gaps in the current guidelines for the prevention of Methicillin-resistant *Staphylococcus aureus* surgical site infections. *Antimicrob Resist Infect Control*. 2018;7(1):112. doi:10.1186/s13756-018-0407-0
100. Huang DB, Magnet S, De Angelis S, et al. Surveillance of iclaprim activity: in vitro susceptibility of Gram-positive skin infection pathogens collected from 2015 to 2016 from North America and Europe. *Diagnostic microbiology and infectious disease*. *Diagn Microbiol Infect Dis*. 2019;93(2):154–158. doi:10.1016/j.diagmicrobio.2018.09.002
101. Grillo S, Puig-Asensio M. The effectiveness of combination therapy for treating methicillin-susceptible *Staphylococcus aureus* bacteremia: a systematic literature review and a meta-analysis. *Microorganisms*. 2022;10(5):848. doi:10.3390/microorganisms10050848
102. Heger ML, Al-Sayyad B. Ceftaroline and daptomycin combination antibiotic therapy for a methicillin-resistant S*taphylococcus aureus* liver abscess in a premature infant. *J Pediatr Pharmacol Ther*. 2022;27(8):754–759. doi:10.5863/1551-6776-27.8.754
103. Blaskovich MA, Hansford KA, Butler MS, Jia Z, Mark AE, Cooper MA. Developments in glycopeptide antibiotics. *ACS Infect Dis*. 2018;4(5):715–735. doi:10.1021/acsinfecdis.7b00258
104. Zhao S, Ren S, Jiang T, et al. Low-dose apatinib optimizes tumor microenvironment and potentiates antitumor effect of PD-1/PD-L1 blockade in lung cancer. *Cancer Immunol Res*. 2019;7(4):630–643. doi:10.1158/2326-6066.CIR-17-0640
105. Davis JS, van Hal S, Tong S. Combination antibiotic treatment of serious methicillin-resistant *Staphylococcus aureus* infections. Paper presented at: Seminars in respiratory and critical care medicine; 2015.
106. Valderrama M-J, Alfaro M, Rodríguez-Avial I, Baos E, Rodríguez-Avial C, Culebras E. Synergy of linezolid with several antimicrobial agents against linezolid-methicillin-resistant Staphylococcal strains. *Antibiotics*. 2020;9(8):496. doi:10.3390/antibiotics9080496
107. Ma H, Cheng J, Peng L, Gao Y, Zhang G, Luo Z. Adjunctive rifampin for the treatment of *Staphylococcus aureus* bacteremia with deep infections: a meta-analysis. *PLoS One*. 2020;15(3):e0230383. doi:10.1371/journal.pone.0230383
108. Bartash R, Nori P. Beta-lactam combination therapy for the treatment of *Staphylococcus aureus* and Enterococcus species bacteremia: a summary and appraisal of the evidence. *Int J Infect Dis*. 2017;63:7–12. doi:10.1016/j.ijid.2017.07.019
109. Creech CB, Al-Zubeidi DN, Fritz SA. Prevention of recurrent staphylococcal skin infections. *Infect Dis Clin North Am*. 2015;29(3):429–464. doi:10.1016/j.idc.2015.05.007
110. Cardona AF, Wilson SE. Skin and soft-tissue infections: a critical review and the role of telavancin in their treatment. *Clin Infect Dis*. 2015;61(suppl_2):S69–S78. doi:doi:10.1093/cid/civ528
111. Bloom G, Merrett GB, Wilkinson A, Lin V, Paulin S. Antimicrobial resistance and universal health coverage. *BMJ Global Health*. 2017;2(4):e000518. doi:10.1136/bmjgh-2017-000518
112. Garcia-Graells C, Antoine J, Larsen J, Catry B, Skov R, Denis O. Livestock veterinarians at high risk of acquiring methicillin-resistant *Staphylococcus aureus* ST398. *Epidemiol Infect*. 2012;140(3):383–389. doi:10.1017/S0950268811002263
113. Köck R, Loth B, Köksal M, Schulte-Wülwer J, Harlizius J, Friedrich AW. Persistence of nasal colonization with livestock-associated methicillin-resistant *Staphylococcus aureus* in pig farmers after holidays from pig exposure. *Appl Environ Microbiol*. 2012;78(11):4046–4047. doi:10.1128/AEM.00212-12
114. Graham DW, Collignon P, Davies J, Larsson DG, Snape J. Underappreciated role of regionally poor water quality on globally increasing antibiotic resistance. *Environ Sci Technol*. 2014;48(20):11746–11747. doi:10.1021/es504206x
115. Ikhimiukor OO, Odih EE, Donado-Godoy P, Okeke IN. A bottom-up view of antimicrobial resistance transmission in developing countries. *Nat Microbiol*. 2022;7(6):757–765. doi:10.1038/s41564-022-01124-w
116. Majumder MAA, Rahman S, Cohall D, et al. Antimicrobial stewardship: fighting antimicrobial resistance and protecting global public health. *Infect Drug Resist*. 2020;Volume 13:4713–4738. doi:10.2147/IDR.S290835
117. Velazquez-Meza ME, Galarde-López M, Carrillo-Quiróz B, Alpuche-Aranda CM. Antimicrobial resistance: one health approach. *Vet World*. 2022;15(3):743–749. doi:10.14202/vetworld.2022.743-749
118. Hutchings MI, Truman AW, Wilkinson B. Antibiotics: past, present and future. *Curr Opin Microbiol*. 2019;51:72–80. doi:10.1016/j.mib.2019.10.008
119. Lin DM, Koskella B, Lin HC. Phage therapy: an alternative to antibiotics in the age of multi-drug resistance. *World J Gastrointest Pharmacol Ther*. 2017;8(3):162. doi:10.4292/wjgpt.v8.i3.162
120. Topka-Bielecka G, Dydecka A, Necel A, et al. Bacteriophage-derived depolymerases against bacterial biofilm. *Antibiotics*. 2021;10(2):175. doi:10.3390/antibiotics10020175
121. Di Martino P. Extracellular polymeric substances, a key element in understanding biofilm phenotype. *AIMS Microbiol*. 2018;4(2):274. doi:10.3934/microbiol.2018.2.274

122. Ajuebor J, Buttimer C, Arroyo-Moreno S, et al. Comparison of Staphylococcus phage K with close phage relatives commonly employed in phage therapeutics. *Antibiotics*. 2018;7(2):37. doi:10.3390/antibiotics7020037
123. Rahimzadeh G, Gill P, Rezai MS. Characterization of methicillin-resistant *Staphylococcus aureus* (MRSA) phages from sewage at a tertiary pediatric hospital. *Arch Pediatr Infect Dis*. 2017;5(1):e39615. doi:10.5812/pedinfect.39615
124. Mohammed-Ali MN, Jamalludeen NM. Isolation and characterization of bacteriophage against methicillin resistant Staphylococcus aureus. *J Med Microb Diagn*. 2015;5(213):2161. doi:10.4172/2161-0703.1000213
125. Kebriaei R, Lev KL, Stamper KC, Lehman SM, Morales S, Rybak MJ. Bacteriophage AB-SA01 cocktail in combination with antibiotics against MRSA-VISA strain in an in vitro pharmacokinetic/pharmacodynamic model. *Antimicrob Agents Chemother*. 2020;65(1). doi:10.1128/AAC.01863-20
126. Hatfull GF, Dedrick RM, Schooley RT. Phage therapy for antibiotic-resistant bacterial infections. *Ann Rev Med*. 2022;73(1):197–211. doi:10.1146/annurev-med-080219-122208
127. Wu Y, Wang R, Xu M, et al. A novel polysaccharide depolymerase encoded by the phage SH-KP152226 confers specific activity against multidrug-resistant *Klebsiella pneumoniae* via biofilm degradation. *Front Microbiol*. 2019;10:2768. doi:10.3389/fmicb.2019.02768
128. Doub JB, Ng VY, Johnson AJ. Salvage bacteriophage therapy for a chronic MRSA prosthetic joint infection. *Antibiotics*. 2020;9(5):241. doi:10.3390/antibiotics9050241
129. Suda T, Hanawa T, Tanaka M, et al. Modification of the immune response by bacteriophages alters methicillin-resistant *Staphylococcus aureus* infection. *Sci Rep*. 2022;12(1):15656. doi:10.1038/s41598-022-19922-x
130. Mendes JJ, Leandro C, Corte-Real S, et al. Wound healing potential of topical bacteriophage therapy on diabetic cutaneous wounds. *Wound Repair Regen*. 2013;21(4):595–603. doi:10.1111/wrr.12056
131. Rodriguez JM, Woodworth BA, Horne BA, Fackler J, Brownstein MJ. Case report: successful use of phage therapy in refractory MRSA chronic rhinosinusitis. *Int J Infect Dis*. 2022;121:14–16. doi:10.1016/j.ijid.2022.04.049
132. Ferry T, Batailler C, Petitjean C, et al. The potential innovative use of bacteriophages within the DAC(®) hydrogel to treat patients with knee megaprosthesis infection requiring "Debridement Antibiotics and Implant Retention" and soft tissue coverage as salvage therapy. *Front Med*. 2020;7:342. doi:10.3389/fmed.2020.00342
133. Leszczyński P, Weber-Dabrowska B, Kohutnicka M, Luczak M, Górecki A, Górski A. Successful eradication of methicillin-resistant *Staphylococcus aureus* (MRSA) intestinal carrier status in a healthcare worker--case report. *Folia microbiologica*. 2006;51(3):236–238. doi:10.1007/BF02932128
134. Seed KD, Miller VL. Battling phages: how bacteria defend against viral attack. *PLoS Pathog*. 2015;11(6):e1004847. doi:10.1371/journal.ppat.1004847
135. Rath D, Amlinger L, Rath A, Lundgren M. The CRISPR-Cas immune system: biology, mechanisms and applications. *Biochimie*. 2015;117:119–128. doi:10.1016/j.biochi.2015.03.025
136. Jurado A, Fernández L, Rodríguez A, García P. Understanding the mechanisms that drive phage resistance in Staphylococci to prevent phage therapy failure. *Viruses*. 2022;14(5):1061.
137. Lu Y, Lu Y, Li B, et al. StAP1 phage: an effective tool for treating methicillin-resistant *Staphylococcus aureus* infections. *Front Microbiol*. 2023;14:1267786.
138. Zhvania P, Hoyle NS, Nadareishvili L, Nizharadze D, Kutateladze M. Phage therapy in a 16-year-old boy with Netherton syndrome. *Front Med*. 2017;4:94. doi:10.3389/fmed.2017.00094
139. Diallo K, Dublanchet A. Benefits of combined phage-antibiotic therapy for the control of antibiotic-resistant bacteria: a literature review. *Antibiotics*. 2022;11(7):839. doi:10.3390/antibiotics11070839
140. Oechslin F. Resistance development to bacteriophages occurring during bacteriophage therapy. *Viruses*. 2018;10(7):351. doi:10.3390/v10070351
141. McGee LW, Barhoush Y, Shima R, Hennessy M. Phage-resistant mutations impact bacteria susceptibility to future phage infections and antibiotic response. *Ecol Evol*. 2023;13(1):e9712. doi:10.1002/ece3.9712
142. León M, Bastías R. Virulence reduction in bacteriophage resistant bacteria. *Front Microbiol*. 2015;6:343. doi:10.3389/fmicb.2015.00343
143. Samir S, Samir S, Omar H, Hassan EA, Abdelazeem E. Basic guidelines for bacteriophages isolation and characterization. *Recent Patents Biotechnol*. 2022;16(3):266–280. doi:10.2174/1872208316666220412105822
144. Lin B, Hung A, Li R, et al. Systematic comparison of activity and mechanism of antimicrobial peptides against nosocomial pathogens. *Eur J Med Chem*. 2022;231:114135. doi:10.1016/j.ejmech.2022.114135
145. Datta M, Rajeev A, Chattopadhyay I. Application of antimicrobial peptides as next-generation therapeutics in the biomedical world. *Biotechnol Genet Eng Rev*. 2023;1–39. doi:10.1080/02648725.2023.2199572
146. Lei J, Sun L, Huang S, et al. The antimicrobial peptides and their potential clinical applications. *Am J Transl Res*. 2019;11(7):3919–3931.
147. Benfield AH, Henriques ST. Mode-of-action of antimicrobial peptides: membrane disruption vs. intracellular mechanisms. *Front Med Technol*. 2020;2:610997. doi:10.3389/fmedt.2020.610997
148. Zhang QY, Yan ZB, Meng YM, et al. Antimicrobial peptides: mechanism of action, activity and clinical potential. *Mil Med Res*. 2021;8(1):48. doi:10.1186/s40779-021-00343-2
149. Moravej H, Moravej Z, Yazdanparast M, et al. Antimicrobial peptides: features, action, and their resistance mechanisms in bacteria. *Microb Drug Resist*. 2018;24(6):747–767. doi:10.1089/mdr.2017.0392
150. Pahar B, Madonna S, Das A, Albanesi C, Girolomoni G. Immunomodulatory role of the antimicrobial LL-37 peptide in autoimmune diseases and viral infections. *Vaccines*. 2020;8(3). doi:10.3390/vaccines8030517
151. Saeed SI, Mergani A, Aklilu E, Kamaruzzman NF. Antimicrobial peptides: bringing solution to the rising threats of antimicrobial resistance in livestock. *Front Vet Sci*. 2022;9:851052. doi:10.3389/fvets.2022.851052
152. Thapa RK, Diep DB, Tønnesen HH. Topical antimicrobial peptide formulations for wound healing: current developments and future prospects. *Acta Biomater*. 2020;103:52–67. doi:10.1016/j.actbio.2019.12.025
153. Patrulea V, Borchard G, Jordan O. An Update on Antimicrobial Peptides (AMPs) and their delivery strategies for wound infections. *Pharmaceutics*. 2020;12(9). doi:10.3390/pharmaceutics12090840

154. Rizzetto G, Gambini D, Maurizi A, et al. Our experience over 20 years: antimicrobial peptides against gram positives, gram negatives, and fungi. *Pharmaceutics*. 2022;15(1):40. doi:10.3390/pharmaceutics15010040
155. Kang SJ, Nam SH. Engineering approaches for the development of antimicrobial peptide-based antibiotics. *Antibiotics*. 2022;11(10):1338. doi:10.3390/antibiotics11101338
156. Demirci M, Yigin A, Demir C. Efficacy of antimicrobial peptide LL-37 against biofilm forming *Staphylococcus aureus* strains obtained from chronic wound infections. *Microb Pathog*. 2022;162:105368. doi:10.1016/j.micpath.2021.105368
157. Garbacz K, Kamysz W, Piechowicz L. Activity of antimicrobial peptides, alone or combined with conventional antibiotics, against *Staphylococcus aureus* isolated from the airways of cystic fibrosis patients. *Virulence*. 2017;8(1):94–100. doi:10.1080/21505594.2016.1213475
158. Ciandrini E, Morroni G, Arzeni D, et al. Antimicrobial Activity of Different Antimicrobial Peptides (AMPs) against clinical Methicillin-resistant *Staphylococcus aureus* (MRSA). *Curr Top Med Chem*. 2018;18(24):2116–2126. doi:10.2174/1568026618666181022140348
159. Linares DM, Ross P, Stanton C. Beneficial Microbes: the pharmacy in the gut. *Bioengineered*. 2016;7(1):11–20. doi:10.1080/21655979.2015.1126015
160. Rueda-Robles A, Rodríguez-Lara A, Meyers MS. Effect of probiotics on host-microbiota in bacterial infections. *Pathogens*. 2022;11(9):986. doi:10.3390/pathogens11090986
161. Ouwehand AC, Forssten S, Hibberd AA, Lyra A, Stahl B. Probiotic approach to prevent antibiotic resistance. *Ann Med*. 2016;48(4):246–255. doi:10.3109/07853890.2016.1161232
162. Tegegne BA, Kebede B. Probiotics, their prophylactic and therapeutic applications in human health development: a review of the literature. *Heliyon*. 2022;8(6):e09725. doi:10.1016/j.heliyon.2022.e09725
163. Raheem A, Liang L, Zhang G, Cui S. Modulatory effects of probiotics during pathogenic infections with emphasis on immune regulation. *Front Immunol*. 2021;12:616713. doi:10.3389/fimmu.2021.616713
164. Silva DR, Sardi J, Pitangui N, Roque SM, Silva A, Rosalen PL. Probiotics as an alternative antimicrobial therapy: current reality and future directions. *J Funct Foods*. 2020;73:104080. doi:10.1016/j.jff.2020.104080
165. Caselli E, Arnoldo L, Rognoni C, et al. Impact of a probiotic-based hospital sanitation on antimicrobial resistance and HAI-associated antimicrobial consumption and costs: a multicenter study. *Infect Drug Resist*. 2019;Volume 12:501–510. doi:10.2147/IDR.S194670
166. Wang L, Hu C, Shao L. The antimicrobial activity of nanoparticles: present situation and prospects for the future. *Int J Nanomedicine*. 2017;12:1227–1249. doi:10.2147/IJN.S121956
167. Nandhini P, Kumar P, Mickymaray S, Alothaim AS, Somasundaram J, Rajan M. Recent developments in Methicillin-Resistant *Staphylococcus aureus* (MRSA) treatment: a review. *Antibiotics*. 2022;11(5). doi:10.3390/antibiotics11050606
168. Moo CL, Yang SK, Yusoff K, et al. Mechanisms of Antimicrobial Resistance (AMR) and alternative approaches to overcome AMR. *Curr Drug Discov Technol*. 2020;17(4):430–447. doi:10.2174/1570163816666190304122219
169. Truong VK, Truong NP, Rice SA. Antibacterial activity of nanoparticles. *Nanomaterials*. 2021;11(6). doi:10.3390/nano11061391
170. Zhang XF, Liu ZG, Shen W, Gurunathan S. Silver nanoparticles: synthesis, characterization, properties, applications, and therapeutic approaches. *Int J Mol Sci*. 2016;17(9):1534. doi:10.3390/ijms17091534
171. Mikhailova EO. Silver nanoparticles: mechanism of action and probable bio-application. *J Funct Biomater*. 2020;11(4):84. doi:10.3390/jfb11040084
172. Wypij M, Jędrzejewski T, Trzcińska-Wencel J, Ostrowski M, Rai M, Golińska P. Green synthesized silver nanoparticles: antibacterial and anticancer activities, biocompatibility, and analyses of surface-attached proteins. *Front Microbiol*. 2021;12:632505. doi:10.3389/fmicb.2021.632505
173. Prabhu S, Poulose EK. Silver nanoparticles: mechanism of antimicrobial action, synthesis, medical applications, and toxicity effects. *Int Nano Letters*. 2012;2(1):32. doi:10.1186/2228-5326-2-32
174. Masimen MAA, Harun NA, Maulidiani M, Ismail WIW. Overcoming Methicillin-Resistance *Staphylococcus aureus* (MRSA) using antimicrobial peptides-silver nanoparticles. *Antibiotics*. 2022;11(7). doi:10.3390/antibiotics11070951
175. Hamida RS, Ali MA, Goda DA, Khalil MI, Al-Zaban MI. Novel biogenic silver Nanoparticle-induced reactive oxygen species inhibit the biofilm formation and virulence activities of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Strain. *Front Bioeng Biotechnol*. 2020;8:433. doi:10.3389/fbioe.2020.00433
176. Das B, Dash SK, Mandal D, et al. Green synthesized silver nanoparticles destroy multidrug resistant bacteria via reactive oxygen species mediated membrane damage. *Arabian J Chem*. 2017;10(6):862–876. doi:10.1016/j.arabjc.2015.08.008
177. Ansari MA, Khan M, Khan AA, Cameotra SS, Alzohairy MA. Anti-biofilm efficacy of silver nanoparticles against MRSA and MRSE isolated from wounds in a tertiary care hospital. *Indian J Med Microbiol*. 2015;33(1):101–109. doi:10.4103/0255-0857.148402
178. Aslam B, Khurshid M, Arshad MI, et al. Antibiotic resistance: one health one world outlook. *Front Cell Infect Microbiol*. 2021;11:1153. doi:10.3389/fcimb.2021.771510