# Invisible Invaders: A Comprehensive Review of Superbug and Their Threat to Human Health

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# Abstract:

Resistance against antibiotics has caused the growth of "superbugs" which do not respond to the present treatment modalities. Antimicrobial resistance (AMR) in bacteria and other microorganisms is a problem that is associated with lots of morbidity and mortality worldwide. The multidrug-resistant pattern in gram-positive and gram-negative microorganisms is hard to deal with and can be ineffective in treating this infection with traditional antibiotics. There are many effective prevention methods and a scarcity of antibiotics, with only a few requiring novel treatment options and alternative treatment therapies. In this article, the different types of antimicrobial resistance are discussed concerning the issue, causes, and obstacles that lie ahead, as well as the strategies that will be urgently needed to lighten the burden across the globe**.** Limiting the spread of AMR will necessitate a coordinated effort involving various educational and research programs. A national plan for managing AMR, antimicrobial policy, standard treatment guidelines, and research about the public health elements of AMR must be developed and strengthened immediately in hospitals and communities worldwide. As antibiotic resistance develops widespread, a better need for replacement therapy emerges.

**Keywords:** Superbug, AMR, antibiotic, resistant pathogen, MRSA, History of superbug, Mechanism of superbug, superbug threat in healthcare

# Introduction

Antimicrobial resistance (AMR) develops when microorganisms learn to adapt and multiply against drugs that kill or inhibit their development [1]. Improper and unnecessary use of antimicrobial agents has led to the rapid development of AMR in our societies and worldwide [2]. Superbugs can be defined as strains of bacteria, fungi, viruses, and parasites that are resistant to most antimicrobial agents and other treatments commonly used to treat the infections they cause [3]. Antimicrobial agents are a group of naturally or synthetically derived agents (viz. antibiotics, antiseptics, antifungal, antiviral, etc.) that inhibit the growth of microorganisms or kill them without causing harm to the host [4]. Superbugs evolve due to misusing antimicrobial agents, specifically antibiotics, thus, superbugs are also labeled as antibiotic-resistant microbes. Nevertheless, excessive use of antibiotics, unreasonable use of antimicrobial agents, insufficient treatment, drugs of inferior quality, substandard disease treatments, and genome mutations likely to be seen among microorganisms are all common causes of superbug formation [5]. The progress of superbugs has seriously threatened human health throughout history [6].

Since the invention of antibiotics in 1928, millions of lives have been saved and positive outcomes achieved. Although, losing their effectiveness over time is the primary threat of antibiotics [7]. Bacteria have developed resistance to nearly every antibiotic class [8]. Resistance to antibiotics has emerged as one of the most serious public health problems, providing significant challenges to disease prevention and treatment [9]. Gram-negative bacteria like *Escherichia coli* have become resistant to almost all present antibiotics [10].

Moreover, *Staphylococcus aureus* is a significant infection source in hospitals and the general public, and it is becoming more virulent and antibiotic-resistant [11]. The recent sequencing of 7 strains of *Staphylococcus aureus* has provided information about the diversity of its genome [12]. Microorganisms resistant to antibiotics, like Methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* are common in hospitals, although recent efforts to combat the problem have been highly effective [13]. This bacterium has been linked to skin infections and a variety of other infections [14]. The Superbug-New Delhi metallo beta-lactamase NDM has emerged and has started to spread around the world. NDM-1 is an antibiotic-resistant superbug. It is a kind of enzyme that is found inside bacteria [15]. It is very important to understand the mechanisms of AMR and the appropriate use of antimicrobial drugs and drug histories [16]. Examples of superbugs described as antibiotic-resistant threats to patients in the healthcare system are shown in table 1[17].

Antimicrobial drug resistance can be conferred by a natural or induced bacterial genetic mutation, and genes conferring resistance may be transmitted horizontally across bacteria by conjugation, transformation, or transduction [18]. As a result, antibiotic resistance genes that emerged naturally might be passed on from generation. Many antibiotic-resistance genes are found on plasmids, which makes them easier to transfer [19].

Antibiotic prophylaxis is extensively used to avoid infections before a range of surgical procedures and for immune-compromised patients receiving chemotherapy [20]. If superbugs continue to spread at its present rate, such preventive measures will become ineffective, thereby limiting the spectrum of surgical operations available to physicians and lowering patients' quality of life [21].

Alternative treatment strategies have been established to tackle the development of antibiotic resistance to reduce the antibiotics used and preserve the current classes of antibiotics used [22]. Antibiotic resistance breakers (ARB) are used to increase the efficiency of current antibiotics by battling the resistance mechanism working against them [23]. Antimicrobial resistance causes an additional 23000 deaths and 2 million illnesses in the USA alone each year [24]. AMR has many serious impacts, including low patient outcomes, more powerful disease states, higher mortality rates, enhancement in treatment failure, etc. Because of the rising AMR, there is a higher requirement for combination therapies, raising treatment costs.

## Table 1: List of Some Commonly Encountered AMR.

|  |  |  |
| --- | --- | --- |
| Antimicrobial drug | Resistant pathogen | References |
| Carbapenem | *Enterobacteriaceae* | [25] |
| Methicillin | *Staphylococcus aureus* | [26] |
| Extended spectrum β-lactamase | *Enterobacteriaceae* | [27] |
| Vancomycin | *Enterococcus* | [16] |
| Multidrug-resistant | *Pseudomonas aeruginosa* | [28] |
| Multidrug-resistant | *Acinetobacter* | [1] |
| Erythromycin | *Group A Streptococcus* | [29] |
| Clindamycin | *Group B Streptococcus* | [30] |
| Ciprofloxacin | *Salmonella typhi* | [31] |
| MDR | *Neisseria gonorrhea* | [1] |
| Fluconazole | *Candida* | [32] |
| Azithromycin | *Shigella* | [33] |
| Ciprofloxacin | *Shigella* | [33] |
| Linezolid | *Staphylococcus* | [36] |
| Ceftriaxone | *Neisseria gonorrhea* | [37] |
| Ceftazidime | *Enterobacteriaceae* | [38] |
| Imipenem | *Enterobacteriaceae* | [39] |
| Ceftaroline | *Staphylococcus* | [27] |

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# History of superbugs

The world is in danger of losing effective antimicrobial agents due to the development and evolution of resistance against antimicrobial drugs [34]. Resistant bacterial pathogens are spreading and account for over 250 infectious diseases of concern in Canada alone [35]. In his Nobel Prize-winning speech, Alexander Fleming (who discovered penicillin in 1928) said that microbes might develop resistance to these remarkable antibiotics [36]. The discovery of each new antibacterial medicine has been followed by developing resistance to that medicine [37]. Resistance is a natural evolutionary process for microbes but is enhanced by the selective pressure put on them by extensive antimicrobial drug usage [38]. Resistant strains can grow and spread where infection control and prevention methods are not followed [39].

Initially, drug-resistant bacteria were discovered in hospitals because of the extensive use of antibiotics. The first penicillin-resistant bacteria, *Staphylococcus aureus*, was discovered in 1943 [40]. In 1967 Penicillin resistance in *Streptococcus pneumoniae* and *Enterococcus faecium* was identified [41]. Methicillin was first used to treat Staphylococcus infection in 1959, and it was originally quite effective in treating penicillin-resistant *Staphylococcus aureus* infections in hospitals [42]. This triumph was short-lived since Methicillin resistance was gained by *Staphylococcus aureus* in 1961, with the first case being reported in a UK hospital [43]. MRSA developed as a focal superbug globally in the 1980s. Following that, together, community-acquired MRSA (CA-MRSA) and hospital-acquired MRSA (HA-MRSA) were found, causing widespread problems [44]. The initial outburst of CA-MRSA was in Western Australia's native peoples, and it quickly spread around the world. MRSA developed resistance to glycopeptides like vancomycin after that, resulting in the formation of vancomycin-resistant *Staphylococcus aureus* (VISA), with the first case being reported in 1997 [45]. Gram-negative bugs that were resistant to antibiotics appeared concurrently with gram-positive bugs. Multidrug resistance was first noted in *Shigella, Escherichia coli*, and *Salmonella* in the late 1950s and early 1960s. Different types of beta-lactamase of extended-spectrum producing bugs dominated Europe and many other countries across the globe [46].

*Clostridium difficile* nosocomial pathogen, which causes diarrhea in hospital patients worldwide, has been identified. Between 1989 and 1992, *Clostridium difficile* resistant to clindamycin was identified as the cause of large outbreaks of diarrhea in hospitals in New York, Florida, Arizona, and Massachusetts. In 2005, there were also outbreaks of *Clostridium difficile* strains resistant to fluoroquinolone drugs like Ciprofloxacin and Levofloxacin in North America [47].

On November 5, 2004, the Centre for Disease Control and Prevention (CDC) reported a rise in *Acinetobacter baumannii* systemic infections in patients treated at military medical facilities in Iraq/Kuwait and Afghanistan during Operation Iraqi Freedom and Operation Enduring Freedom, respectively. The majority of these isolates were MDR, with a small number being resistant to all the medications examined [48].

The first report of NDM-1, in 2009, was from a strain of *Klebsiella pneumoniae* isolated from a patient in Sweden who had recently been hospitalized in New Delhi, India. By convention, the new gene was named for the city of origin and its biochemical function (New Delhi Metallo-beta-lactamase) and numbered '1' as the first gene of its kind. Since 2009, the NDM element has spread to many other pathogenic bacteria, including *Pseudomonas, Escherichia coli, and Acinetobacter,* and has spread to dozens of countries across the globe [49]. The CDC has classified NDM-containing enteric bacteria as an urgent threat and the highest level of antibiotic resistance in concern [50].

*Mycobacterium tuberculosis* and *Pseudomonas aeuroginosa* strains resistant to four or more lines of antibiotics are known as extremely drug-resistant (XDR) and drug-resistant strains and other multidrug resistance bugs became common in the twenty-first century [51]. In 2001, the first isolate of XDR was reported. New antimicrobial agents are brought to light to fight against resistant strains while the pathogens alter their genetic materials and develop resistance against these drugs through a selection process, posing a problem for doctors in treating the diseases [52]. A list of some AMR identified is shown in Table 2.

## Table 2: Development of AMR and their timeline.

|  |  |  |
| --- | --- | --- |
| Year | AMR identified | References |
| 1943 | *Staphylococcus* resistant to Penicillin | [53] |
| 1959 | *Shigella* resistant to Tetracycline | [54] |
| 1961 | Staphylococcus resistant to Methicillin | [55] |
| 1967 | *Pneumococcus* resistant to Penicillin | [56] |
| 1968 | *Streptococcus* resistant to Erythromycin | [57] |
| 1979 | *Enterococcus* resistant to Gentamycin | [58] |
| 1987 | *Enterobacteriaceae* resistant to Ceftazidime | [59] |
| 1988 | *Enterococcus* resistant to Vancomycin | [60] |
| 1996 | *Pneumococcus* resistant to Levofloxacin | [61] |
| 1998 | *Enterobacteriaceae* resistant to Imipenem | [62] |
| 2000 | XDR tuberculosis | [63] |
| 2001 | *Staphylococcus* resistant to Linezolid | [64] |
| 2002 | *Staphylococcus* resistant to Vancomycin | [65] |
| 2004 | PDR *Acinetobacter* and *pseudomonas* | [1] |
| 2005 | Ciprofloxacin-resistant *clostridium difficile* | [47] |
| 2009 | Ceftriazone resistant *Neisseria gonorhoeae* | [66] |
| 2011 | Ceftaroline resistant *staphylococcus* | [67] |
| 2012 | Fidaxomycin-resistant *M. tuberculosis* | [68] |
| 2017 | Anti-malarial drug resistant *P. falciparum* | [69] |

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## Some major epidemics due to antibiotic resistance

The extent to which antibiotic-resistant bacteria have increased the number and severity of major human illness epidemics may never be discovered. Table 3 represents a summary of some of these outbreaks [70].

Table 3: List of some major outbreaks due to antibiotic resistance.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Date | Causative organism | Illness | Country affected | Antibiotic used | References |
| Mid-1950s | Shigella | Dysentery | Japan | Upto12 differentantibiotics | [71] |
| 1967-1980 | E coli | Bacterimias or septicemias | USA | Penicillin | [1] |
| 1969 | Shigella | Dysentery | Guatemala | ChloramphenicolTetracyclineStreptomycinSulfonamide | [72] |
| 1969-77 | Salmonellawien | Diarrhea | Algeria, Austria,France, Iraq, India | Ampicillin with or without gentamicin | [70] |
| 1969-74 | Shigella | Dysentery | USA | ChloramphenicolTetracyclineStreptomycinSulfonamide | [71] |
| 1970s | Salmonella | Diarrhea | England | PenicillinTetracyclineSulfa drugs | [70] |
| 1972 | Shigella | Dysentery | Central Mexico | Chloramphenicol | [73] |
| 1974 | Proteus, pseudomonasE. coli | Bactrimias or septicemias | USA | β-lactam and an aminoglycoside | [74] |
| 1976 | Pneumococci | G –ve infection | USA | Penicillin | [75] |
| 1977 | Enterotoxic E. coli | Travelers diarrhea | USA | Nalidixic acid | [76] |
| Late 1970s | Vibrio cholerae | Cholera | Tanzania | Tetracycline | [77] |
| 1981 | E coli | Bacterimia or septicaemia | USA | Penicillin | [78] |

# Mechanism of action of superbugs

The evolution of resistant strains is the outcome of selection pressure caused by extended or inappropriate use of antimicrobials, and their transmission results in the growth of resistant strains which is resistant to the environment [79]. Continuous administration of the same antibiotic supports the emergence of resistant strains to that antibiotic and additional antibiotics in the same class [80]. The availability of mobile genetic components such as plasmids, bacteriophages, transposons, bare DNA, and others allows resistance traits to spread among diverse ecological and taxonomic groupings. Progressive gene mutation helps in small to large levels of antibiotic resistance [81]. These resistant strains obstruct the smooth movement of antibiotics through the cell wall, alter their targets, and inactivate them by generating enzymes due to the selection and mutation of distinct genes [82]. Resistance to Vancomycin and Methicillin is induced by alterations in the cell wall and cell membrane of Gram-positive bacteria like S. aureus, whereas resistance to Linezolid is caused by a mutation in the 23S subunit of ribosomal RNA [83]. Like gram-positive bacteria, gram-negative bacteria, including *Pseudomonas, Klebsiella*, *Acinetobacter,* and *Enterobacter*, resist a variety of antibiotics by various processes. They produce the enzymes carbapenemases, cephalosporinases and extended spectrum beta-lactamases to resist the effect of beta-lactam antibiotics [84]. Impulsive mutations acquire antibiotic resistance in MDR, TDR, and XTR tuberculosis bacteria in several genetic loci. Resistance to many antibiotics, including macrolides, is mostly caused by rRNA modifications that affect their ribosome binding [81][85]. Enzymatic inhibition, Penicillin-binding protein (PBP) modifications, Porin mutations, Efflux pumps, and Target changes are the five most frequently detected, with a high incidence in clinical isolates [86].



**Figure 1**: Schematic diagram of the most frequently observed mechanism of bacterial resistance adapted from [87].

## Enzymatic inhibition

Enzymatic inhibition is the most important microbial pathogen resistance mechanism. This mechanism is associated with a number of antibacterial chemical structural modification strategies, including functional group transfer (thiol, acyl, phosphoryl, glycosyl, nucleotides, ADP-ribosyl), which occurs with many antibacterial, including chloramphenicol, aminoglycoside, rifamycin, and lincosamide; hydrolysis, which occurs primarily with β-lactam antibiotics; and additional chemical alterations such as redox, lyase which found in Rifamycin, Tetracycline, and Streptogramin [88]. β-lactamases antibiotics are challenging in handling Gram-negative bacterial disease, among a vast number of enzymes that can alter antimicrobial agents [89]. Penicillinases impart penicillin resistance while also being able to hydrolyze penicillin and numerous cephalosporins, which can escape β-lactamase inhibitors such as sulbactam, tazobactam, and clavulanic acid [90]. This set of enzymes confers all cephalosporins, such as ceftazidime and cefotaxime including penicillin resistance [27].

## Penicillin-binding protein modification

PBPs are proteins that play a role in the formation of peptidoglycan, which is a key component of the cell walls of bacteria [91]. Such enzymes catalyze the cross-linking glycan chain, known as transglycosylation and transpeptidation. However, some categories of penicillin-binding proteins do not have transglycosylation properties [92]. The active site of transpeptidase is the primary target of β-lactam antibiotics. These molecules mimic the D-Ala-D-Ala dipeptide in peptidoglycan, forming a stable acyl-enzyme complex, deactivating enzyme [93]. There is various altered penicillin-binding protein; some are more prevalent, including PBP4 and PBP5, which confers resistance to penicillin; and PBP1aand PBP2x, responsible for providing varying resistance to penicillin and other β-lactams [94]. PBP2a (or PBP20), a mutated protein that gives resistance to both cephalosporins and penicillin the most concerning [95]. These modified penicillin-binding proteins alter the active site, making the β-lactam antibiotics drop or reduce their attraction to the desired target, encouraging resistance [96].

##  Porin modifications

Outside the cell wall, Gram-negative bacteria have an outer membrane, which is made up of a lipid bilayer. The lipopolysaccharide is the major component of this bilayer, and hydrophilic substances have a hard time passing through due to the hydrophobicity of the membrane. These porins, also known as outer membrane porins (OMP), are essential to help hydrophilic solutes pass through lipid bilayer membranes. The ability of an antibiotic to pass through porins is influenced by several parameters, including its size, charge, and shape [97]. OmpC, OmpF, and OmpE are three of the most common porins. Each species of bacteria built its porins, and the damage or degradation of these OMPs is a major cause of resistance development. For example, in *P. aeruginosa*, the inactivation of OmpD imparts resistance to meropenem and imipenem; in most species, the destruction of OmpF can produce multidrug-resistant organisms [95]. As a result of this phenomenon, minimum inhibitory concentrations for hydrophilic antibiotics have increased, limiting the antibacterial therapy options available in medical care [98]. A decrease in porin synthesis is a property of some microorganisms, like *P. aeruginosa,* that are less effective to antibiotics such as β-lactam [99].

##  Efflux pumps

The efflux pump is a proton-based method that influences the energetic elimination of the drug from inside the bacterial cell and is a very efficient resistance mechanism [100]. Major facilitators (MFs), resistance nodulation cell division (RND), small multidrug resistance (SMR), ATP-binding cassette (ABC), and multidrug and toxic substance ejection (MATE) are the five families of membrane-spanning efflux and proteins [101]. One single transporter of the MF, SMR, or ABC located in the cytoplasmic membrane is usually responsible for drug efflux from Gram-positive bacteria. Because of an outer membrane, Gram-negative bacteria are more complicated [102]. The propulsive energy for drug effluence appears to be an electrochemical energy gradient across the cell membrane in SMR and MF family transporters [103]. They work on three mutual motifs: motif A, which works as a cytoplasmic door, regulating substrate transport; motif B, which is related to energy coupling; and motif C, which fixes the direction of the vacant substrate-binding target and guides the transport route [104]. The tetracycline transporter from *E. coli* is the highest considered participant of this family, having been demonstrated to have a role as an electroneutral antiport system, quickening the interchange of a divalent metal cation complex of tetracycline for a proton [95].

##  Molecular modification of antibiotic target

Many antibiotics target the ribosome in protein synthesis, and changes in the construction of this organelle account for antibiotics' selective nature in bacteria and eukaryotic cells [105]. Minor differences in the structure of ribosomes may bring about species-specific or idiosyncratic interactions among the antimicrobial agents and their targets (14). Antimicrobial agents that aim at a bacterial cell's translational component are powerful inhibitors of prokaryotic microorganisms [106]. However, these microbes have developed resistance to antimicrobial agents that inhibit protein synthesis [107]. The alteration of antibiotics' molecular targets is a prominent mechanism of resistance [108]. This is most commonly caused by mutations in certain genes, producing comparatively quick and effortless resistance with little effect on microbial fitness [109]. A minute variation in an amino acid order alters the protein assembly adequately to obstruct the binding of antibiotics and action. However, the target alteration can occur from catalytic resistance strategies [110]. Ribosome methyltransferase is an example of this category, where the Erm enzyme changes the 23S ribosomal RNA of the ribosomal larger subunit at position A2058in *E. coli*. This leads to lincosamides, type B streptogramins and macrolides resistance [111].

# Superbugs: A global threat to the healthcare system

In the twenty-first century, serious complications caused by bacteria that have developed resistance to regularly used antimicrobials have become a major global healthcare concern. They are more serious, need elongated and more sophisticated treatments, and are much more costly to treat and diagnose [8]. Anti-microbials are often used inappropriately in food production (particularly in meat and seafood, as well as some fruits) associated with MDR infections in humans [112]. The fast proliferation and expansion of multidrug-resistant bugs worldwide is a foremost public health concern [113]. Antibiotic development reduced animal and human mortality, increasing life expectancy [114]. The concern for doctors has increased significantly with the development of Multidrug-resistant tuberculosis, Methicilin-resistant *Staphylococcus aureus*, hospital-acquired MRSA, and community-acquired MRSA. These infection outbreaks are the most feared hospital or community-acquired illnesses today, and they can be a nightmare for a hospital or a community, as well as a serious public health problem. The emergence and spreading of carbapenemase resistance in gram-negative bugs are also considered a foremost public health issue globally [115]. Gram-negative bacteria, such as *Klebsiella pneumoniae, E. coli, Acinetobacter baumannii,* and *Pseudomonas aeruginosa,* are among the most common causes of hospital and community-acquired infections in public, and resistance to an antibiotic in these bacteria is a rising issue. The latest advancement in nanotechnology-based drug delivery systems could be the answer to battling these resistant microorganisms [116]. On the other hand, laws and regulations should be developed to prevent the spread of resistance among bacteria [117].

The emergence of a superbug in the healthcare setting poses a serious concern to human health. Because practically everyone will get medical treatment at some point in their lives, the problem can touch everybody [118]. Furthermore, patients in treatment environments like hospitals and during long-standing treatment amenities are frequently exposed due to weakened immune systems and undergoing ailments [119]. AMR infections are seriously harmful to these people. Patients' breaths are kept safe, and their well-being can be better conserved by preventing antibiotic resistance in hospital settings [120].

Additionally, systems, healthcare facilities, patients, and insurers can save money that would otherwise be expended on further complicated care and antimicrobial agents to treat antimicrobial-resistant infections [121]. Antibiotic resistance has a fitness cost, characterized as a reduction in competitive capability in the absence of antibiotics. When bacteria meet an antibiotic-free environment, this cost plays an important role in the dynamics of resistance by creating selection against resistance [122].

The opportunistic pathogen *Pseudomonas aeruginosa* is very common. It has a low antibiotic susceptibility, one of its most concerning traits. This poor sensitivity is due to the coordinated activity of multidrug efflux pumps with genetically expressed antibacterial resistance genes and the bacterial cellular envelopes' less permeability. Salmonella and *Escherichia coli* are bacteria that can be found in contaminated food. Serious complications develop when both microorganisms are introduced. Several people are admitted to hospitals each year after being infected, and some die. Shigella has developed resistance to the antibiotics Azithromycin and Ciprofloxacin. Tuberculosis is one of the most prevalent pathogenic infections globally and a leading cause of death. Mycobacterium tuberculosis causes tuberculosis, which is transmitted primarily through the air. The bacteria can infect any portion of the body, but the lungs are the most common site of infection. Tuberculosis is usually correctable and treatable using first-line anti-tubercular medications, but *Mycobacterium tuberculosis* can become resistant to one or more of the medications utilized to treat it in some cases. Drug-resistant tuberculosis is more difficult to cure since it is more complicated, takes longer, and requires more expensive medications with more adverse effects.

AMR is a difficult problem to solve. Putting appropriate infection prevention and control strategies in place can be difficult [123]. It is also difficult to use current antibiotics appropriately in animals and humans, which means choosing the right antibiotic and utilizing it only when necessary [124]. The CDC has classified microorganisms in this into three main categories based on their level of concern: urgent, serious, and concerning (Table 4)[125].

Table 4:Three main categories for microbial resistance against antibiotics [126].

|  |  |  |
| --- | --- | --- |
| Urgent Threats | Serious Threats | Concerning Threats |
| Carbapenem-resistant *Enterobacteriaceae* (CRE), Drug-resistant *N. gonorrhoeae*, *Clostridium difficile* | Drug-resistant *S. Typhi*, Drug-resistant Campylobacter, Methicillin-resistant *S. aureus*. Drug-resistant *tuberculosis*, Multidrug-resistant *Acinetobacter*, Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *P. aeruginosa*, Fluconazole resistant *Candida*, Drug-resistant non-typhoidal *Salmonella*, Drug-resistant *Shigella*, Drug-resistant *S. pneumonia*, Extended-spectrum β-lactamase producing *Enterobacteriaceae* | Erythromycin-resistant Group A *Streptococcus*, Vancomycin-resistant *Staphylococcus aureus*, Clindamycin resistant Group B *Streptococcus* |

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# Update on AMR

Antibiotic resistance threatens the capacity to treat common diseases in the hospital and community [127]. Resistance to antibiotics emerges because of natural processes. Certain human behaviors, on the other hand, accelerate their development and transmission [128]. There is a present scarcity of effective medicines, and preventive measures, and only a few new antimicrobial agents, necessitating the discovery of novel therapeutic alternatives. Improper use of antimicrobial agents in animal husbandry promotes the establishment and development of resistant strains; additionally, inadequate infection prevention and control techniques promote the spreading of resistant strains [129]. In many places, third-generation cephalosporins have refused to treat infections caused by gonococcal. Enhanced rates of disease and abnormalities, including infertility, poor pregnancy, and infant blindness, can be caused by resistant bacteria (superbugs) [130]. The most extensively used antibacterial medications, fluoroquinolones, including first-line treatments against *Staphylococcus aureus*, are ineffective against *Escherichia coli* infections [131]. In most places worldwide, the last-resort treatment for life-threatening illnesses, carbapenem antibiotics, has failed [132]. Multidrug-resistant tuberculosis, including resistance to all fluoroquinolones and any second-line injectable drug, was first detected in the 92nd century and is still a big concern in all parts of the world [133].

The development of artemisinin-resistant *Plasmodium falciparum* is a burning public health issue that is putting the continuing worldwide effort to minimize the malaria load in danger [134]. Despite the significant growth of anti-retroviral medicine access in recent years, resistance is becoming a growing concern. Increased resistance to the nonnucleoside reverse transcriptase class of medication utilized in recent human immunodeficiency virus (HIV) infections, notably in Africa, have been observed [135]. Evidence shows a link between higher levels of anti-retroviral medication usage and higher levels of HIV drug resistance [136]. Antiviral medication resistance is constantly developing in the treatment of endemic and pandemic influenza. By 2012, nearly all influenza A viruses spreading in people had developed resistance to common antiviral medicines such as rimantadine and amantadine [137]. Resistance to the neuraminidase inhibitor oseltamivir, on the other hand, is uncommon (1-2 percent). The World Health Organization (WHO) global surveillance and response system monitors antiviral susceptibility [138].

WHO published a list of bacteria in February 2017 for which new antimicrobial agents are immediately required. The list emphasizes the dangers posed by gram-negative bugs resistant to various antibiotics [139]. These microorganisms have evolved the capacity to develop novel pathways to fight the treatment mechanism and can convey genetic material to the next generation of microbes, allowing them to develop resistance. According to the urgency of the requirement for novel antibiotics, the WHO list is classified into three categories: critical, high, and medium priority [140].

Multidrug-resistant bacteria are the most critical, posing a serious concern in nursing homes and hospitals, especially among patients using ventilators and blood catheters. They can cause serious and often fatal infections, including bloodstream infections and pneumonia [141]. These microbes have developed resistance to a wide range of antibiotics, particularly carbapenems and third-generation cephalosporins, the best medications currently available for treating extensive drug-resistant bacteria. This group includes- carbapenem resistant *Pseudomonas aeruginosa*, carbapenem resistant *Acinetobacter baumannii* and carbapenem resistant *Enterobacteriaceae* [142]. The second tier in the list consists of the high-priority vancomycin-resistant *Enterococcus faecium*, MRSA, *Helicobacter pylori* resistant to clarithromycin, and *Campylobacter spp*. resistant to fluoroquinolone, *Salmonellae* resistant fluoroquinolone, *and Neisseria gonorrhoeae* resistant cephalosporin. The third tier contains medium urgency categories, including *Haemophilus influenzae* resistant to ampicillin, *Shigella* resistant to fluoroquinolone, and *Streptococcus pneumoniae resistant* to *penicillin* [143]. According to Deng *et al*. 2019, Wang-Lin *et al*. 2018, Zhou *et al*. 2019 antimicrobial antibodies and antibiotics can be used jointly to treat infections. Promising approaches for combining antibodies with antibiotics include AAC and antibody-conjugated nanoparticles. DSTA4637S, the first clinically tried AAC, had already completed the phase Ib study [144]. De Vor *et al.* 2022, showed in a study that numerous previously identified mAbs against S. aureus surface antigens can recognize *S. aureus* biofilms *in vitro* and *in vivo*. Additionally, mAbs detection may offer a different method for determining implant- or catheter-related infections [145]. According to Nandhini *et al.* 2022, bypassing bacterial resistance mechanisms, the combination of antibiotics and NPs can set a new precedent for distributing the appropriate concentration of a medicine in the desired target sites. Millions of lives can be saved by combining antibiotics and NPs, which can fulfil all the parameters of a powerful antibacterial agent. Utilizing *in vivo* and *ex vivo* investigations, it is possible to examine the efficacy and biosafety of the planned and manufactured medications [146]. According to Li *et al.* 2021, recent synthetic efforts are summarised by their effects on analog design and numerous AMP development applications. It covers alterations shown to improve antimicrobial action, such as lipidation, glycosylation, and multimerization, as well as the widespread use of innovative biorthogonal chemistry and opinions on the course of future research. The main focus of the topic is the selective, logical chemical alteration of AMPs in order to produce next-generation antimicrobial agents [147]. In this study, Alharthi *et al.* 2021, concentrate on bacteria that express antimicrobial resistance (AMR) and SrtA as a potential target to combat AMR. The mechanism of SrtA function and its inhibition by different inhibitors, including peptides, small synthetic molecules, and natural compounds are described. Future SrtA research directions for the development of antibiotic substitute medications are also suggested [148].

# Prevention of AMR

Antimicrobial-resistant microorganisms are one of today's most serious dangers. Most diseases are transferred and occur due to contact with infected people and a lack of hygiene procedures. Antibiotics are misused when they are used for longer than necessary, when they are prescribed incorrectly, or when they are used without infection [149]. Developments in diagnostic technology that make it easier to isolate and diagnose microorganisms resistant to antibiotics, for example, MRSA in hospitals, have allowed fast detection of these microbes instead of days or weeks, within hours. Furthermore, with the discovery of penicillin and broad-spectrum antibiotics in the 1940s, efforts to combat microorganisms by attacking them with bacteriophages were pretty much abandoned (114). Appropriate antibiotic use may lower the risk of the emergence of opportunistic infection by antibiotic-resistant bugs as a result of dysbacteriosis [150].

Clinical studies have shown that topical dermatological treatments comprising tea tree oil and thyme oil may successfully stop the spread of CA-MRSA [151]. Furthermore, additional Phytotherapeutic medications can help to decrease or eliminate the need for antibiotics [152]. New strains may emerge that evade vaccine-induced protection. Vaccines have shown poor efficacy due to immunological differences across Staphylococcus bacteria and the short duration of antibody activity [153]. In 2013, the WHO established the Strategic and Technical Advisory Group on AMR at its first meeting, which recommended that the WHO should lead in developing a global action policy to address AMR[154].

In May 2015, the World Health Assembly authorized a work plan to be effective globally to combat the rising issue of antibiotic resistance and different antimicrobial drugs [155]. The plan aims to advance global knowledge and understanding of antibiotic resistance via effective communication, learning, and practice [156]. The strategy directs the WHO to examine people's knowledge and understanding of the situation and develop and conduct worldwide communication programs and initiatives to raise awareness [157].

To decrease the transmission and development of antibiotic resistance, as well as to stimulate the development of novel therapies, control, and preventative measures should be undertaken [158]. Superbugs can be prevented by maintaining appropriate sanitation and hygienic practice[149]. Public education about the proper use of antibiotics and the need to follow a full regimen as prescribed should be implemented [159]. Both developing and developed countries should implement policies and regulations to prevent wasteful drug promotion. Measures should be undertaken to comply with WHO guidelines to reduce the use of dual-use antibiotics, which are related to human health and food safety. Restricting the human-to-human spread of resistant organisms, minimizing the usage of broad-spectrum medicines, and developing new antibiotics are all ways to combat AMR [160].

# Conclusion

Anti-microbials are broadly employed in both human and animal health across the globe to treat and control a wide range of infections. The improper use of these medications helped to create favorable conditions for the appearance, distribution, and growth of antibiotic-resistant microorganisms. These can lead to the development of illnesses that are far more treatment-resistant. Even though there are regulations for the proper utilization of antimicrobial agents in human and veterinary medicine, antibiotic misuse by healthcare workers, inexperienced practitioners, and medication consumers is continually being reported.

All these, together with the fast emergence of resistant pathogens, may result in increased death, treatment costs, and failure of production in animals. A coordinated response incorporating multiple key steps will assist us in combating these lethal diseases and address the major health issues brought on by the rapid spread of MDR strains around the globe. They include preventing infections, especially those caused by MDR strains, inhibiting the formation and spread of antimicrobial resistance, monitoring resistant bacteria by using current antibiotics more effectively, and developing novel antibiotics and diagnostic tools for resistant strains. These urgent actions require combined national and international action and significant financial expenditure from the pharmaceutical sector. Additionally, in-depth teamwork between pharmaceutical company research and academic research is significant for expanding novel effective antibiotics. Governments may need to incentivize pharmaceutical companies to encourage them to concentrate on developing antimicrobial drugs, which don't appear to be hugely profitable.

The development of novel drug-resistant strains that can lead to serious disease outbreaks is rising globally due to the widespread overuse of presently available antibiotics. Therefore, we must move quickly to establish circumstances that lower the likelihood of new emerging AMR and stop the propagation of already-existing resistance. Additionally, we must build novel antibiotic drug discovery pathways that are considerably quicker and simpler to modify to the increasing number of new drug-resistant strains than the conventional antibacterial drug developing techniques. First, using antibiotics as little as possible in humans and animals can lower the rate at which new, drug-resistant microorganisms arise. Accurate and precise diagnostics that determine the infection's origin and employ the appropriate medications to treat it can help. Narrow-spectrum antibiotics should be used when possible because they cause less AMR than broad-spectrum medications. We also need to develop novel antibiotics much more quickly and with greater efficacy. In order to be successful in this attempt, we must significantly broaden the scope of our molecular tools for the production of antibacterial drugs.

The superbug is one of the global most serious public health concerns and a substantial financial burden on global economies. Limiting the spread of AMR will necessitate a coordinated effort involving various educational and research programs. One of the key factors, which may be linked to the hospital culture, is the incorrect use of antimicrobial drugs. Governments, public health groups, and healthcare workers must work together. Most new medications, particularly antibiotics, are modifications of older ones; therefore, novel antibiotics should be utilized with caution. Employing the correct antibiotics to treat the ailment will block the development of microorganisms, causing them to die without replicating further, preventing bacterial resistance.

Different therapeutic approaches have been introduced to fight the increased frequency of AMR, with the ultimate goal of lowering the number of antibiotics used while keeping the present-day antibiotic groups for future therapeutic use. ARB are substances that can boost the efficacy of present-day antibiotics by battling the resistance mechanisms used to counteract them. ARBs can be given in conjunction with or conjugated with failed antibiotics, and they may or may not have direct antibacterial activities. The most significant advantages are the combination agents' intrinsic flexibility and the likelihood of synergy between the two treatments. However, there are numerous drawbacks, including the additional governing burden that comes with merging two medications and the requirement that the combined treatments' pharmacokinetic characteristics be identical. Gram-negative bacteria have a permeability barrier that could be bypassed with a unique nano-carrier delivery platform. Nano-carriers can also be utilized to administer high doses of antibiotics to specific locations, minimizing systemic adverse effects. Antibiotics can be administered using different methods, such as nanoparticles, antimicrobial polymers, liposomes, etc. Although these strategies have had mixed results, it is predicted that with more investigation and technological developments, nano-delivery will become a powerful weapon in the battle against microbial resistance. Nanoscience has the potential to provide several precise, cost-effective, and time-saving ways of preventing microbial growth and its effects. Using surface-enhanced Raman spectroscopy, a team of research workers from Jackson State University in the United States created unique iron-magnetic core gold plasmonic shell nanoparticles, which are popcorn-shaped for MDR Salmonella bacterium identification and photothermal death (SERS). They also observed that the same core-shell nanoparticle might be coupled with near-infrared (NIR) light to construct MDR hyperthermia light-directed Nano heaters.

Another potential avenue is using nucleic acid-based aptamers, which can be utilized to recognize infectious pathogens and suppress their actions precisely. Researchers are using the systematic evolution of ligands by exponential enrichment (SELEX) technology to find aptamers that can detect specific infections. These Aptamers may be utilized to create nucleic acid-based recognition systems that can directly identify bacteria in a compound matrix lacking the need for pre-concentration, which is commonly a stumbling block in developing quick diagnostics. Aptamers that can detect and often disrupt essential functions in *M. tuberculosis, S. aureus,* and *S. enterica* have already been reported, and this is a significant step toward developing such diagnostic platforms. Most β-lactamase inhibitors appeared on the scientific picture decades succeeding their companion β-lactams antibiotics were officially licensed certainly reflects the relatively recent push to fight AMR. When used with broader efforts like antimicrobial stewardship and enhanced public awareness of AMR, a more active diagnostics method for AMR Breaker progress might maximize the lifespan of present antibiotics.

While the research on antibiotics is slowing, vaccination technology is improving. Vaccines can help to reduce AMR by avoiding bacterial and viral infections, lowering antibiotic use and overuse, and preventing antibiotic-resistant diseases. Vaccines have a lower risk of causing resistance. Vaccines, combined with other treatments, can aid in reducing AMR by preventing (resistant) illnesses and lowering antibiotic use. To successfully reduce AMR, industry and governments must focus on developing novel vaccines and drugs against resistant infections.

**List of Abbreviation**

* AMR: Antimicrobial resistance
* MDR: Multidrug resistant
* MRSA: Methicillin-resistant *Staphylococcus aureus*
* NMD: New Delhi metallo beta-lactamase
* ARB: Antibiotic resistance breakers
* CA-MRSA: Community-acquired methicillin-resistant staphylococcus aureus
* HA-MRSA: Hospital-acquired methicillin-resistant staphylococcus aureus
* VISA: Vancomycin-Resistant *Staphylococcus aureus*
* CDC: Centre for Disease Control and Prevention
* XDR: Extremely drug-resistant
* PBP: Penicillin-binding protein
* OMP: Outer Membrane Porins
* MF: Major facilitators
* RND: Resistance Nodulation Cell Division,
* SMR: Small Multidrug Resistance
* ABC: ATP-binding cassette
* MATE: Multidrug and Toxic Substance Ejection
* HIV: Human Immunodeficiency Virus
* WHO: World Health Organization

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