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## Review Article

# Assessment of critical impact of superbugs in human health: A known beyond

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### ABSTRACT

A superbug is described as a bacterium that has seen to develop resistance to traditional treatment of antibiotics. The World health organization has produced the first-ever fulfilled report on the AMR danger, which consists the information from 114 nations and ranks it amongst the one of the severe global health hazards of the 21<sup>st</sup> century. Every year, about 1 million people die due to the non-treatable drug-resistant diseases caused by these superbugs.

Bacterial resistance is on the rise, putting many of our current antibacterial treatments in danger. Discovery of brand-new antibiotics has lagged behind the growth of germs resistant to them. Numerous novel approaches to target different substances in bacterial cells have been developed and are being researched. The present review emphasizes on the various types of superbugs with its possible solution. Also, it illustrates that, we should not be startled by the fast emergence of resistant pathogens dubbed "superbugs" by the media but what has been astonishing is the rapidity with which these superbugs have evolved and spread resistance, frequently at little or no cost to their health. The article provides an overview of the most prevalent forms of superbugs and potential novel medicines that might be utilized in a clinical setting shortly to fight these superbugs.

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## 1. Introduction

A bacterium which have developed resistance for standard antibiotic treatments is referred to as a superbug. It is a bacterium that kills when it should not and can cause untreatable disorders that cannot be cured. Diseases get harder to treat when more of these bacteria develop resistance to the available antibiotics. A superficial bacterial infection can be deadly in some circumstances.<sup>1,2</sup> We should not have been surprised by the quick appearance of resistant infections, which the media has termed "superbugs"<sup>3</sup> yet, what has been surprising is how quickly these superbugs have developed and spread resistance, usually at little or no cost to their health. AMR is one

of the twenty-first century's most serious global health threats, according to the first and most comprehensive report on the subject ever produced by World Health Organisation (WHO), which includes data from 114 countries. Approximately 1 million people worldwide die from superbug-caused, non-treatable drug-resistant diseases each year. These figures are expected to reach 10 million by the middle of the century, placing Antimicrobial Resistance (AMR) on par with the Human Immunodeficiency Virus (HIV) issue and calling for a concerted worldwide response.<sup>4</sup>

## 2. Historical Background

The clinical application of antibiotics began in the 1930s with the therapeutic use of sulphonamides.<sup>5</sup>

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In addition, the discovery of penicillin in the early twentieth century marked the beginning of the antimicrobial revolution. Afterward, various semi-synthetic and synthetic antibacterial agents and more recent antimicrobials were found. Antimicrobial drugs have been used to treat several cases of potentially fatal bacterial infections, which has helped the patients' suffering. Sadly, the uncontrolled use of antibiotics over the past 50 years has put pressure on susceptible bacterial populations, leading to the survival of drug resistance, with some strains being resistant to numerous medicines. Resistance as a means of survival for bacteria exposed to antimicrobials generated by other bacteria in their environment was widely known even before the therapeutic use of antibiotics. The use of antibiotics to treat infectious disorders brought on by bacteria, fungi, parasites, and viruses is becoming more problematic due to antibiotic resistance. All commonly used antibiotics are now susceptible to bacterial resistance, and even some more recent agents, like streptogramins and new generation fluoroquinolones, are experiencing high levels of resistance as a result of the use of related substances in recent years in both medicine and agriculture.<sup>6</sup> Superbugs are presently ubiquitous around the world and considered an epidemic. Multi Drug-Resistant (MDR), Methicillin-Resistant *Staphylococcus aureus* (MRSA) Superbugs include, but are not limited to, *Mycobacterium tuberculosis*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Clostridium difficile*, *Neisseria gonorrhoeae*, *A. baumannii*, *Salmonella spp.*, *E. coli*, *P. aeruginosa*, and vancomycin-resistant *Enterococcus spp.* (Figure 1).<sup>7</sup> The Multidrug-resistant (MDR), pan-drug-resistant (PDR), and extensively drug-resistant (XDR) microorganisms are been used to describe AMR.<sup>8</sup> The key players are the seven bacteria that cause common, serious diseases like sepsis, diarrhea, pneumonia, urinary tract infections, and gonorrhoea's, such as MRSA, carbapenem-resistant *Klebsiella pneumonia*, and others. This is as per the WHO's "Antimicrobial resistance: global report on surveillance," published in 2014. (Figure 2).<sup>9</sup> The Centres for Disease Control and Preventative (CDC) created a framework to categorize the severity of antibiotic resistance risks in 2013 while the crisis was in full swing, concentrating on the urgent and severe threats that demand careful monitoring and prevention measures to avoid cataclysmic outcomes. The 2019 revision of the CDC Priority List for AMR Bacteria is referenced in Table 1.

### 3. Drug-resistant Tuberculosis

Worldwide, tuberculosis is a chronic illness that threatens the most vulnerable members of society, as well as immunocompromised individuals and neonates.<sup>10</sup> Although the brain, kidneys, and spine may also be affected, the lungs are most affected. Every year, drug-resistant TB claims the lives of almost 1.7 million individuals worldwide.<sup>11</sup>

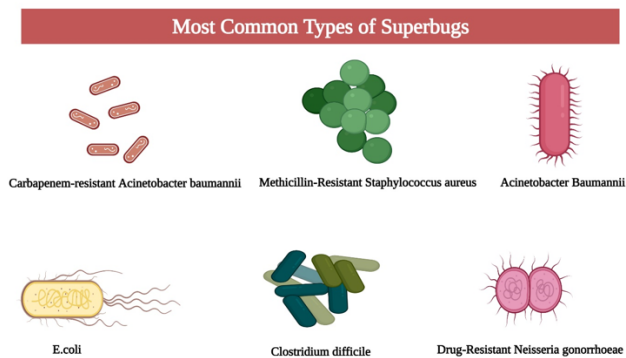
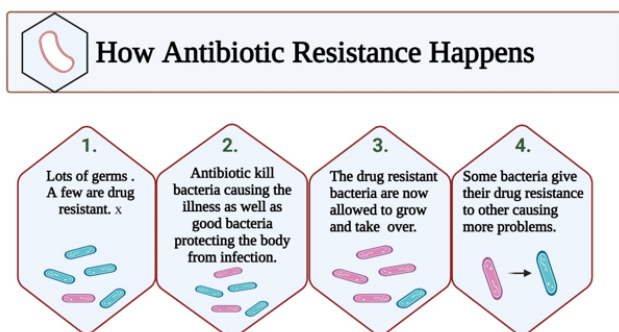


Figure 1: Type of superbugs

Table 1: CDC Priority List for AMR bacteria

<b>A. Serious Threats</b>	Drug-resistant <i>Campylobacter</i>  Drug-resistant <i>Candida</i> Extended-spectrum beta-lactamase (ESBL)-producing <i>Enterobacteriaceae</i> Vancomycin-resistant <i>Enterococci</i> (VRE) Multidrug-resistant <i>Pseudomonas aeruginosa</i> ( <i>P. aeruginosa</i> ) Drug-resistant nontyphoidal <i>Salmonella</i> Drug-resistant <i>Salmonella</i> serotype Typhi Drug-resistant <i>Shigella</i> Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) Drug-resistant <i>Streptococcus pneumoniae</i> ( <i>S. pneumoniae</i> ) Carbapenem-resistant <i>Acinetobacter</i>
<b>K. Urgent Threats</b>	<i>Candida auris</i> ( <i>C. auris</i> ) <i>Clostridioides difficile</i> ( <i>C. difficile</i> ) Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE) Drug-resistant <i>Neisseria gonorrhoeae</i> ( <i>N. gonorrhoeae</i> )
<b>P. Concerning Threats</b>	Erythromycin-resistant group A <i>Streptococcus</i> Clindamycin-resistant group B <i>Streptococcus</i>
<b>R. Watch List</b>	Azole-resistant <i>Aspergillus fumigatus</i> ( <i>A. fumigatus</i> ) Drug-resistant <i>Mycoplasma genitalium</i> ( <i>M. genitalium</i> ) Drug-resistant <i>Bordetella pertussis</i> ( <i>B. pertussis</i> )

Source: <https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-treats-report508.pdf>



**Figure 2:** Antibiotic resistance

Initially used in the 1940s to stop relapse and the development of resistance, as well as to treat symptoms and microbiologically eradicate Mycobacterium, the multidrug treatment uses a combination of four medicines (at least two active drugs). However, resistance swiftly emerged. The first and second lines of antitubercular treatment are ineffective against MDR-TB.<sup>12</sup> Especially rifampin and isoniazid (INH). XDR-TB (kanamycin, amikacin, or capreomycin) refers to MDR-TB with additional resistance to the third line of drugs (any fluoroquinolone) and at least one of three injectable medicines. Around the world, there were around 9 million cases of TB in 2013, with MDR-TB making up 3.5 percent of all cases (480,000 cases). Nearly 9% of persons with MDR-TB advance to XDR-TB (WHO), according to the Global Tuberculosis Report from the World Health Organization.<sup>13</sup> Additionally, approximately 100 countries have reported extensively drug-resistant tuberculosis (XDR-TB).<sup>14</sup>

#### 4. Drug-Resistant *Neisseria gonorrhoeae*

Gonorrhea is a sexually transmitted illness (STD) that affects both men and women and has a variety of symptoms, including infertility (*Neisseria gonorrhoeae*). Around 87 million new cases were reported globally in 2016, mainly affecting adults between the ages of 15 and 49 and with a global rate of 20 per 1000 women and 26 per 1000 males.<sup>15</sup> *Neisseria gonorrhoeae* has exhibited a tremendous natural inclination to acquire resistance to all antimicrobials due to its capacity to modify its DNA through mutations. The majority of AMR genes are located on the chromosome of bacteria, except the for-penicillin resistance (blaTEM) and tetracycline resistance (tetM) genes.<sup>16</sup>

#### 5. Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Our skin contains *Staphylococcus aureus*, which has been connected to several nosocomial and community-acquired illnesses. The 1950s saw the emergence of penicillin-resistant *Staphylococcus aureus* strains, and the year after the introduction of methicillin in 1959 saw the

emergence of methicillin-resistant strains.<sup>17</sup> Methicillin-resistant *Staphylococcus aureus*, sometimes MRSA, was given to these resistant types. If not treated properly, it survives in human tissues and develops resistance.<sup>18</sup> MRSA initially resulted in relatively small skin infections like pimples, spider bites, or boils that might later develop into purulent lesions that were large, painful, or heated to the touch, which resulted in fever. The probability of dying is increased by 64% in MRSA carriers compared to non-carriers of the infection.

#### 5.1. *Clostridium difficile*

Due to patients' prolonged or repeated use of antibiotics, *Clostridium difficile* has become a superbug.<sup>19</sup> Overusing antibiotics alters gut flora, making it easier for *C. difficile* germs to proliferate and take control, making an initially harmless illness fatal.<sup>20</sup> Antibiotic-induced modifications in antibiotic target sites, differences in metabolic pathways, and the creation of biofilms are only a few of the mechanisms that help bacteria survive. Any modifications to the antibiotic targets might spread rapidly across the population through the cells. Relapses are anticipated as a result of spore germination from *C. difficile*, which results in treatment failure.<sup>21</sup> The ribotype 027 of *C. difficile* has been linked to an upsurge in outbreaks during the early 2000s, which has led to greater mortality and higher medical expenses globally.<sup>22</sup>

#### 6. Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

very resistant to drugs Fluoroquinolones, cephalosporins, and carbapenems are only a few of the medicines that Gram-negative bacteria have become resistant to, with resistance rates in some regions of the world reaching 90%. One of the hardest diseases to treat, CRAB can be either extensively drug-resistant (XDR) or completely drug-resistant (PDR).<sup>23</sup> The blaOXA-51-like, blaOXA-23, and blaOXA-58 acquired resistance genes (hotspots) build up in sizable resistance islands on the bacterial chromosome. Due to its capacity to withstand desiccation, disinfectants, and powerful antimicrobials, CRAB has developed as an important hospital pathogen. In hospitalized patients, it can lead to a number of infections, including as pneumonia, wound infections, and blood infections. Mortality rates for the most prevalent HAP and bloodstream infections (BSI) are close to 60%.<sup>24</sup>

#### 7. Carbapenem Resistant *Pseudomonas aeruginosa* (CRPA)

*Pseudomonas aeruginosa* can cause rashes and ear infections in healthy people, but it can also lead to pneumonia and severe blood infections in immunocompromised patients, particularly those

hospitalized. It is one of the most problematic bacteria to get rid of.<sup>25</sup> Verona Since its discovery in the United States in 2001, Integron-Mediated (VIM) Metallo-beta-lactamase has been the most common carbapenemase found in *P. aeruginosa* around the world. Metallo-lactamases (MBL) carbapenemases were found in the US in 2010. These carbapenemase genes are located on movable genetic components that may move across species and bacterial strains, spreading resistance widely and presenting a severe threat to public health.<sup>26</sup>

## 8. Extended-spectrum beta-lactamases (ESBL) producing Enterobacteriaceae

The majority of transmissible beta-lactamases, or ESBLs, are resistant to beta-lactam medicines. The beta-lactam antibiotic was introduced in Europe in the 1960s, and within five years, resistance developed. After the patient (Temoniera) from whom it was collected, the first ESBL was given the name TEM. The most common Enterobacteriaceae bacteria that produce ESBLs include *Klebsiella pneumoniae*, *E. Coli*, and other Enterobacteriaceae bacteria.<sup>27</sup> In immunocompromised individuals and young children, *Klebsiella pneumoniae* is a bacterium that can cause potentially fatal nosocomial infections such as pneumonia and bloodstream infections. *E. coli* and urinary tract infections are commonly connected. The widely antibiotic-resistant *E. coli* sequence type 131 (ST131) subclones H30, H30-R, and H30-Rx have spread quickly around the world, with H30 being the most prevalent.<sup>27</sup> The most popular medicines for treating ESBL bacteria up until recently were carbapenems and fluoroquinolones, however antibiotic resistance to these drugs is spreading across the globe. For carbapenem-resistant Enterobacteriaceae (CRE), colistin is now the only therapy of last resort, however resistance has been discovered in a number of countries and regions.<sup>28</sup>

## 9. Newer Antibiotics

### 9.1. Single target antibiotics

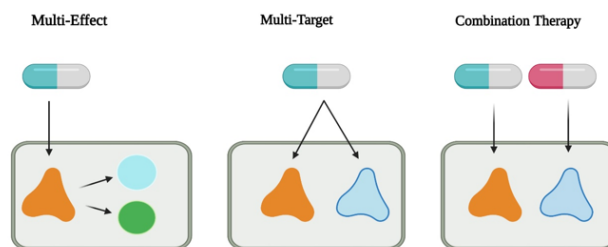
Drug development and screening procedures have traditionally necessitated the use of antibiotics that target a specific protein. Single-target antibiotics were marketed as the best option, with the idea that more specific targeting meant fewer side effects.<sup>29</sup> As a result, genomics has been the main force behind the development of antibiotics, with single protein targets being researched. However, drugs with several or complex targets were thought to be non-specific and unsuited for further advancements. The awareness that candidates with numerous targets are desirable to examine because to their slower rates of resistance development, however, has emerged in recent decades as a result of the too fast emergence of resistance to antibacterial with a singular target protein.<sup>30</sup> Long-standing antibiotics with

a good track record in the clinic virtually ever target just one molecule; for instance, beta-lactam antibiotics often target several transpeptidases, whereas quinolones inhibit both topoisomerases II and IV. Sulphonamides, which target a folate synthesis enzyme, and rifampicin, which targets RNA polymerase, are two antibiotics that target a single protein and are renowned for rapidly developing resistance. They are frequently employed in combination regimens because of this.<sup>31</sup>

Antibiotics found in nature can target a wide range of organisms. Antibacterial peptides are the most common type of natural antimicrobial agent and are found in almost all species. These chemicals attack complex bacterial structures such as the cell wall, cell membrane, or both.<sup>32</sup> Additionally, producers of antibiotics typically combine different compounds with similar structural properties. Examples of this include

1. Gramicidin (which comprises gramicidin A-C and tyrocidine A-D).
2. Polymyxins (which, depending on the kind of polymyxin, are composed of a vast number of peptides with minor structural variations).
3. Tyrothricin.

For many different reasons, antibiotic combinations are often utilized in clinical practice. For instance, trimethoprim and sulphonamides are routinely used together with penicillin to stop the fast emergence of resistance from a single target mutation. However, because of their synergistic effects, erythromycin and penicillin are routinely provided together.<sup>33</sup> It is crucial to thoroughly research multitarget approaches to treat resistant germs as illnesses grow more difficult to cure with a single antibiotic<sup>34</sup> (Figure 3).



**Figure 3:** Newer antibiotics used to target the superbugs

### 9.2. Multitargeted antibiotics

We discriminate between various levels of multitargeting when evaluating medicines with several targets. Although this molecule or structure only has one target for medications that are naturally multi-effective, it also comprises several processes that are all impacted by its blockage. The two forms of multitarget antibiotics bind to different molecules involved in numerous biological



processes to target several isoenzymes or highly associated proteins in the same pathway. Multifunctional chemicals not only have a direct antibacterial target but also indirect antibacterial actions including anti-inflammatory characteristics. Table 2 provides a list of some of the clinic's most commonly utilized drugs in these areas.<sup>35</sup>

The most frequent antibacterial target is the cytoplasmic membrane, and blocking it can have various physiological effects. The clinic uses only a few membrane-active antibiotics systemically. Investigations have been done on several of their various impacts on bacterial cells. The structurally similar peptide gramicidin S, which has less of an influence on membrane potential and fluidity and does not cause distinct membrane holes, only affects the proteins involved in cell division and the creation of the cell envelope.<sup>36</sup> Daptomycin, one of the few membrane-targeting antibiotics used systemically, has been shown to interfere with fluid membrane microdomains that house the machinery necessary to create lateral cell walls, causing peptidoglycan and phospholipid formation to be disrupted.<sup>37</sup> Most of the antibiotics in the above list focus on a single biological component with many roles. On the other hand, many antibiotics have the ability to bind to two or more distinct substances. Quinolone antibiotics, including the inhibitors of cell wall formation Fosfomycin and D-cycloserine, target topoisomerases II and IV, which, respectively, target DNA supercoiling and resolved DNA concatemers.

There are a number of antibiotics that can obstruct two or more distinct targets that are unrelated to one another in the same pathway or process. Target-based resistance in two separate compounds is more difficult to build. The capacity of bacteria to effectively adapt to stress is constrained by the need to respond to two separate stress responses in order to prevent antibiotic activity.<sup>38</sup> Such medications are commonly used in clinics, and novel compounds with many targets are frequently discovered. As a last option, antibiotics known as polymyxins, such as colistin and polymyxin B, are used to treat multi-resistant Gram-negative infections.<sup>39</sup>

Due to the therapeutic effectiveness of these multitarget antibiotics, efforts are being made to develop multiple target medications. These may be cleavable compounds with a different target than the cleavage product or stable hybrids that integrate two actions into one molecule. Other forms of Cefilavacin are used in clinical practise for difficult skin and soft tissue infections. Cadazolid is a stable quinolone-oxazolidinone hybrid that is now being investigated in phase III clinical research to treat *Clostridium difficile* infections.<sup>40</sup>

### 9.3. Combinations of antibiotics

Combination regimens are becoming more used in the clinic, mostly to increase effectiveness against infections

with multiple resistances and inhibit the emergence of new resistances. For example, sulphonamides and trimethoprim are routinely used as a treatment for urinary tract infections.

## 10. Antibiotic Synergism

Inhibiting the same target molecule at several binding sites is one suggested mechanism for synergistic effects. An illustration is the interaction of the peptidoglycan precursor lipid II with teicoplanin, plectasin, and dalbavancin<sup>41</sup>. When two medications block different targets in the same pathway, this is another illustration of synergy. An example of this is the antituberculosis drug D-cycloserine, which prevents the intracellular phase of peptidoglycan synthesis. Penicillin and the ribosome inhibitor erythromycin are two examples of medications that interact synergistically in some situations<sup>42</sup>. The most recent identified mechanism causing antibiotic synergy is an increase in target accessibility. (Figure 4)

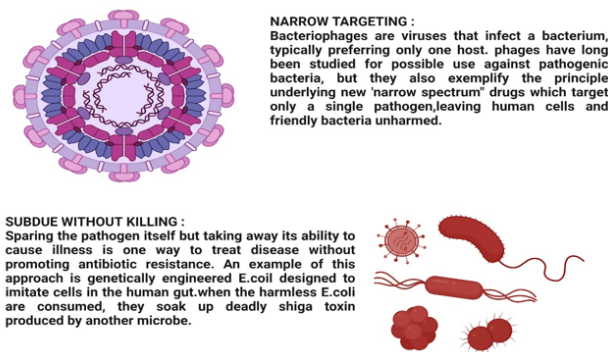


Figure 4: Novel ways to beat superbugs

## 11. Permeabilizers

Potentiating antibiotic combinations have become more well-liked recently in addition to synergistic antibiotic combos. Sensitizers or resensitize bacteria to currently used antibiotics, potentiators generally target innate or acquired antibiotic resistance mechanisms.<sup>43</sup> Colistin and polymyxin B, two commonly used antibiotics, are known to damage Gram-negative bacteria's outer membrane. Both synergize with antibiotics that target intracellular targets, partly because of increased outer membrane permeability.<sup>44</sup>

## 12. Sensitizers

An alternate method for enhancing their effectiveness is to make microorganisms more susceptible to the effects of currently used antibiotics. By blocking the stress response pathways in bacteria, antibiotic exposure-induced adaptation and survival can be prevented. Only a few numbers of DNA repair inhibitors have been identified

**Table 2:** Antibiotics and their Mechanism of action (MoA).

Antibiotics	Targets	MoA
Tetracycline	Ribosome and Membrane	Blocks attachment of loaded aminoacyl tRNA to the A-site of the ribosome; also impairs membrane
Ciprofloxacin	Topoisomerase II and IV	Inhibits topoisomerase II and IV
Penicillin	Penicillin-binding proteins	Several penicillin-binding proteins are inhibited, which prevents loaded aminoacyl tRNA from attaching to the ribosome's A site and damages membrane function.
Clindamycin	50S rRNA	Anti-inflammatory
Macrolides	50S rRNA	Anti-inflammatory and Immunomodulatory

to till date. For instance, it has been demonstrated that ciprofloxacin is more effective against *Listeria monocytogenes* because p-coumaric acid blocks RecA from binding to DNA in this pathogen. Zinc inhibits RecA's capacity to bind to single-stranded DNA, according to another study, suggesting that zinc ionophores may one day be useful.<sup>2</sup>

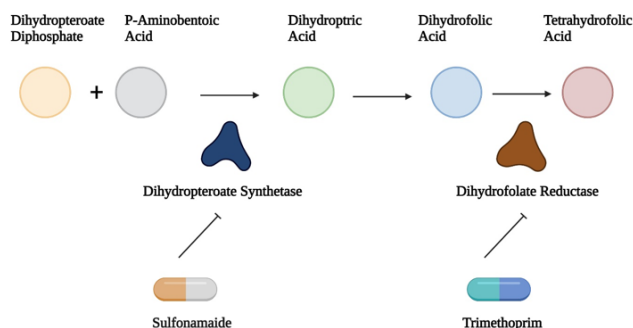
On the other hand, the quantity of external zinc affects the cytotoxicity and efficacy of zinc ionophores. Finding inhibitors of these systems that may be used as antibiotic potentiators has been the subject of a microscopic investigation. Even though multiple stress response systems have been related to antibiotic adaptation and resistance. This approach needs additional examination, given the pressing need for novel antibacterial methods.<sup>45</sup>

### 13. Anti-Resistance Agents

Directly attacking the bacterial resistance mechanisms is a similar tactic that is far more often used. The suppression of lactamase activity is the most well-known example.<sup>46</sup> It was the first resistance-busting technique applied in a clinic, having established the field. Except for synergistic combinations with the outer membrane-permeabilizing peptides colistin and polymyxin B, it is also the only antibiotic and potentiator combination in clinical use.<sup>47</sup> (Figure 5). More research is required to completely comprehend the function of multidrug efflux pumps and their interactions with other resistance mechanisms, such as the outer membrane, in order to move forward with effective inhibitor design.<sup>48–50</sup> (Tables 1 and 2 in supplementary material is a list of the hybrid compounds with some of the Examples)

### 14. Conclusion

The discovery and development of antibiotics for the treatment of bacterial illnesses must rank among the most important medical advances of the 20th century. Unfortunately, as the century approaches, bacterial resistance is on the rise, putting many of our current antibacterial treatments in danger. Additionally, the discovery of brand-new antibiotics has lagged behind the growth of germs that are resistant to them. The discovery



**Figure 5:** Prevention resistance

of novel drugs is necessary because antibiotic-resistant pathogens present a serious threat. Numerous novel approaches to target different substances in bacterial cells have been developed and are being researched. These strategies, which range from dual-activity hybrid compounds, natural multitargeting drugs, and antibiotic adjuvants to antibiotics with a variety of downstream effects, have shown promise and offer hope for antibiotic research. Recent research has expanded the concept of polypharmacology by developing antibiotic adjuvants with several mechanisms, such as outer membrane permeabilization and efflux pump inhibition, that work in concert to raise the intracellular antibiotic concentration. In-depth research is necessary to properly understand the complex mechanisms underlying some of these diverse activities, which provides an essential lesson. While developing novel therapies, we should not fear complex mechanisms and numerous targets but rather work to maximize their potential. Any drug recently approved for clinical use has the risk of acquiring resistance. The only long-term, practical choice is to follow it. This will call for considerable adjustments in the way these therapies are applied, such as the introduction of stewardship initiatives to encourage responsible application and more targeted therapy. Furthermore, implementing appropriate preventive measures like vaccines and quicker diagnostic tools, as well as improving hygiene and reducing the use of antibiotics in animals, will be the only way to safeguard the usefulness of antibiotics for future generations and guarantee a

healthy future for the global population. The molecular, evolutionary, and ecological factors that control the spread of antibiotic resistance must also be better understood.

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None.

### 16. Conflict of Interest

None.


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