

Global governance is necessary to coexist with superbugs

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Abstract. Antibiotics have become the main drug for humans to combat bacteria since their discovery. However, because of the abuse of antibiotics and the increase in bacterial resistance, a variety of superbugs have emerged, and refractory infections have become more and more common. The spread of AMR has become an international public health crisis. This article reviews the research progress on the emergence and current status of superbugs, as well as the important role of antibiotic resistance in global health. Emphasize the need for global governance mechanisms to mitigate the emergence and spread of MRSA, VRE, and *Pseudomonas aeruginosa* in response to borderless threats such as superbugs and antibiotic resistance.

Keywords: Antibiotics; Drug resistance; Superbugs; Global governance.

1. Introduction

Superbug resistance is a very rare and invincible global problem that poses a threat to entire societies. MRSA, VRE, and *Pseudomonas aeruginosa* are the most deadly infectious strains. The second half of the 20th century saw two major developments in the field of infectious diseases: the discovery of antibiotics and the emergence of antibiotic resistance in pathogenic bacteria. In 1929, synthetic antibiotics emerged, and a microbiological platform for antibiotic production was established when British bacteriologist Fleming discovered a substance capable of effectively inhibiting bacterial growth for the first time. Subsequently, during the Second World War, Fleming, along with two other scientists, Florey and Chinn, meticulously purified penicillin and developed it into a medicinal drug that could effectively combat bacterial infections. Antibiotics are small molecules of microbial origin that can inhibit the growth of and even selectively destroy other bacteria at low concentrations (Reygaert, 2018). The discovery of antibiotics and their wide application in public health has undoubtedly become an important milestone in the history of modern medicine and is regarded as one of the most influential achievements of the 20th century. This epoch-making breakthrough not only greatly improved human health but also profoundly changed the knowledge and understanding of disease treatment and prevention (Uddin et al., 2021).

2. The emergence of superbugs

The widespread use of antibiotics in public health plays a crucial role in the prevention and control of the spread of infectious diseases. Antibiotics are natural products produced by microorganisms or their semi-synthetic derivatives, and these chemicals are present within the natural environment for long periods of time. As a result, bacteria need to evolve resistance to sustain themselves. Antibiotic resistance is responsible for hundreds of thousands of deaths each year, and the number of deaths due to antibiotic resistance will continue to increase as bacterial resistance develops. Antibiotic resistance has become a major problem, posing a serious threat to human life and economic livelihood. Bacteria with strong adaptive ability gradually develop into mono-resistant, multi-resistant, pan-resistant, or even fully drug-resistant bacteria through changes in genetic material and structural components.

Superbug does not specifically refer to a particular type of bacteria but refers to bacteria that are resistant to multiple antibiotics, also known as "multi-drug-resistant bacteria." Genetic mutations are the root cause of superbugs. The development of bacterial resistance is the result of the widespread use of antibiotics in clinical practice, and the misuse of antibiotics has accelerated this process. The abuse of antibiotics makes the contradiction between antibacterial drugs and bacterial resistance in a

state of equilibrium intensified, and bacteria with drug-resistant ability also obtain the ability to be resistant to different antibacterial drugs through continuous evolution and mutation. This ability is continuously strengthened in the contradictory struggle, and the bacteria gradually go from single-drug-resistant to multi-resistant or even pan-drug-resistant and ultimately become drug-resistant superbugs (Davies .2010).

3. Current status of superbugs

The main superbugs of particular concern at present are:MRSA、VRE、MDRSP... The term "superbugs" denotes microorganisms exhibiting heightened morbidity and mortality rates, resulting from numerous mutations that confer substantial resistance to antibiotics specifically prescribed for their treatment. Consequently, these microorganisms have diminished therapeutic options, leading to extended hospital stays and increased healthcare costs. In certain instances, superresistant strains have further developed augmented virulence and enhanced transmissibility. Consequently, antibiotic resistance can realistically be viewed as a virulence factor.

3.1. MRSA

Methicillin-resistant *Staphylococcus aureus* has become the major cause of nosocomial infections globally; it is one of the top three problems worldwide, along with HBV and HIV. The multidrug resistance demonstrated by MRSA bacteria and the rapid evolution of drug resistance are important challenges in the clinical management of MRSA. *Staphylococcus aureus* was first discovered in 1880 in Aberdeen, Scotland, by surgeon Alexander Ogston from a patient's ulcerated abscess (Wertheim, 2005). MRSA can cause a series of suppurative infections, food poisoning, toxic shock syndromes, etc., and its suppurative infections range from small skin infections such as boils and carbuncles to severe infections such as tissue necrosis and necrotizing pneumonia. The suppurative infections range from small skin infections such as boils and carbuncles to serious infections such as tissue necrosis, necrotizing pneumonia, osteomyelitis, and endocarditis. The inappropriate use of topical antibiotics has resulted in a high rate of drug resistance in *S. aureus*, which has become an adverse factor affecting wound healing (Tong et al, 2015). The emergence of multi-drug-resistant bacteria such as methicillin-resistant *S. aureus* has made *S. aureus* a true superbug (Patel ,2009). MRSA has a high rate of infection and lethality. CDC statistics show that the mortality rate of MRSA infection has exceeded that of AIDS, Parkinson's, and murder (Arede et al, 2012).

3.2. VRE

Vancomycin-resistant enterococci (VRE) was first isolated in the late 1980s (Dixson et al,1985). VRE is rapidly spreading to the United States, Europe, and beyond, becoming one of the leading pathogens of infection within most hospitals worldwide. Because of its widespread resistance, VRE infections tend to occur in patients who are critically ill or have multiple concurrent systemic diseases. These infections are difficult to control effectively with conventional drugs, and the ability of VRE's drug-resistant genes to be transferred to other gram-positive bacteria via plasmids has led to a significant increase in patient morbidity and mortality. Thus, the presence of VRE poses a significant challenge to infection control within hospitals and to the prevention of multi-drug-resistant strains.

Enterococci can produce one or more of seven resistance genes to vancomycin, including *vanA*, *vanB*, *vanC-1*, *vanC-2*, *vanC-3*, *vanD*, *vanE*, etc., from which corresponding resistance factors can be expressed to produce seven different VRE phenotypes. Among them, *vanA* and *vanB* are the most common VRE phenotypes. These resistance genes can be transferred to other enterococci through plasmid-mediated mechanisms, resulting in polyclonal transmission. In particular, the *vanA* phenotype resistance is mediated by the transposon *Tn1546* and its analogues, which are usually located on VRE plasmids and can easily transmit resistance genes to other Gram-positive bacteria, such as *Staphylococcus aureus*, through splicing and transposition (Grayson et al,2010).

3.3. *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a Gram-negative bacterium with no pods, no spores, specialized aerobic, mostly flagellated, and capable of movement. *Pseudomonas aeruginosa* is widely distributed in nature. The bacterium is found in soil, swamps, animal and plant tissues, as well as in the skin, respiratory tract, and intestines of normal human beings. *Pseudomonas aeruginosa* is an opportunistic pathogen, and when the body's normal defenses are disrupted or the body's immune function is reduced, the bacterium is prone to infecting the host and often endangers the patient's life. *Pseudomonas aeruginosa* is capable of releasing a wide range of pathogenicity factors, including the secretion of enzymes, toxic chemicals, hemolysins, etc., which in turn cause complex pathophysiological changes in the host. (Dietrich et al,2006)

Pseudomonas aeruginosa is the main superbug found in hospital settings. The main risk factors for antibiotic-resistant superbugs have been found to cover the following: prolonged hospitalization, previous antibiotic treatment, failure to take antibiotics regularly as prescribed by a doctor, presence of comorbidities in the patient, prophylactic use of antibiotics, and the patient's dietary habits (Chandrasekhar et al, 2023). Statistics show that globally, 2 million people are infected with *Pseudomonas aeruginosa* each year, and 90,000 people die as a result of this infection (Horcajada et al,2019). All these factors may increase the risk of patients being infected with antibiotic-resistant superbugs and need to attract the attention of healthcare practitioners and the public at large.

4. Superbug resistance mechanisms and antimicrobial resistance

The proliferation of superbugs is closely related to antimicrobial resistance. The drug resistance mechanism of superbugs is the result of long-term bacterial evolution and is a means used by some bacteria to gain a survival advantage. Therefore, contact with antibiotics is the main source of acquired drug resistance in bacteria. There are two main forms of antibiotic resistance: natural resistance and acquired resistance.

4.1. Natural resistance

It refers to certain genera, strains, or individual bacteria within a strain of bacteria in nature that are naturally insensitive to certain antibiotics and have the genetic characteristics of bacteria. May be innate (usually expressed within the organism). It may also be mediated, i.e., the gene is normally present in the bacterium but is only activated to resistance levels after antibiotic treatment (Reygaert, 2018). It determines the antibacterial spectrum of antibacterial drugs. For example, intestinal-negative bacilli are resistant to penicillin, *Pseudomonas aeruginosa* is resistant to ampicillin, and streptococci are resistant to gentamicin.

4.2. Acquired resistance

It refers to the result that after bacteria are exposed to antibiotics, the bacteria obtain genetic material through the translation, combination, transcription, or mutation of their own chromosomal DNA, making themselves resistant to being killed by antibacterial drugs (Culyba et al, 2015). This kind of resistance Bacteria can develop high and multiple drug resistance through passage, transfer, dissemination, spread, and mutation of resistance genes. In addition to acquiring drug resistance through genetic mutation, bacteria can also spread drug resistance by carrying transferable genetic elements, including plasmids, transposons, and phages. These genetic elements themselves carry one or more resistance genes and are spread within *Salmonella* species or between bacterial species through horizontal gene transfer (HGT), resulting in the continuous broadening of the bacterial resistance spectrum and the enhancement of drug resistance. For example, MRSA is resistant to antibiotics such as methicillin.

5. Artificial intelligence combating superbugs

Scientists from the Broad Institute of Massachusetts Institute of Technology and Harvard University have utilized the power of artificial intelligence (AI) to screen millions of compounds and discover a new class of antibiotics (Wong et al,2023). This type of antibiotic can kill two different types of drug-resistant bacteria, bringing new hope for addressing the global challenge of antibiotic resistance. Scientists have tested the effects of over 39000 compounds on *Staphylococcus aureus* and three types of human cells from the liver, skeletal muscle, and lungs. These test data are used to train the AI model, enabling it to predict the antibacterial activity of compounds and their potential toxicity to human cells. After training, the AI model conducted computer simulation analysis on 12 million compounds and ultimately discovered 3646 compounds with ideal drug-like properties. More importantly, they also identified chemical substructures that can explain the properties of each compound. By delving into the chemical substructures of these compounds, scientists have successfully identified a new potential class of antibiotics and discovered two non-toxic compounds. The experimental results on mice showed that these two newly discovered antibiotics have significant therapeutic effects on both methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. Data shows that in 2019, over 1.2 million people died due to antibiotic resistance. It is expected that this number will continue to rise in the coming decades. Currently, only a few new antibiotics, such as oxazolidinone and lipopeptides, are effective against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*. This research achievement demonstrates the enormous potential of AI in the field of drug discovery. Through AI's guidance, scientists can not only predict the biological effects of compounds but also gain a deeper understanding of the chemical mechanisms behind them. This method is expected to accelerate the development process of new antibiotics and may also provide new ideas and methods for drug development in other fields.

The emergence of artificial intelligence (AI) and machine learning methods provides a promising opportunity to strengthen antimicrobial drug management and precision medical strategies, thereby addressing the current urgent crisis of antibiotic resistance. The development of this field has brought a new dawn to the medical industry, providing more scientific, precise, and efficient solutions for the management of antibiotics and precision medicine (Lv et al,2020).

Traditional antimicrobial drug management often relies on the experience and intuition of doctors, but due to the increasing severity of antibiotic resistance, this management approach is no longer able to meet current needs. AI and machine learning can deeply mine and analyze a large amount of clinical data and antibacterial drug information, accurately predict the occurrence of antibiotic resistance, and provide doctors with more scientific and reasonable medication recommendations. This not only helps to improve the efficiency of antibiotic use but also reduces drug abuse and misuse, thereby reducing the development of drug resistance and resisting the proliferation of superbugs (Marra et al, 2023).

AI utilizes advanced algorithms and models, which can provide personalized treatment plans for patients based on their specific conditions and disease characteristics. In the field of antibiotics, this means that the most suitable antibiotics can be selected for each patient, thereby improving treatment effectiveness and reducing the risk of drug resistance. In addition, AI can also analyze data from various aspects, such as patient genes and lifestyle habits, to predict patient reactions and effects to antibiotics, providing more comprehensive and accurate information for clinical decision-making. These technologies can not only improve the efficiency and therapeutic effect of antibacterial drugs but also reduce the risk of drug resistance, providing new solutions for addressing the urgent crisis of antibiotic resistance.

6. The risk of AMR

Pseudomonas aeruginosa and methicillin-resistant superbugs, two powerful pathogens, have been proven to be the main representatives of superbugs in hospital environments. These super-bacteria

are a concern because they have developed strong resistance to traditional antibiotics, making conventional treatment methods ineffective. A recent study delved into these drug-resistant superbugs, revealing the main risk factors behind them and providing valuable insights for preventing and controlling their spread in hospital environments.(Chandrasekhar et al,2023).

Research has found that long-term hospitalization is a major risk factor for the spread of antibiotic-resistant superbugs. Long-term hospitalized patients often require frequent use of antibiotics due to the severity and complexity of the disease itself, thereby increasing the risk of drug resistance. In addition, various devices and surfaces in the hospital environment may become carriers of superbugs, making these patients more susceptible to infection.

Having received antibiotic treatment in the past is also an important risk factor. Frequent use of antibiotics may not only lead to bacterial resistance but also disrupt the balance of microorganisms in the human body, giving some previously harmless bacteria the opportunity to transform into harmful superbugs.

Not taking antibiotics according to the doctor's prescription is also a factor worth noting. Not following the prescription to take antibiotics may prevent bacteria from being completely killed, thereby giving them the opportunity to develop resistance. This behavior not only increases the risk of patients being infected with superbugs themselves but may also pose a threat to the entire hospital environment.

7. Discussion

In 2015, the World Health Organization (WHO) solemnly launched the Global Action Plan for Antimicrobial Resistance (WHO.2015), marking a firm and powerful step toward addressing the major public health challenge of antibiotic resistance worldwide.

Antibiotic resistance has become a serious problem facing the world. With the growing number of antibiotic-resistant bacteria, infectious diseases are becoming intractable and pose a serious threat to human life and health.

The key to reducing superbugs and antimicrobial resistance is to reduce the emergence and spread of resistance and to increase global awareness and response capacity to the problem. (Majumder et al,2020). The following is a brief discussion of some actions.

One is to strengthen surveillance and evaluation. Each country needs to establish a robust antibiotic resistance surveillance system to track the types, levels, and distribution of antibiotic-resistant bacteria in real time and to provide solid support for the scientific formulation of prevention and control strategies.

The second is to promote the rational use of medicines. By developing and promoting guidelines for the use of antibiotics, strengthening professional training for medical personnel, reducing unnecessary use, and reducing the risk of antibiotic resistance,.

The third is to strengthen international cooperation. Countries need to strengthen cooperation in areas such as drug resistance research and new drug development, share experiences and data, and work together to address global challenges.

The fourth is to enhance public awareness. Through extensive publicity and education, enhance public awareness and prevention of drug resistance, and jointly maintain public health safety (Fletcher-Miles.2019).

In addition, the preventive use of antibiotics is also a factor to consider. Although preventive use of antibiotics can reduce the risk of certain infections, excessive or improper use may lead to bacterial resistance, thereby increasing the risk of infection with superbugs.

The WHO has provided clear guidance for global efforts to address drug resistance issues. However, achieving this goal requires the joint efforts and cooperation of governments, medical institutions, researchers, and the general public of various countries. Only by working together and establishing a global governance mechanism can we effectively reduce the occurrence and spread of

antibiotic resistance, face new borderless security threats, and effectively safeguard human health and life safety.

8. Conclusion

With the rapid advancement of medical science and technology, antibiotics have built a solid defence for mankind against diseases. However, the misuse of and over-dependence on antibiotics have become a major hidden danger that has exacerbated the global health crisis. This crisis has attracted great concern and attention from countries all over the world. The misuse of antibiotics not only encourages the survival and reproduction of pathogenic bacteria, but also makes these microorganisms gradually evolve strong drug resistance, giving rise to the so-called "superbugs". These superbugs are increasingly resistant to traditional antibacterial drugs, posing an increasingly serious threat to human health. The number of deaths caused by drug-resistant infections is rising year by year, and if not controlled in a timely manner, they will pose a serious threat to human lives and health and well-being. In the face of this grave situation, global governance has become a task that brooks no delay. In the face of the threat of superbugs, it has become our common mission to establish a global governance system. This is a serious challenge concerning human health and life safety, which requires the participation and efforts of each and every one of us. Let's join hands to tackle this global health crisis and work hard to protect human health and life safety.

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