

Research on the history and countermeasures of superbacteria

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Abstract. Superbugs are bacteria that are highly resistant to antibiotics. With the widespread use of antibiotics around the world, the resistance of superbugs is also evolving and developing, and some scholars now predict that we may enter a "post-antibiotic era" in 2050. Superbugs not only pose a threat to individual health, but also pose a major concern to public health and healthcare systems. According to statistics, the number of deaths due to bacterial resistance has reached 1.29 million in 2019. According to this development, the number of deaths per year is expected to be 10 million by 2050, and the cumulative loss of global GDP will reach 100 trillion US dollars. This article will introduce the history of superbugs, the public health problems faced by superbugs, and discuss the feasible ways to combat superbug resistance, in order to call for people's attention to superbugs as a global public health threat, increase people's understanding of superbugs, and improve people's sensitivity to the use of antibiotics.

Keywords: Antibiotics; Superbugs; Public health.

1. History of the development of superbugs

A long time ago, every infected wound on a person's body could be life-threatening, and countless people died as a result, but since Fleming first discovered penicillin in 1928[1], people have had a way to fight bacterial infections. The first generation of penicillin came out in the 1940s, marking the beginning of the golden age of antibiotic development, in which penicillin shone in the course of World War II, launched an irreplaceable therapeutic effect, saving countless soldiers who should have died of bacterial infections. In the 1950s, under the approval of the US Food and Drug Administration (FDA), antibiotics were first widely used as feed additives in the field of animal breeding, playing an important role in the prevention of animal diseases[2].

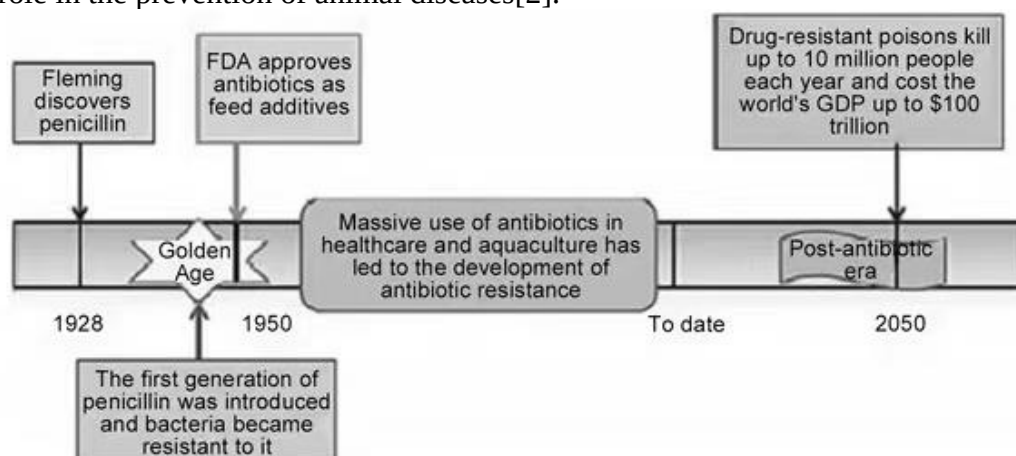


Fig.1 The history of human society from the "discovery of antibiotics" to the "golden Age" and then to the "post-antibiotic era"[3]

However, since the discovery of antibiotics, bacteria have begun to accelerate the evolution of drug resistance, from single resistance to multiple resistance, from the initial methicillin-resistant *Staphylococcus aureus* to the later multi-drug resistant *Streptococcus pneumoniae*, multi-drug resistant tuberculosis bacillus, etc., bacteria in natural selection step by step to improve their defense structure, so that people are increasingly unable to do anything about them. Some scholars estimate that by 2050, we may enter a post-antibiotic era of "no drugs available" because of bacterial resistance[3].

2. Superbugs pose public health problems

2.1. The gap in antibiotic discovery

The remarkable antibacterial effect of penicillin in World War II led to the search for new antibiotics, and a large number of new antibiotics were discovered and used from the 1940s to the 1960s. Unfortunately, this 20-year "golden age" was followed by a "blank period" of antibiotic discovery. During this gap, the discovery of new antibiotics slowed down, while bacteria continuously evolved new resistance mechanisms through mechanisms such as natural selection and horizontal gene transfer. As the level of development of new antibiotics fails to keep pace with the development of resistance in new armies, clinicians are faced with fewer and fewer treatment options, prompting healthcare systems to reevaluate antibiotic use strategies and strengthen infection control measures to prevent the further spread of superbugs[4].

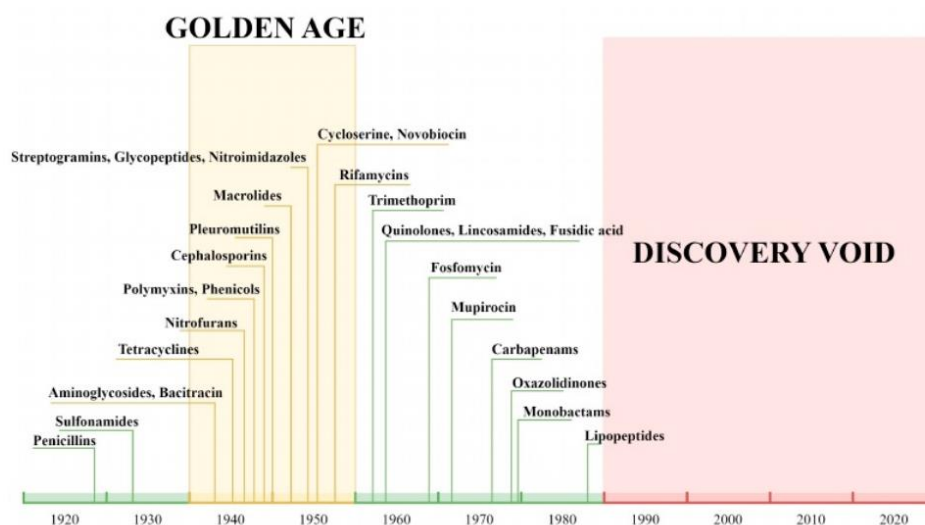


Fig. 2 Timeline showcasing the discovery of various antibiotic classes used clinically. The “golden age” spans the period from the 1940s to 1960, during which sources of half of today’s commonly prescribed drugs were discovered. In contrast, the “discovery void” encompasses the period from roughly 1990 to the present, a time in which limited new clinical discoveries have been made [4].

2.2. Overuse of antibiotics

2.2.1 Overuse of antibiotics in the clinical field

In the early years of China, we often heard that the medical skills of township or community doctors were very "divine", and the patients did not have a headache or fever after an Injection of antibiotics, but should antibiotics be used no matter what infectious diseases? Of course not. Although clinical use is the main use of antibiotics, however, in the face of infection, some doctors directly use antibiotics to treat patients regardless of the severity of symptoms, which will inevitably lead to excessive and unnecessary use of antibiotics, thus accelerating the development and evolution of superbugs. In the short term, antibiotics are indeed the most effective and direct means for clinical fight against infectious diseases, with the obvious advantages of quick and good results. However, in the long term, superbacteria caused by the abuse of antibiotics will further compress the drug choice of future doctors, and there is nothing to do when the real threat of death is faced. In the investigation and analysis of antibiotic use in grass-roots hospitals by Yang Yanlin, Wang Chao et al., the utilization rate of antibiotics in hospitals was 39.64%, and the drug utilization index of all departments was > 1. The proportion of antibiotic treatment course > 14 days was 9.85%, and the number of antibiotics used more than 3 kinds accounted for 4.81% [5]. These indicate that there is still a problem of overuse of antibiotics in primary hospitals in China.

The same is true in the United States, where, according to two papers published in Oxford Press, of 326,173 residents admitted to 1,348 nursing homes in 2017 (9 percent of all nursing homes in the

United States), 45 percent received antibiotics, including a long-term course of antibiotics (> 30 days) accounted for 5% of the course of treatment and 30% of the total dispensing days. If excluded; A 30-day course with an average duration of 7.5 days per course [6]. In the 2018 survey, out of 3,452,011 outpatient emergency departments at 49 U.S. children's hospitals, 62,648 (1.8%) were prescribed parenteral antibiotics, an average of about 1 in 55 outpatient pediatric emergency department visits [7]. It can be seen that the clinical use of antibiotics is quite frequent in the United States, both in the elderly and in children.

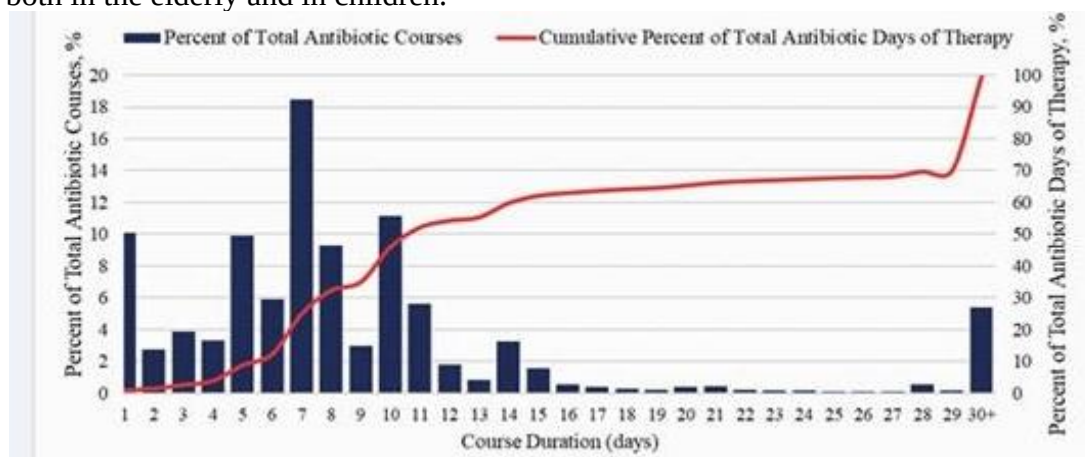


Fig. 3 Distribution of antibiotic course duration and cumulative percent of total antibiotic days of therapy for 324,306 antibiotic courses dispensed to 1,348 nursing homes from a long-term care pharmacy in 2017.[6]

According to the above survey and data, antibiotics have a very high frequency in clinical treatment in the East and West, and the extensive and large-scale clinical use will inevitably accelerate the evolution of bacterial resistance, resulting in the birth of more superbugs.

2.2.2 Overuse of antibiotics in animal husbandry

As mentioned above, in 1928, Fleming found penicillin in the Second World War, which played a great role in medicine and inspired the extensive exploration of new antibiotics, thus ushered in the "golden age" of the development of human antibiotics. With the continuous discovery of antibiotics such as chloramphenicol (1948), oxytetracycline (1950) and nmycotin (1950), No longer satisfied with the clinical use of antibiotics, the target has shifted to the animal husbandry to deal with the intensive animal husbandry effects (in the form of the spread of pathogenic microorganisms) caused by the increase in population. However, the widespread use of antibiotics in farming has further accelerated the evolution of antibiotic resistance.

Antibiotic resistance spreads in two ways: vertically and horizontally. Vertical transmission, mainly through the transfer of genetic material from the parent organism to the offspring organism. In aquaculture, where vertical transmission is most common, it directly results in the transmission of antibiotic resistance whenever farmed animals reproduce. Horizontal transmission is mainly achieved by combination, transformation and conduction. Combination refers to the formation of a stress environment in the animal gut due to the overuse of antibiotics in aquaculture that allows resistant bacteria to transfer their resistance genes to other bacteria of the same or different species through coupling. When a virus transfers DNA from one host bacterium to another, the same virus can accidentally infect both bacteria. In addition, integration of foreign DNA into bacteria can also facilitate the transfer of antibiotic resistance genes[8].

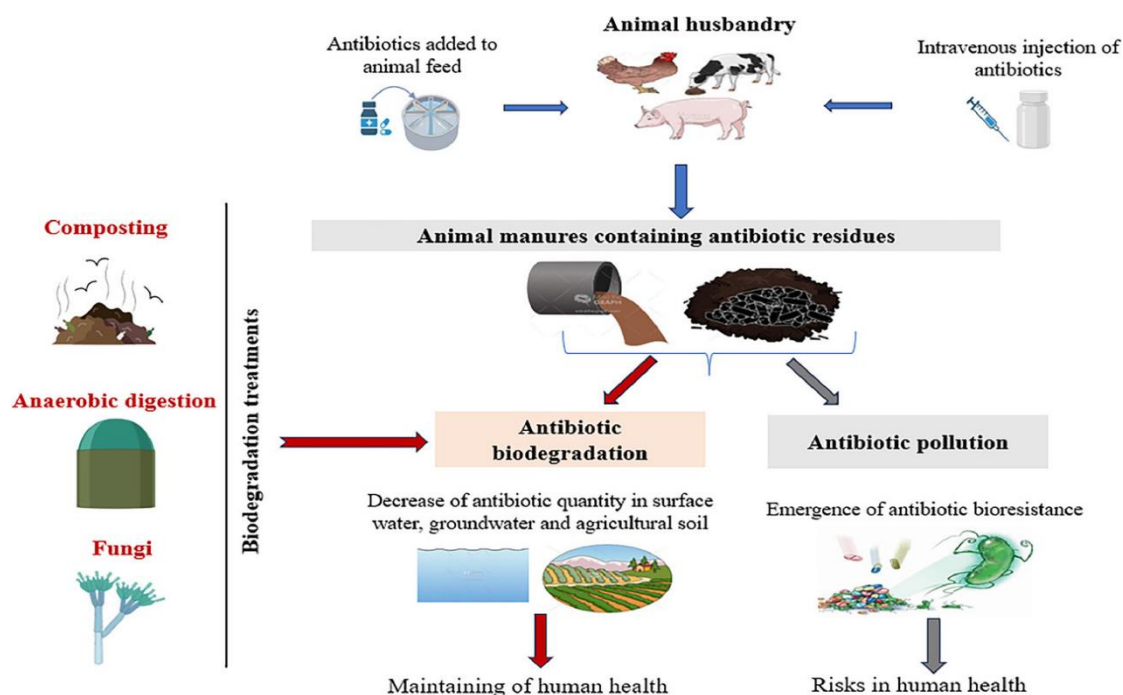


Fig. 4 The flow route of antibiotics in aquaculture[8]

The use of antibiotics in animal agriculture, either as feed additives or through direct injection, leads to an increased presence of antibiotics within the animals. Consequently, the emergence of drug-resistant bacteria facilitates horizontal transmission of antibiotic resistance among individuals and vertical transmission from parents to offspring during reproduction. While some microorganisms such as fungi and anaerobic bacteria biodegrade certain antibiotics and drug-resistant superbugs present in feces excreted by infected animals, a portion remains undegraded and enters the ecological environment. Humans can become contaminated directly or indirectly by consuming meat from these animals or vegetables grown using their fecal matter.

3. Viable solutions

3.1. Make use of digital tools for science popularization

In many township and community hospitals in underdeveloped areas, it is a phenomenon that some doctors will blindly prescribe drugs containing large amounts of antibiotics to treat patients' symptoms, most of which do not need to be treated with antibiotics. I believe that this situation cannot be blamed solely on the community physician, because for some patients, only an immediate treatment that works will persuade them to remain in care and maintain trust in physician professionalism. If doctors adopt other palliative and conservative treatment methods, some patients may lose patience and give up treatment. In this case, the misuse of antibiotics is actually a humanistic problem caused by a lack of knowledge and popular science. Therefore, in today's information age, the science of "superbugs" is essential, and digital tools are the most rapid, effective, and widespread way to disseminate knowledge.

With COVID-19 limiting outreach and education activities, Superbugs websites have been created at Cardiff University and Swansea University to increase public understanding of microbes and their drug resistance. The site has been online for two years and has attracted more than 19,000 online visitors, 33 visitors and more to 500 pages and generated more than 77,500 Twitter impressions. As shown in Figure 5, when the website was just established, it was found that 79% of the 247 children gave "excellent" or "good" evaluation, and 38% were very willing to share with their classmates [9], which fully proved the great potential of digital science knowledge.

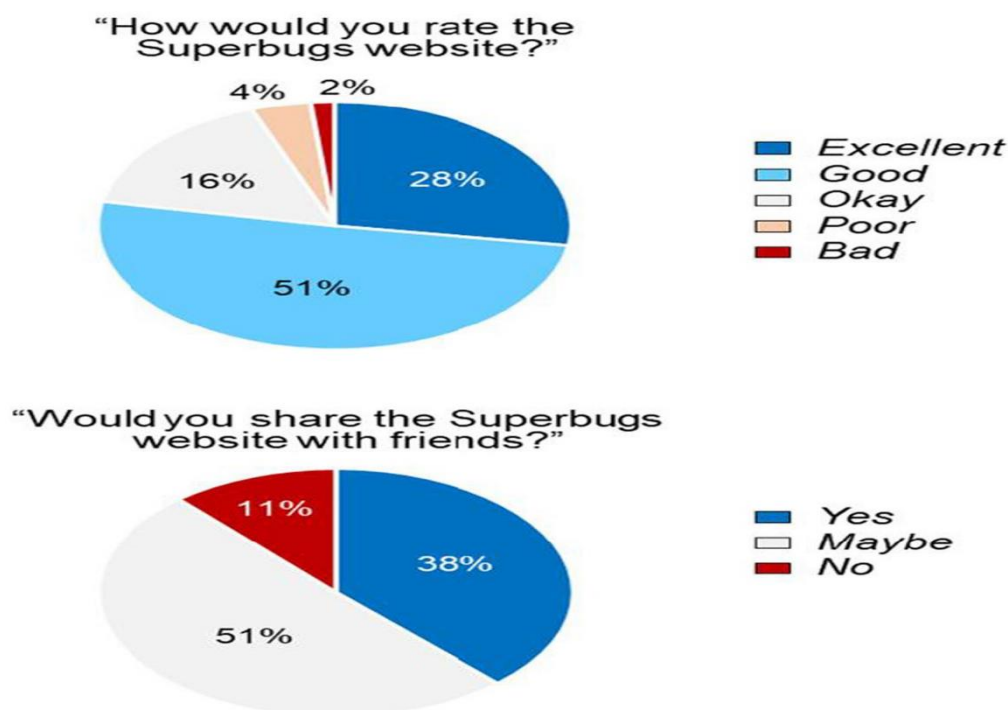


Fig. 5 Feedback from 247 pupils attending primary and secondary schools in Wales regarding an early prototype of the Superbugs website. Pupils were from schools including Deri View Primary School (Abergavenny), Tredegarville Church in Wales Primary School (Cardiff), Ysgol Clywedog (Wrexham), and St Alban's Roman Catholic High School (Pontypool) and completed feedback forms in July 2021, three months before the official launch of Superbugs.online.[9]

In addition, the use of games to popularize the knowledge of superbugs is also a good choice. The Commonwealth Antimicrobial Stewardship Partnership (CwPAMS) has developed a board game to encourage players to understand the seriousness of antimicrobial resistance. When queried about their enjoyment of playing AMS games, an overwhelming majority (91.9%) of the respondents affirmed their positive experience. Additionally, a significant proportion (75.7%) acknowledged that they had acquired a deeper understanding of AMS through gameplay, while 93.3% of the participants expressed willingness to share their game experience with colleagues[10]. The SWICEU team has achieved satisfactory results in these five years of communication and gamification activities. In terms of media dissemination, they have been published in more than 40 different Spanish media. In the 2020-21 school year alone, the total media audience for news about SWICEU team activities reached 3,362,938. In addition, the information content of SWICEU team activities between 2017 and 2022 has been viewed 185,475 times in the science news section of Actualidad CEU, the website of CEU UCH, the most viewed content on this site[11]. The aforementioned examples undeniably demonstrate the remarkable efficacy of digital games in promoting the popularization of science.

Imagine if we could further improve our new media technologies, or use more digital tools (such as TikTok, Twitter, TV, etc.), could we make people more willing to share what they learn from them, thus further popularize science? Without a doubt.

3.2. Control pharmaceutical wastewater containing antibiotics

As mentioned above, the abuse of antibiotics mainly stems from two aspects: clinical practice and animal husbandry. Such abuse can accelerate the development of bacterial resistance, and antibiotics are indispensable both in clinical practice and in the aquaculture industry. Therefore, the preparation process of antibiotic drugs is crucial. However, it is difficult to avoid the production of wastewater containing antibiotic components during the preparation process. If the waste water enters the natural environment without proper treatment, it will lead to environmental pollution. Therefore, I call for strict control of pharmaceutical wastewater to combat the public health crisis caused by superbugs.

Our surface waters become contaminated when antibiotic-contaminated pharmaceutical wastewater is discharged through a series of physical and natural changes in nature and enters the water cycle. Whether rivers, glaciers, lakes or swamps, they can contain large amounts of antibiotics. According to an article in *Frontiers in Microbiology*, sea urchins have been found to contain drug-resistant *Shewanella* [12]. Sea urchins are consumed in many countries and pose a threat to human health. Of greater concern is that this is just one example of environmental antibiotic accumulation in humans through the food chain.

Concerted efforts from pharmaceutical manufacturers, governments, and the international community are imperative to address the issue of pharmaceutical wastewater discharge. In terms of treatment strategies, advanced oxidation processes (AOP), membrane filtration combined with activated carbon adsorption, chlorination and ultraviolet disinfection, biological treatment, and other methods have significantly enhanced wastewater treatment efficiency while curbing the proliferation of antibiotic resistance. Regarding industry guidance, the Antimicrobial Resistance Industry Alliance has collaborated with the British Standards Institute (BSI) to develop Antibiotic Manufacturing Standards that offer comprehensive instructions for antibiotic production. Furthermore, stringent regulatory measures on active pharmaceutical ingredient (API) emissions advocated by the AMR Industry Alliance and other organizations aim to combat antibiotic generation. On an international level, WHO in collaboration with FAO has formulated a Global Plan of Action to tackle antimicrobial resistance; meanwhile, the United Nations Environment Programme oversees WATER - a Global Monitoring System for Freshwater Environments enabling member states to comprehensively monitor water quality and report observations to UNEP's global Water quality database[13]. The collective endeavors of these global organizations may still fall short, but fortunately we are all dedicated to safeguarding the natural environment, human health, and public well-being. Over time, it is anticipated that they will further enhance their mechanisms and more effectively accomplish their missions, thereby making substantial contributions to global human welfare.

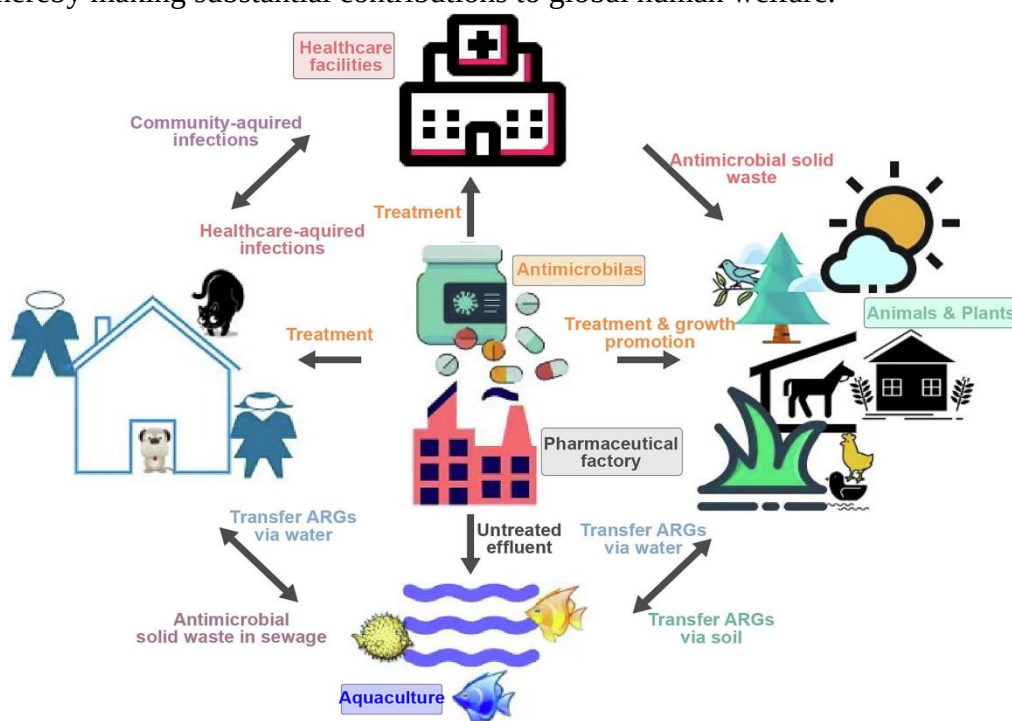


Fig. 6 The spread of antibiotics in medical supplies in nature and human society [13]

3.3. Balance the level of global public health development

The impact of superbugs as a global public health problem transcends local or regional boundaries and is universally significant. However, not all countries possess robust responses when confronted with this challenge.

Resource-rich countries often possess more advanced healthcare facilities, superior infection control measures, and more effective strategies for antibiotic utilization - factors that contribute to the deceleration of superbug generation and dissemination. However, in the presence of substandard medical conditions, rampant misuse of antibiotics, and inadequate surveillance systems, superbugs proliferate at an accelerated pace and become arduous to manage within low-resource areas such as township community hospitals in underdeveloped regions.

In addition, the global movement of populations exacerbates the cross-border transmission of drug-resistant bacteria. The findings indicate that social factors, including migration, have an impact on the health of approximately 12% of the global population[14]. Furthermore, travelers may bring back drug-resistant bacteria from their trips, particularly if they have received antibiotic treatment during their journey, thereby further contributing to resistance development. If the destination country's public health system fails to effectively identify and control the spread of these bacteria, there is a risk of rapid emergence and dissemination of superbugs within local communities.

Globalized supply chains can also act as pathways for the transmission of drug-resistant bacteria. International trade in food and medicine can inadvertently facilitate the transportation of superbugs from one country to another, posing a significant challenge to countries that may lack preparedness in dealing with this threat.

To address the challenges posed by this imbalance, the international community needs to increase cooperation and share surveillance data and best practices. At the same time, improving health care around the world, especially in resource-limited countries, developed countries can help them build stronger defenses against the further spread of superbugs. Pacific Island countries, for example, have relatively insufficient capacity to respond to public health emergencies. China has carried out public health cooperation with Pacific island countries through the Belt and Road Initiative and the Health Silk Road, and used the high-speed rail platform to regularly share epidemic prevention information and exchange experiences through virtual meetings, webinars and conferences. Building reliable public health cooperation for security and stability[15]. In addition, the superbug threat can be reduced globally through rational use of antibiotics, improved infection control, and increased public awareness.

4. Discussion

Although this article introduces the development and history of superbugs and discusses some methods to combat drug resistance of superbugs, it does not cover the resistance mechanism of superbugs and the cutting-edge scientific progress in combating drug resistance. The scientific knowledge of superbugs is only briefly introduced, aiming to improve the level of public awareness of them.

To understand the superbug problem more fully, we need to study the mechanisms by which they develop drug resistance in depth. It has been found that superbugs acquire drug resistance mainly through gene mutation, gene exchange and exogenous gene transfer. These mechanisms enable them to rapidly adapt to the antibiotic pressure in the environment and continuously evolve novel defense strategies.

In response to this challenge, scientists are actively looking for innovative ways to combat superbug resistance. These include developing new antibiotics, using immunotherapy to boost the body's immune system to fight infections, and exploring the use of nanotechnology to kill superbugs. These cutting-edge scientific advances give us hope for more effective weapons in the fight against superbugs.

However, in addition to relying on the unremitting efforts of scientists, the public also has a vital role to play. Only when everyone recognizes the enormous global public health challenge superbugs pose, and maintains the necessary sensitivity with which they are used, can we truly contain and reduce their impact.

Therefore, in daily life, please rationally use the prescribed drugs under the doctor's advice, and follow the guidance of medical staff to complete the treatment process correctly. At the same time, personal hygiene habits and preventive measures should be strengthened, and prevention work should be done in diet and environmental cleaning. We can also improve our knowledge of superbugs and the rational use of antibiotics by participating in relevant health education activities and paying attention to authoritative information channels.

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