

NEW DRUGS TARGETING ANTIBIOTIC-RESISTANT BACTERIA

RECENT ADVANCES

Editor:
Mariano Martínez-Vázquez

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New Drugs Targeting Antibiotic-Resistant Bacteria: Recent Advances

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PREFACE

Bacterial strains' resistance to bactericides is a natural process that arises from the selection pressure of antibiotics against these pathogens. The continuous assault of drugs on bacteria prompts these organisms to develop various defense mechanisms, such as β -lactamase biosynthesis, which targets the hydrolysis of the β -lactam ring in different penicillin and carbapenems. Other resistance mechanisms exist, such as changes in cell membrane proteins or the increased activity of efflux pumps. These changes are derived from gene information from surviving bacteria to pharmacological treatments. The dissemination of this information is done very efficiently both by vertical and transverse routes. It is known that penicillin resistance emerged only a few years after the implementation of penicillin as a worldwide antibacterial drug. This was the beginning of a recurring phenomenon: a new drug was synthesized to treat a complex infection, and a time later, strains were resistant to this new medication. The misuse of antibiotics in livestock production and among humans, where antibiotic medication was unnecessary, has accelerated the emergence of Multidrug-Resistant Strains (MDR). Upon reaching concerning levels of bacterial resistance worldwide in 2017, the World Health Organization launched a list called ESKAPE, which identifies the main resistant drug bacteria that constitute a threat and require new drugs with new routes of action. Recently, the Centers for Disease Control and Prevention (CDC-USA), considering the rise of infections and deaths induced by microorganisms, classified the infections as urgent, serious, and concerning threats. It is worth noting that the CDC list differs from that proposed by the World Health Organization in 2017. As Chapter One indicates, antibiotic resistance is one of humanity's most immense health challenges. Virtually any bacterium can develop resistance, either by its evolution, by antibiotic pressure, or by genetic exchanges. Additionally, in this chapter, the author emphasizes the need for a one-health approach, addressing MDRO comprehensively in humans, animals, soil, water, and manure. The focus is on infection prevention and control, as well as optimizing antibiotic use to break the chain of resistance acquisition and transmission. In chapter two, the authors cover various aspects of phage therapy, including isolating and characterizing bacteriophages, the development of suitable formulations, and their administration for treating human infections. It also examines successful cases of phage therapy in treating life-threatening infections that cannot be cured with current antibiotics. Moreover, the chapter highlights the advantages and limitations of phage therapy compared to traditional antimicrobials. Chapter three focuses on the ongoing efforts and strategies to find new antibacterial compounds from natural sources. It discusses traditional methods and innovative techniques for dealing with non-culturable microorganisms. The positive outcomes of these approaches offer hope for a potential resurgence in discovering these valuable molecules, marking a second golden age for the field. As indicated in Chapter Four, clinicians have limited options when choosing antibiotics. The only available option for them is carbapenems. To develop new pharmacological strategies, clinicians must identify enzymes that break down these antimicrobials. Identifying these enzymes is crucial to reduce the selection pressure and ensure the correct use of antibiotics. The length of time a molecule stays active in the body is determined by its persistence. Clinical microbiology laboratories play a crucial role in guiding the administration of drugs. This chapter discusses the importance of carbapenemases-mediated resistance, its classification, impact, and detection strategies. Chapter Five identifies the most effective bactericidal-drug combinations against drug-resistant bacteria. Combining the carbapenem antibiotic and a β -lactamase inhibitor is considered one of the best combinations for clinical treatments. The chapter also discusses the use of Quorum-sensing inhibitors to inhibit virulence. Research on virulence inhibitors based on halogen furanone-type compounds has shown efficient virulence inhibition *in vitro*. However, there are currently no QS inhibitors in clinical evaluation.

Additionally, the synthesis of nanoparticles to counteract drug-resistant bacteria is explored. Nanoparticles synthesized with biological activity have shown significant results, especially those made from metals like silver and those synthesized using polymeric materials with biodegradable substances. Further studies are needed to determine their effectiveness and toxicity.

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CHAPTER 1

Multidrug Resistance, An Unmeasurable Epidemic (MDRO)

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Abstract: Despite the undeniable benefits of antibiotics, the emergence of resistance presents a formidable challenge. This section examines the evolution of Multidrug-Resistant Organisms (MDROs), highlighting the complexities of systematic reporting and advocating for comprehensive surveillance to understand the true extent of the epidemic.

Initial successes of antibiotics, exemplified by penicillin, were short-lived as resistance swiftly emerged, marking the onset of the antibiotic resistance era. The current scenario reveals elevated resistance rates, particularly in low- and middle-income countries.

Medical concerns and reports highlight the ongoing apprehensions within the medical community regarding multidrug resistance, which dates back to the 1960s. Recent reports emphasize a global crisis of antibiotic scarcity and the rapid development of resistance. Livestock, pets, and other animals, as well as water and vegetables, are also contributing to the MDRO epidemic. The involvement of environmental animals and vegetables emphasizes the need for active epidemiological surveillance across all these sectors to prevent the transmission of MDRO, reinforcing the importance of environmental sanitation.

In conclusion, the origin and extent of the MDRO epidemic remain challenging to determine despite recent global surveillance efforts. The impact on health indicates a high association with mortality. There is a need for a One Health approach, addressing MDRO comprehensively in humans, animals, soil, water, and manure. The focus is on infection prevention and control, as well as optimizing antibiotic use to break the resistance acquisition and transmission chain.

Keywords: Antibiotic resistance, Epidemiological surveillance, Multidrug-resistant organisms.

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INTRODUCTION

Diseases with high prevalence, incidence, and mortality, especially if they are contagious, typically require epidemiological surveillance. They have established and generally standardized reporting systems. However, there is an epidemic that started several decades ago. Despite its high prevalence and lethality, antibiotic resistance does not have mandatory reporting in every country, at least not in a generalized and extended manner. Antibiotic resistance has been documented for over a century, almost simultaneously with the discovery of some drugs that have prevented the most deaths, such as antibiotics.

Antibiotics have prevented millions of deaths and are regarded as one of the most significant discoveries in healthcare. Furthermore, critical medical advances, such as organ transplants, implants, cancer treatments, and complex surgeries, would not have been possible without antibiotics. The benefits and medical achievements made possible by antibiotics are undeniable. Additionally, the use of antibiotics is widespread in veterinary medicine, as well as in the cattle, poultry, and swine industries, and even agribusiness.

Antibiotic resistance is one of humanity's most significant health challenges. Virtually any bacterium can develop resistance through evolution, antibiotic pressure, or genetic exchange [1 - 4]. Infections caused by resistant bacteria are difficult or impossible to treat, often require complex microbiological or molecular technology for diagnosis, and are generally more lethal than their antibiotic-sensitive counterparts [5, 6]. Furthermore, antibiotic resistance affects not only humans but also animals and plants. Therefore, antibiotic resistance has been complex to study, analyze, prevent, and control.

Antibiotic resistance has gradually and continuously evolved at an alarming rate. There are multiple reports of drug resistance worldwide, and despite being local or partial reports, it is evident that the resistance epidemic has progressed to multidrug resistance, with its incidence on the rise. Unfortunately, recent systematic review studies or studies that estimate the global burden of disease due to multidrug resistance indicate that antibiotic resistance is ranked third in deaths worldwide [7].

The source of MDRO is not just the use of antibiotics in humans and poor infection control in hospitals. The use of antibiotics in chickens, cattle, and pigs, as well as the use of manure as a fertilizer for plants, plays an important role, but their reporting is poorly standardized [8].

However, with the growing epidemic, alert MDRO reporting is not yet subject to standardized epidemiological surveillance as a cause of death. Although reported

by researchers with extensive international mathematical models, the reporting of data about the implications of morbidity and mortality is poorly standardized. The low perception of damage, the lack of diagnostic methods, and the little interaction between the participants in its genesis, i.e., doctors, antibiotic prescribers, veterinarians, farmers, chicken breeders, pigs, and even farmers, among other factors [8, 9], are some of the factors that could contribute to the lack of measurement of the absolute magnitude of the epidemic.

This chapter provides the reader with a general overview of the emergence and widespread evolution of MDROs, including notions about the importance and difficulty of systematic and mandatory reporting and the extension of the epidemic in humans and beyond.

THE BEGINNING AND EVOLUTION OF THE PANDEMIC

Antibiotics have saved millions of lives since their systematic use; they are undoubtedly a remarkable achievement in the fight against bacteria [1]. However, the evolution of bacteria towards resistance has been so rapid that it has exceeded the discovery of new antibiotics. It is calculated by mathematical modeling studies that currently, deaths associated with antibiotic resistance are among the most frequent, only surpassed by stroke and ischemic heart disease [5, 6].

It is indisputable that antibiotic resistance is a natural aspect of microorganism evolution and that resistance to other organisms occurred before the widespread use of antibiotics. Some microorganisms have developed mechanisms to resist antibiotics; therefore, they produce antibiotics themselves [1, 2]. The first antibiotics used were substances produced by resistant microorganisms to kill other microorganisms [1, 2].

Since Hippocratic medicine, antibiotics have been used empirically. The empirical use of baker's yeast to treat wounds has been documented for over two thousand years in Egypt, Greece, and Serbia. About a thousand years ago, a recipe for plant-based eye drops with activity against *Staphylococcus* was found. This eye drop was recently recreated, and its effectiveness was demonstrated [1, 2, 11].

In 1871, Joseph Lister discovered that the fungus *Penicillium brevicompactum* inhibited bacterial growth. The extract was used to treat an infected wound on a nurse in 1893, hence the hypothesis that bacteria caused the infection. Bartolomeo Gosio isolated mycophenolic acid in 1893, which he used to treat Anthrax. Its use was forgotten until 1912, when it was revived by C.L. Alsberg and O.M. Black, who discovered it inhibited mitosis. Mycophenolic acid was forgotten until its immunosuppressive properties were later found [12 - 14]. It is currently known

CHAPTER 2**Bacteriophages**

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Abstract: Bacteriophages are the most abundant biological entities on the planet and are specific viruses that target only bacteria. The use of these viruses to combat bacterial infections is known as phage therapy, a concept that was implemented in the early 20th century. However, its application in Western medicine was halted following the discovery and use of antibiotics. Still, due to the alarming increase in antibiotic resistance we are experiencing, phage therapy is gaining acceptance in Western countries, and several successful cases have been documented. In this chapter, we discuss various aspects of phage therapy, from bacteriophage isolation and characterization to the development of phage-suitable formulations and their administration for treating human infections. We also examine successful cases of phage therapy in treating life-threatening infections that are untreatable with current antibiotics, highlighting the advantages and limitations of phage therapy compared to traditional antimicrobials.

Keywords: Antibiotic resistance, Bacteriophage, Bacterial infections, Clinical cases, Clinical trials, Persister cells, Phage administration, Phage cocktails, Phage isolation, Biofilms.

INTRODUCTION

Bacteriophages are viruses that infect bacteria and were discovered independently by Frederick Twort and Felix d'Herelle. In 1915, Frederick Twort reported the appearance of lytic plaques at the edge of some *Staphylococcus* colonies and obtained the same pattern when he spotted the filtrate supernatant of the cultures of that bacterium on the lawn of different *Staphylococcus* strains; unfortunately,

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he was unable to explain this phenomenon. Later, in 1917, Felix d'Herelle performed research focused on an outbreak of severe hemorrhagic dysentery among French troops. To get a vaccine, he obtained bacterium-free filtrates of the patients' fecal samples and incubated them with *Shigella* strains isolated from the patients. He observed the appearance of clear lysis plaques. D'Herelle published these results and suggested that the causal agent was a virus capable of infecting bacteria (this was confirmed later by the development of electron microscopy), and he also named them bacteriophages. Immediately after the discovery, the potential of these bacteria to treat human diseases was realized by D'Herelle and other scientists, and hence, they were used successfully for the treatment of dysentery, cholera, and other infections [1]. George Eliava was a Soviet scientist who founded the Eliava Institute of Bacteriophage, Microbiology, and Virology (EIBMV) in 1923. He was aware of D'Herelle's research and invited him to collaborate at his institute. At that time, the institute produced phage preparations against many enteric pathogens, such as *Staphylococcus*, *Pseudomonas*, and *Proteus*. Nowadays, this institute is a worldwide reference for phage cocktail production for various purposes; its collection spans over 1000 phages active against human, plant, and animal bacterial pathogens isolated worldwide. In this chapter, we explain the procedures for isolating and characterizing bacteriophages suitable for phage therapy, including the advantages and limitations they have and how preparations are formulated and administered, as well as discuss several well-documented examples of their utilization for the treatment of recalcitrant bacterial infections in Western medicine.

ISOLATION AND CHARACTERIZATION OF BACTERIOPHAGES SUITABLE FOR PHAGE THERAPY

Bacteriophages are nature's most abundant biological entity, outnumbering bacteria by an order of magnitude. They can be found in any place where bacteria are also found. It is estimated that there are 10^{31} phages in Earth's ocean; meanwhile, there are around 10^{22-24} stars in the observable universe [2]. They are commonly obtained from water sources, such as sewage, contaminated rivers, lakes, and the sea, but can also be obtained from soil, feces, saliva, sputum, and other secretions [3 - 6]. They are intracellular parasites that rely on a bacterial host to replicate their genome and assemble into mature forms called virions. The infection begins with the viral recognition of phage receptors located on the bacterial surface, and then the phage injects its genome into its bacterial host. Once the genome enters the cell, the phage can adopt two life cycles: a lytic or a lysogenic cycle. During the lytic cycle, the phage genome starts its replication, transcription, and translation. The viral particles then assemble, and finally, the bacterial host is lysed. In the lysogenic cycle, the phage genome integrates into

the bacterial DNA to form a non-infective form called a prophage, which is replicated along with the bacterial genome. Nevertheless, the prophages can excise the bacterial genome stochastically or upon exposure to certain types of stress and switch to a lytic life cycle [7]. For their application in phage therapy, lytic phages are strongly preferred over temperate ones since their life cycle involves invading and killing their host. In contrast, although temperate phages can undergo lytic cycles, they typically remain dormant most of the time. At the same time, their genomes are replicated each time their host replicates, becoming active or lytic under certain environmental conditions, often triggered by factors such as oxidative stress or quorum sensing [8].

However, since most phages are temperate, they could be engineered to produce obligate lytic versions by removing genes essential for the lysogenic cycle, such as repressors and integrases. This approach could enhance phage therapy, thereby increasing the repertoire of phages available for clinical use.

An established technology in phage engineering is phage display, which involves using viroid particles or capsid proteins to deliver substances, drugs, or plasmids, taking advantage of host specificity. This process leads to the creation of phagemids. It has been studied for inducing the expression of antimicrobial peptides that signal an immune response (immunization/vaccination), as well as for anticancer therapy, and other applications [10].

Other vital points that must be considered are that it should be avoided utilizing phages that contain potentially dangerous genes, such as those encoding virulence factors or antibiotic resistance determinants, since they may increase the resistance and/or virulence of their host and other bacteria. Hence, it is advisable to sequence the phage's genomes before their utilization and either exclude those that carry dangerous genes or engineer them to remove those genes that encode harmful components. Furthermore, phages should be thoroughly purified prior to their administration to avoid the delivery of toxic bacterial components like LPS that could cause septic shock [9].

An important feature of phage therapy is that it should be implemented not with single phages, but rather with a combination of several different ones, since single phages can easily select for bacterial resistance. The probability that bacteria with resistance against multiple phages will emerge is very low if the phages used are different, for example, if they do not share the same receptor [9].

Although, in principle, phage therapy could be applied to any pathogenic bacteria, to develop robust phage therapies, it is necessary to have extensive collections of different phages targeting the bacterial host; the optimal size of the collection is variable, since for some bacteria like *Staphylococcus aureus* phages usually can

CHAPTER 3

The Revival of Natural Products in Developing New Antimicrobial Drugs: An Opportunity for Sustainable Management

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Abstract: The global health crisis caused by antimicrobial resistance presents a challenge that demands a rapid response. For decades, the development of antibiotics has significantly improved our quality of life. Shortly after their discovery, diseases and pests that had caused numerous deaths were controlled. Similarly, antibiotics facilitated advancements in medical and surgical practices, as well as enhanced food supply through agricultural applications. The marketed antibiotics were developed based on research into natural products of microbial origin. Therefore, this chapter examines various ongoing efforts and strategies to discover new antibacterials from natural products. It explores both traditional methods and innovative techniques for managing non-culturable microorganisms. The results inspire hope for a second golden age for these molecules. However, we must exercise greater responsibility in their use.

Keywords: Antimicrobials, Antibiotics, Natural products, Non-culturable organisms, RiPPs, iChip technology.

INTRODUCTION

Microorganisms are the first living beings to appear on Earth and have evolved for over three billion years. However, we became aware of their existence only after Anton van Leeuwenhoek discovered them 348 years ago [1]. Likewise, the eighteenth century was a period of essential advances in microbiology, of which the association of some microorganisms as etiological agents of diseases and early attempts to eliminate them are outstanding [2].

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One of the diseases that scientists have sought to eradicate is syphilis, an infectious disease caused by the *Treponema pallidum* bacterium that has coexisted with humans for thousands of years [3]. It is a disease that has caused contempt and fear due to its origins and devastating consequences. It has caused the death of millions of people and continues to affect many individuals today [4]. For centuries, without knowing the causative agent or understanding the biology of the disease, various treatments were developed in an attempt to cure it. One of the most popular remedies was the use of poisons, such as mercury salts, which acted nonspecifically, affecting both the microorganism and the patient [5].

It would not be until the beginning of the 20th century that Paul Ehrlich established the bases of antimicrobial chemotherapy with the revolutionary idea of “magic bullets,” molecules aimed at eliminating disease-causing microorganisms without affecting the host cells [6]. This chapter aims to provide an overview of the discovery and nature of antibiotics, antibiotic resistance, and future perspectives, as well as new antimicrobials and new alternatives to reduce antimicrobial use.

AN ORGANOARSENIC COMPOUND

Salvarsan (compound 606) was Ehrlich's first magic bullet to treat syphilis; curiously, he developed it from organic compounds with the lead structure of arsenic, the favorite poison of medieval assassins [7]. Similarly, it should be noted that Salvarsan was initially developed to eliminate trypanosomes. Later, Ehrlich decided to evaluate its effect on the *T. pallidum* bacterium, as its discoverers, Schaudin and Hoffmann (1906), erroneously described it as a trypanosome-type parasite [8].

Although the effectiveness of salvarsan and the subsequent neosalvarsan (compound 914) in treating syphilis was controversial due to the side effects and deaths associated with its application, it is recognized that it kept the disease under control and saved the lives of millions [9].

It is essential to note that Salvarsan was used to understand the biology of the disease and its consequences in its late stages. In this regard, in 1913, Hideyo Noguchi managed to associate neurological disorders with *T. pallidum* infection by identifying them in the brains of patients with what would later be known as neurosyphilis [10].

THE RISE AND DECLINE OF ANTIBIOTICS

Despite the advances achieved with Salvarsan and Neosalvarsan, effective treatment against syphilis and many other diseases of microbial origin would not be possible until the discovery and development of penicillin by Alexander

Fleming in the 1940s [11]. These investigations, along with the development of synthetic sulfonamides in 1935 [12], gave rise to the discovery of antibiotics, one of humanity's most important scientific achievements [13]. In the 1950s, antibiotics ushered in a “golden age” in which the control and eradication of infectious diseases that had caused millions of deaths for centuries was achieved [14, 15].

Research on natural products made the discovery of antibiotics possible. By 1970, more than twenty classes were introduced to the market (Fig. 1).

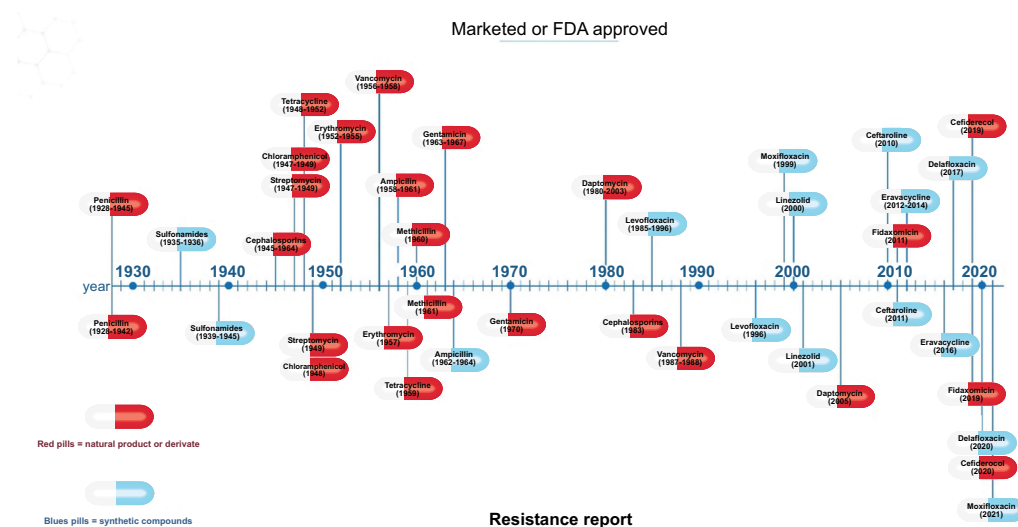


Fig. (1). Development of resistance to commercial antibiotics and some FDA-approved antimicrobials in recent years. Natural products of microbial origin were the basis for the discovery and development of commercial antibiotics in the “golden age” of the 1940s to the 1960s. Subsequent decades saw a sharp decline in the number of antibiotics entering the market. In addition, the pharmaceutical industry shifted its focus from discovering new classes of natural product antibiotics to synthesizing them from chemical libraries, which at the time were considered a more cost-effective strategy for developing new antibiotics. However, resistance is advancing rapidly, and chemical scaffolds from natural products are becoming obsolete, as microorganisms previously exposed to them have already developed strategies to generate resistance in a shorter time.

However, along with these discoveries came the warning that if the “magic bullets” were misused, they would lose their effectiveness due to the induction of bacterial resistance [16]. We have not taken this warning seriously for decades and favored the rapid spread of multidrug-resistant organisms [17]. Given this situation, various authors point out that we are entering the beginning of what has been defined as the post-antibiotic era, in which there are resistant microbial strains against which antibiotics are no longer effective [18]. Thus, an urgent call

CHAPTER 4

Carbapenemases: Impact, Perspectives, and Identification Methods

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Abstract: Multidrug resistance is a global and severe public health concern; according to data from Jim O'Neil, in 2050, deaths could rise to 10 million. Each time, clinical options are decreasing. The outlook is discouraging, not considering the increased resistance during the COVID-19 pandemic.

The last line of defense for clinicians is the use of carbapenems, and developing new clinical pharmacological strategies involves the use of site-specific inhibitors. Identifying the enzymes that degrade these types of antimicrobials is crucial. It is the key to reducing the selection pressure and ensuring their proper use. The half-life of a molecule is dictated by its prescription, and this is where the clinical microbiology laboratory comes in. It is not just a place for testing; it serves as the guiding axis for the correct, adequate, and rational administration of drugs. In this chapter, we will delve into the importance of carbapenemases-mediated resistance and its classification, impact, and detection strategies.

Keywords: Carbapenemase, Carbapenemase classification, Detection strategies, Global concern, Identification tools.

INTRODUCTION

Antimicrobials are molecules that increase life expectancy, being different before and after 1900. According to “Our World in Data,” before 1900, life expectancy

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was around 30-40 years; after 1900, life expectancy increased to the current expectancy [1]. For example, in 2015, life expectancy in the United States of America increased to 79 years, in Canada to 82 years, in Europe to around 80 years, and in Mexico to 77 years. The lowest age rates are identified in Africa (around 60 years) (Fig. 1). These changes may be associated with introducing the first and subsequent antimicrobial molecules. The first molecule introduced to cure infectious diseases was a synthetic one, discovered by Paul Ehrlich's research group: Salvarsan, also known as the magic bullet, designed to treat syphilis. The following molecule, discovered by serendipity, was penicillin by Alexander Fleming in 1928 [2]. However, thanks to the work of H.W. Florey et al, penicillin reached mass production [3].

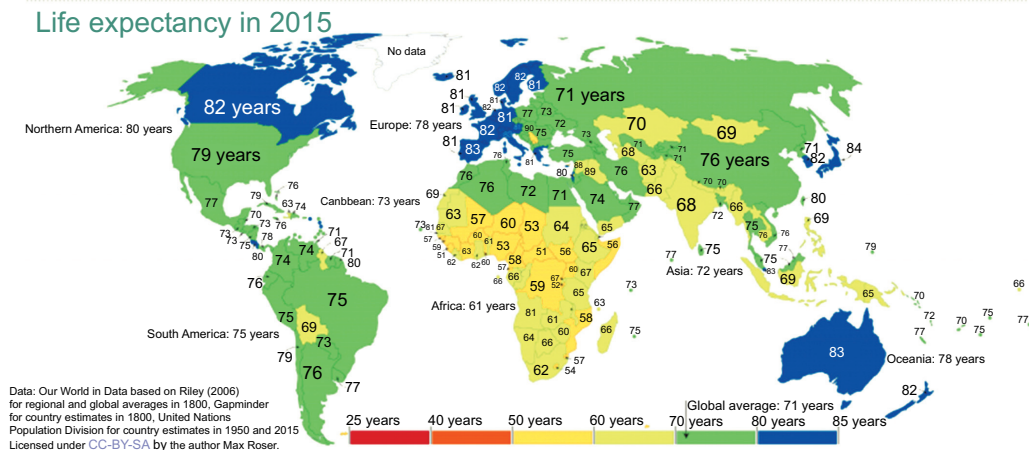


Fig. (1). Life expectancy in 2015 taken from <https://ourworldindata.org/life-expectancy> [1].

Despite new molecules being discovered as soon as they were announced, the response from microorganisms also began to appear. For example, resistance to penicillin appeared just a year after its commercial launch [4]. In response, the study of antimicrobial resistance began to gain strength as physicians had fewer medicines to treat patients' infections, and mortality rates associated with antimicrobial resistance increased. At this point, various governments and researchers worldwide showed interest in this topic. One of the most cited works is those belonging to Sir. Jim O'Neill. He has published various essays about the importance of addressing multidrug resistance. He has made projections about the impact of multidrug resistance until 2050. According to his work, this year, there will be more deaths associated with multidrug resistance than those with pathologies with mortality associated per se, such as cancer—it has been calculated that there will be approximately 10 million deaths [5]. The region with the highest death rate will be Asia, with 4,730,000 deaths attributable to

antimicrobial drug resistance, followed by Africa, with 4,150,000 deaths. According to projections for the American continent, the number of deaths is expected to rise to 709,000. This data shows that the cumulative economic impact since 2014 will have a negative influence on the gross domestic product [6]. However, O'Neill's prediction seems inaccurate since, in January 2022, Dr. Mohsen Naghavi and collaborators published "The Global Burden of Bacterial Antimicrobial Resistance in 2019." In this paper, the authors estimated that 4.95 million deaths are associated with bacterial antimicrobial resistance. This estimate shows that in 2019, the deaths related to bacterial resistance were nearly half of the 10 million predicted for 2050. The highest rate of deaths attributable to bacterial antimicrobial resistance was observed in sub-Saharan Africa, with 27.3 deaths per 100,000 inhabitants, while Australia had the lowest rate [7].

In 2017, the World Health Organization (WHO) created a list of primary pathogens that require immediate attention to combat antimicrobial resistance. The microorganisms were prioritized based on their level of threat. Priority was given to infections associated with healthcare, such as *Enterobacterales*. These are resistant to third and fourth cephalosporin generations as well as carbapenems. *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, which are resistant to carbapenems, were also prioritized [8].

In addition to the misuse of antibiotics, the COVID-19 pandemic is also a leading cause of pressure selection in microorganisms. On 11 March 2020, the WHO declared a pandemic that began in Wuhan and spread to the rest of the world [9]. Unfortunately, this disease was initially misdiagnosed as bacterial pneumonia and treated with antibiotic administration. As a result, antibiotic misuse and abuse contributed to the rapid rise of antimicrobial resistance. Several works have listed the pandemic's role in this phenomenon.

For example, in Mexico, the use of antibiotics was compared between the pre-pandemic and pandemic stages, resulting in increased resistance to oxacillin, erythromycin, and clindamycin for *Staphylococcus aureus*, as well as to imipenem and meropenem for *Klebsiella pneumoniae*, as determined in blood samples [10]. Before the pandemic, the Pan-American Health Organization reported that around 10-15% of antibiotics were administered for secondary infection. During the pandemic, antibiotics increased by around 94-100%, of which 72% were broad-spectrum [11].

On the other hand, in the USA, the Centers for Disease Control and Prevention (CDC) reported an alarming increase in resistant infections by around 15% from 2019 to 2020. According to their report, there was an increase of 78% in carbapenem-resistant *A. baumannii*, 32% more *P. aeruginosa* multidrug-resistant,

CHAPTER 5

Post-antibiotic and Resistance Era

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Abstract: The Centers for Disease Control and Prevention (CDC-USA) has categorized bacterial infections as urgent, serious, and concerning threats. In this chapter, we will discuss the antibiotics suggested by the CDC-USA to combat the urgent threats caused by drug-resistant bacteria, including carbapenem-resistant *Acinetobacter* and *Enterobacteriaceae*, *Candida auris*, *Clostridioides difficile*, and Drug-resistant *Neisseria gonorrhoeae*.

The chapter reviews the efficacy of carbapenem antibiotics when combined with β -lactamase inhibitors. Additionally, it discusses using quorum-sensing inhibitors to prevent virulence factors, focusing on halogen furanone-type compounds. Interestingly, such inhibitors are effective *in vitro*, but none are currently being evaluated in clinical settings. Finally, some syntheses of nanoparticles to counteract drug-resistant bacteria are reported. Nanoparticles made from metals, especially silver, and those synthesized using biodegradable polymeric materials have shown promising results in cytotoxic activity. However, further studies are needed to determine their effectiveness and toxicity.

Keywords: Bactericidal-drugs combination, Bactericidal nanoparticles, CDU-USA classification, Hybrids, Quorum Sensing System.

INTRODUCTION

Recent research has shed light on microorganisms' pivotal role in the human body throughout their lifespan. The human microbiome comprises various organisms, including bacteria, fungi, viruses, and other microbes. Its functions include aiding food digestion, vitamin synthesis, regulating the immune system, and protecting against pathogenic agents. Traditional research in human microbiology focused on identifying individual microbes, such as bacteria, fungi, and viruses, primarily from clinical isolates. However, contemporary molecular and biochemical analyses such as genomics, transcriptomics, proteomics, and metabolomics have

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facilitated the detection and classification of diverse microorganisms in different body parts, such as the gastrointestinal tract, skin, airway system, and urogenital tract.

These analyses have demonstrated that everyone possesses microbiota that contributes to health maintenance and disease prevention. This progressive understanding has significantly advanced our comprehension of the pathogenesis of various human diseases. These insights are expected to pave the way for developing diagnostic, therapeutic, and preventive measures in personalized/precision medicine [1].

Disrupting the balance of the microbiome can result in bacterial infections. These infections are caused by harmful bacteria invading and multiplying in the body, leading to symptoms like fever, pain, inflammation, and organ damage.

Bacterial infections can result in various illnesses, including strep throat, meningitis, sepsis, and pneumonia. They could also induce food poisoning. The microorganisms responsible for some of these diseases include *Streptococcus* spp., *Staphylococcus aureus*, *Escherichia coli* (*E. coli*), and *Salmonella* spp.

Maintaining a healthy microbiome through good hygiene practices, a balanced diet, and judicious use of antibiotics is crucial to mitigate the risk of bacterial infections. The human microbiota consists of bacteria, viruses, archaea, molds, yeasts, and protozoa. It resides in the skin, mucous membranes of cavities, and secretory glands. The symbiotic relationship between the human microbiota and the host helps modulate the host's physiological development and immune functions throughout life.

However, throughout history, there have been instances where new microorganisms have infected humans, causing widespread death and destruction. The Black Death is an example of such an infection, which ravaged Eurasia from 1347 to 1351, resulting in the deaths of millions. *Yersinia pestis* is believed to have caused Justinian's Plague in the 6th century and killed millions of people in the Byzantine Empire [2].

Conversely, it is generally assumed that the number of microorganisms in the human body is much greater than that of human cells. However, in 2016, a study was published in which, using new calculation techniques, it was concluded that there is an almost 1:1 relationship between the number of human cells and microorganisms [3].

A balance between human cells and microorganisms is essential for proper growth and development. When this equilibrium is broken, it can lead to health

complications. The balance could be restored by antibiotic drugs, reducing the number of microorganisms causing the infection. However, these drugs are non-selective and can lead to complications such as the formation of kidney stones when taking sulfonamides, abnormal blood clotting when taking some cephalosporins, sensitivity to sunlight when taking tetracyclines, blood disorders when taking trimethoprim and deafness when taking erythromycin and aminoglycosides. Some people, especially older adults, may experience intestinal inflammation, which can cause severe bloody diarrhea [4].

Therefore, it is crucial to exercise caution while using such drugs to prevent adverse effects and ensure the well-being of individuals. Recent research on the human microbiome has demonstrated that even healthy individuals display significant variations in microorganisms in areas such as the skin, gut, and vagina. While the factors contributing to this diversity are not yet fully understood, diet, environment, genetics, and initial exposure to microorganisms have been identified as possible influencers. The Human Microbiome Project examined many people and studied microbial communities in or on the human body. This project showed that each habitat has a diverse range of microbes that vary among healthy individuals. It was also found that each person has unique microbial niches within their body, and the diversity and abundance of these microbes can differ significantly from person to person. The study estimated that the healthy Western microbiome contains a great diversity of genera, enzyme families, and community configurations [5].

Antibiotics have long been used to treat bacterial infections. However, the emergence of antibiotic-resistant strains has made it difficult to eradicate these infections. Thus, the prevalence of resistant strains in clinical settings has made it challenging to eliminate bacterial infections.

Unquestionably, the evolution of drug-resistant bacteria was due to selection pressure, which increases an organism's ability to survive and reproduce. Organisms with advantageous traits are more likely to pass them on to future generations, leading to their prevalence in subsequent generations. For that, the microorganisms that are best suited to new conditions are the ones that have the highest likelihood of survival and reproduction, and their characteristics become increasingly common in future generations.

Antibiotic resistance (ABR) in microorganisms is caused by the selection pressure they face when exposed to different drugs. In the past, antibiotic resistance was limited to a specific place where a microbial strain developed resistance to a particular type of drug. However, the widespread and inappropriate use of antibiotics in humans and animals has led to multiple microorganisms being

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This insightful book brings together key perspectives on the escalating crisis of antimicrobial resistance. Covering topics ranging from multidrug resistance and carbapenemases to innovative solutions such as bacteriophages and natural products, it offers valuable insights and a forward-looking perspective on how science can address the challenges of the post-antibiotic era.

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Martínez-Vázquez earned Ph.D. in organic chemistry from CINVESTAV in 1993. He began his academic career as a chemistry professor for undergraduates at the chemistry faculty in 1974 and advanced through various research roles, attaining the rank of professor in 2005. He has held significant positions in academia, including supervising 23 doctoral theses, 14 master's theses, and 67 bachelor's theses, as well as editing several scientific journals. His research focuses on isolating and characterizing secondary metabolites, assessing their potential as anticancer agents and against drug-resistant bacteria. His discoveries include identifying triterpenes from *Parthenium argentatum*, showing anti-inflammatory and antitumor properties, leading to multiple patents and doctoral theses. He has also investigated the synthesis of compounds that inhibit virulence factors in drug-resistant *Pseudomonas aeruginosa*. He has published 146 articles and received honors, including an Emeritus Researcher at SNII. His work has greatly contributed to understanding phytochemistry in Mexico and to developing potential therapies against drug-resistant bacteria, highlighting the synergy between natural compounds and clinical drugs.