DRUG DISCOVERY TARGETING DRUG-RESISTANT BACTERIA

Edited by
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This book is dedicated to the unsung heroes of the entire antibacterial drug discovery and development community, who have toiled far too long in the shadows to bring life-saving drugs to the market in spite of multiple hindrances. Without these drugs, most of us including the editors and readers would not have been alive today. May the force be with you!

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Foreword 1

Our history with antibiotics is remarkably short. In 1906, Paul Ehrlich developed Compound 606 or Arsphenamine, the first chemotherapeutic agent that was able to selectively attack a bacterial organism (spirochetes, which causes syphilis). However, the modern age of antibiotics that were safe to humans but able to kill bacteria at the site of infection goes back only to 1928 with the discovery of penicillin. In fact, the first person to be treated with an antibiotic was as recent as 1942, within current living memory. Nevertheless, resistance has arisen to most antibiotics soon after they were introduced into clinical practice. But that is not unexpected. As many antibiotics are derived from naturally occurring compounds that are derived from fungi, it is but natural that the genetic basis for resistance is present in a small proportion of bacteria. The massive selection pressure we have applied on these "resistant" strains of bacteria through the use of millions of tons of antibiotics, in humans, animals, and the environment, has ensured that resistance is no longer a rare phenomenon. Indeed, in the case of many bacteria pathogens, a significant proportion of bacteria causing infections no longer respond to antibiotics.

Antimicrobial resistance (AMR) has been compared to climate change. Resistance can emerge in any part of the world because of antibiotic overuse or misuse and the rapid dissemination of resistant pathogens globally. There are 10 million people on an airplane on any given day and bacteria do not need passports or visas to move around the world. Like with climate change, individuals and countries are not fully incentivized to tackle the AMR problem on their own. However, there is one important respect in which AMR is not like climate change. The potential for drug resistance was known even before penicillin was used on a single patient, unlike with climate change, where the impact on climate was not understood at the dawn of the fossil fuel age.

Alexander Fleming warned of drug resistance in his Nobel Lecture in 1945, "It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." Despite these early warnings, we have failed to ensure that penicillin and other antibiotics are not bought by anyone without medical knowledge. And we have seen the consequences.

In this book "Antibiotics: Past, present and future," the editors Prashant Kesharwani, Arunava Dasgupta, and Sidharth Chopra have put together a remarkable compendium of papers addressing various aspects of the AMR challenge. AMR is global, and it is but natural that science to address the problem of resistance including on discovery of new

antimicrobial agents should also be global. India, as the world's large consumer of antibiotics for use in humans, and as a country with a challenged public health and sanitation system, is bearing the brunt of the AMR burden. It is timely that researchers in India have enthusiastically taken up the scientific challenge of tackling AMR.

There may come a time when we are no longer dependent on antibiotics because of advances in science that we cannot yet see. Perhaps phage therapies, vaccines, monoclonal antibodies, and probiotics would have advanced to a stage where our reliance on antibiotics is much diminished. But until that time, we owe it to future generations to ensure that they do not enter a world where antibiotics no longer work, for no fault of their own.

Ramanan Laxminarayan

Foreword 2

Antimicrobial Resistance (AMR) is one of the biggest challenges the world faces today. The issue is as complex as global warming and global poverty, requiring coordinated efforts of all stakeholders, including the medical community, scientists, policymakers, pharmaceutical industry, politicians, and the public. One of the basic reasons for the current AMR scenario is the dry anti-infective pipeline. The reasons behind this dry pipeline are well known.

The book "Drug Discovery Targeting Drug-Resistant Bacteria" is very comprehensive, with an introductory chapter on why there is an urgent need for newer anti-infectives, and multiple well-written sections covering very important aspects such as mechanisms of drug resistance, drugs targeting various groups of bacteria, newer approaches to drug discovery including peptides and a detailed discussion on the role of phages.

The monogram is an excellent resource that helps us to delve deep into the intricacies of the current AMR scenario and a souvenir on the light at the far end of the tunnel.

I congratulate Dr. Sidharth Chopra and team for their sincere effort on a topic of high public health significance.

Abdul Ghafur

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Editors

CHAPTER 1

Antibiotics: past, present, and future

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1 Introduction

1.1 History and discovery of antimicrobials

Selman Waksman, one of the very first investigators in the field of antimicrobial chemotherapy and bacteriology, coined the term "antibiotic" [1]. The term was singularly used to refer to a molecule that was used against bacteria and exhibited bacteriostatic or bactericidal activity. However today, the term antibiotics or antimicrobials is often used interchangeably for compounds used in the treatment of bacterial, fungal, protozoan, or other microbial infections. As has been well documented, infectious diseases have a significant impact on human morbidity and mortality and have shaped human evolution and history. The discovery of antimicrobials is one of the most significant breakthroughs that revolutionized human medical sciences as antibiotics have saved millions of lives and increased life expectancy all across the globe.

Paul Ehrlich started the never-ending quest of discovery of antimicrobials along with Sahachiro Hata. They identified a compound, marketed as Salvarsan, that showed antibacterial activity against *Treponema pallidum*, the causative agent of syphilis that had a major impact on health care in 19th century Europe. The discovery of salvarsan gave the concept of magic bullet, a compound that specifically acts on the disease-causing agent but does not damage the host. The discovery of salvarsan was followed by the discovery of sulfa drugs by Gerhard Domagk in the 1930s [2]. Soon, penicillin was discovered by Sir Alexander Fleming from *Penicillium notatum* in 1928 [3]. The discovery of penicillin was a real game-changer because in the past we were dependent on synthetic antimicrobial discovery, but this opened up the avenue of natural products as antimicrobials. Penicillin came into clinical use in the 1940s and was a miracle drug. Suddenly, one's untreatable infections that had been death sentence before now were cured in days. The finding led to the understanding that a microorganism can produce substances that could inhibit the growth of other microorganisms. The best source of new antibiotics was from a naturally occurring microorganism, and every effort was made to reach all the parts of the world to isolate the antibiotic-producing organism [4]. After the successful introduction of penicillin, there was a huge expansion in the arsenal against microbial infections through

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the discovery of new molecules. Waksman and Schatz discovered streptomycin from *Streptomyces* sp. that was active against both Gram-positive and Gram-negative bacteria, including tuberculosis caused due to *Mycobacterium tuberculosis* [5]. In subsequent years, many new antibiotics such as chloramphenicol, tetracycline, macrolides, quinolones, etc. were deployed in clinical settings. In fact, so many molecules were discovered in between 1950s and 1970s that is considered to be the "golden era of antibiotics." Most of the classes of antibiotics were discovered and introduced in the health-care system but since then almost no new class of antibiotics has been discovered [6].

In the current economic scenario, India and China mass produce antibiotics and sell them globally. In the United States in 2011, total antibiotic use in human medicine was 3290 t and the use of medically important antibiotics in food animals was almost three times higher than human use [7]. According to a recent study in China, the annual consumption of antibiotics is 138 g per person which is 10 times more in comparison to that in the United States. Interestingly, an average growing pig excretes 175 mg of antibiotics per day [8]. According to Wang et al. [9], 21 different types of antibiotics were reported in the urine of Chinese primary students who have not been treated by antibiotics for years. Adding to the perfect storm, the Indian subcontinent is proving to be perfect superbug petri dish mainly due to substandard antibiotic policies, lack of strict regulation from authorities, poor sanitation, and overcrowding [10,11]. The global consumption of antibiotics has increased by 40% in the last decades without any exception [12].

Apart from their central role in treating infections, antibiotics are used to prevent infections in surgical patients, in organ transplant, as adjunct to chemotherapy as well as to stave of infections in critically ill patients in ICUs. Taken together, most of the advances in human medicine would not have been possible without antibiotics. In time, a perception was generated that antibiotics could cure anything, so they were used extensively, many times unnecessarily and inappropriately. Inappropriate use of antibiotics all over the world has led to antimicrobial resistance (AMR).

AMR is defined as the ability of microbes to grow in the presence of antimicrobial that would usually kill them [13]. It is not a new phenomenon. In fact, in 1940, Abraham and Chain [14] demonstrated that *Escherichia coli* cell extract could destroy the antimicrobial activity of penicillin by enzymatic action. Incidentally, Sir Alexander Fleming also warned about the development of AMR in his Nobel lecture. He mentioned that it is not difficult to make microbes resistant to penicillin in the laboratory and the same thing can occasionally happen in the body "The ignorant man may easily under dose himself and by exposing his microbes to non-lethal quantities of the drug and make them resistant" [15]. Unfortunately, his words turned out to be true.

Extensive use of antimicrobials causes a spread of resistant phenotypes and the emergence of multidrug-resistant (MDR) pathogens across the globe. Over the years, the microbes have adapted and evolved in a way that even our last precious antibiotics become potently useless against these superbugs. Pathogens are acquiring resistance to multiple antibiotics and these resistances are being disseminated rapidly. Resistance in

microorganisms is happening due to mutation in preexisting DNA or by the acquisition of foreign DNA containing the antibiotic resistance gene. These genes confer a variety of resistance mechanisms to bacteria. According to Infectious Diseases Society of America, the emergences of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus*, multidrug resistance in Gram-negatives especially ESKAPE pathogen and in *M. tuberculosis* have led to the many challenges during their treatments [16].

Furthermore, AMR is a global problem and is not restricted to a particular part of the world. Although there are considerable variations in the pattern of AMR, it affects all the parts of the world and all classes of people. Even in a modern, well-funded health-care system where the patient gets easy access to the second- and third-line therapies, these are often associated with higher mortality rates in infections caused due to drug-resistant bacteria. According to Centers for Disease Control and Prevention, each year in the United States, at least 2 million people get an antibiotic-resistant infection and out of those, 23,000 people die. Antimicrobial-resistant infections claimed 50,000 lives each year in Europe and the United States [17]. However, lower middle-class countries suffer from emerging resistance to treatment of tuberculosis, malaria, and HIV in addition to lack of access to medicines. The drug-resistant strains of tuberculosis are prevalent in many parts of the world. Majority of these cases are often left untreated due to late or no diagnosis, inaccessibility to second- or third-line therapy and associated cost of treatment [18].

It is estimated that superbugs are on track to kill 10 million people by the year 2050 [17]. The rapid dissemination of AMR and the emergence of MDR pathogens have created a pressing need for new classes of antimicrobial agents. Currently, the complexity and speed of international global travel create new opportunities for the drug-resistant pathogen to disseminate globally. Therefore, no country in isolation can tackle AMR and needs a coordinated, dedicated international multidisciplinary effort.

2 Current status

2.1 Dwindling drug discovery pipeline: no new class of antibiotics from the last three decades

A new report from the World Health Organization (WHO) mentioned that the antibiotics currently in clinical development are not sufficient to counter rising AMR, especially against those pathogens that posed the greatest threat to human health. Currently, only a few molecules in clinical trials can potentially counter the multidrug resistance in Gram-negative bacteria. Many of these drugs are modifications of existing antibiotics classes and add little to the already existing arsenal of resistance mechanisms. Potential treatment options are lacking for most critical resistant bacteria, especially for multidrug and extensively drug-resistant Gram-negative pathogens. As per the report in May 2017, antibacterials under clinical development include 51 antibiotics (including combinations) and 11 biologicals that have the potential to treat serious bacterial infections and were in phase 1–3 clinical trials.

Recently, WHO also published the list of bacteria for which new antibiotics are urgently needed [19]. The list contains priority pathogens that are categorized in critical, medium, and high, depending upon the urgency of treatment and increasing drug resistance to existing antibiotics. The critical category contains three Gram-negative bacteria that are resistant to multiple antibiotics carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Acinetobacter baumannii*, and carbapenem-resistant, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*. The WHO listed nine bacteria, including *S. aureus*, *Salmonella*, *Neisseria gonorrhoeae*, and *Shigella* as high-priority pathogens. In treatment options, only 12/33 antibiotics are active against these pathogens that are in the current drug pipeline and only two agents, GSK-3342830 (phase 1) and cefiderocol (phase 3), are expected to be active against all three critical priority pathogens. Cefiderocol is siderophore cephalosporin with a novel mechanism to penetrate the outer membrane of Gram-negative pathogens. None of these targets vancomycin-resistant *Enterococci* or fluoroquinolone-resistant *Salmonella*, both listed as high-priority pathogens.

On the other hand, drug pipeline for other priority pathogens is robust with most of 16 new antibiotics (which include 2 new antibiotic classes and 7 biological agents) specifically targeting MRSA. Modifications in existing antibiotic classes are a valuable short-term approach, but innovative approaches to antibacterial treatment are required to overcome resistance sustainably. Collectively, only 8 of the 51 new antibiotics act with a novel mechanism of action. In the past decade, only six new agents, namely, telithromycin, gemifloxacin, daptomycin, tigecycline, linezolid, and quinupristin–dalfopristin have been approved for clinical use by the US FDA. Majority of the newly approved drugs exhibit a narrow spectrum and are active against Gram-positive pathogens only. Only tigecycline is active against Gram-negative and Gram-positive human pathogens.

2.2 Pharmaceutical companies dropped out the research and development of antibiotics

Most pharmaceutical companies have dropped their programs on new antibiotic discovery and development (Fig. 1.1). Unfortunately, recent hunts for novel targets by genomic and proteomics-based approaches have also produced limited success [20,21]. The reason for this drop was because of lack of return on investment on antiinfectives amongst a multitude of factors. The antibiotic market is no longer attractive to the pharmaceutical investors due to developmental cost and stringent policies of regulatory authorities. If the drug molecules passed these hurdles and gained approval, then it was held in reserve and only prescribed for the resistant infection, thus further lowering the return on investment. Furthermore, as compared to other drugs for chronic diseases, antibiotics are administered for a very short duration and include inherent risk of resistance. So in the long run, investors find antibiotic drug development less profitable than other drugs. Given the upsetting situation, the search for new antimicrobial agents against the drug-resistant pathogen is an urgent and unmet medical need.

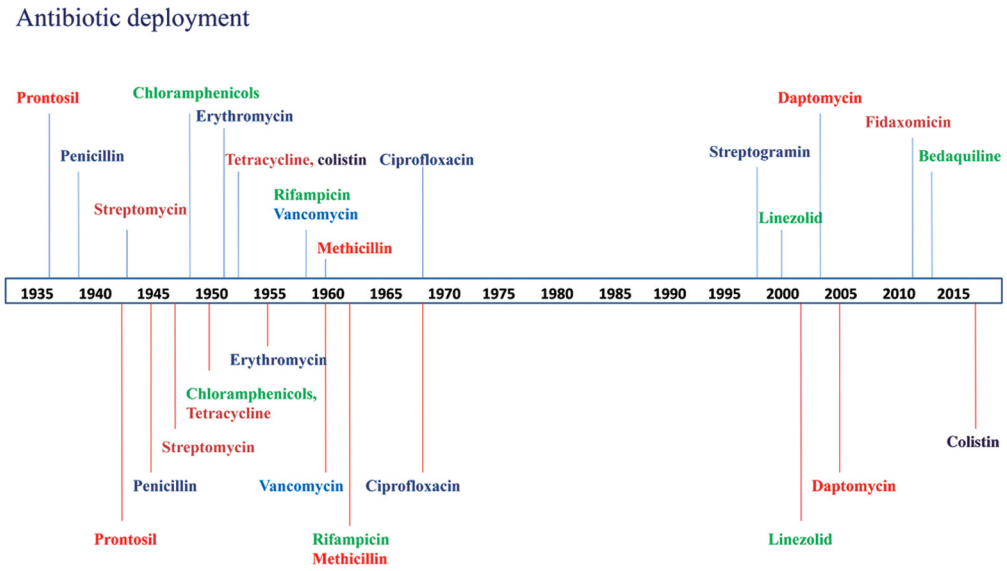

Figure 1.1 ***Timeline of antibiotic discovery and deployment and emergence of AMR. AMR, antimicrobial resistance.***

3 Solution to the problem: what can be done?

3.1 A surveillance system to monitor the escalating antimicrobial resistance

According to a report by the Food and Agriculture Organization of the United Nations, World Organisation for Animal Health (OIE) and the WHO, 100 countries now have national action plans for AMR and 51 countries have plans under development. The report includes surveillance, education, monitoring, and regulating consumption and use of antimicrobials in human, in animal health and production, as well as plants and the environment as recommended in the Global Action Plan published in 2015. Progress in implementing plans is greater in high- than low-income countries [22].

The Government of India has recognized AMR as a key priority and in April 2017 and finalized India's National Action Plan on Antimicrobial Resistance [23]. Surveillance findings are playing an important role to inform clinical therapy decisions, guiding policy recommendations, and assessing the impact of resistance globally. WHO has launched Global Antimicrobial Resistance Surveillance System to support a standardized approach to the collection, analysis, and sharing of data on AMR at a global level [24]. Surveillance and epidemiological data are essential to keep an eye on increasing global resistance pattern in pathogens. Surveillance data help one to track the changes in microbial populations and permit the early detection of resistant strains. Further, the

European Antimicrobial Resistance Surveillance System and the European Surveillance of Antimicrobial Consumption program have also joined the venture.

3.2 One Health approach

One Health is defined as a collaborative, multisectoral, and transdisciplinary approach to work at the local, regional, national, and global levels to achieve optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment (Fig. 1.2) [25]. It encourages collaborative efforts of many experts such as physicians, veterinarians, and ecologists working together to monitor, control, and learn about public health threats, the spread of diseases among the animal, human, and environment. The health of the people is strongly related to the health of the animal and environment. Many human diseases are shared between animals and people and hence they can serve as an early warning sign for the potential human illness in the future. The diseases include zoonotic diseases such as rabies, Salmonella infection, West Nile virus fever, and Q fever.

The One Health concept is not new but now it is extremely important in the context of a current situation where many factors have changed the interaction in between

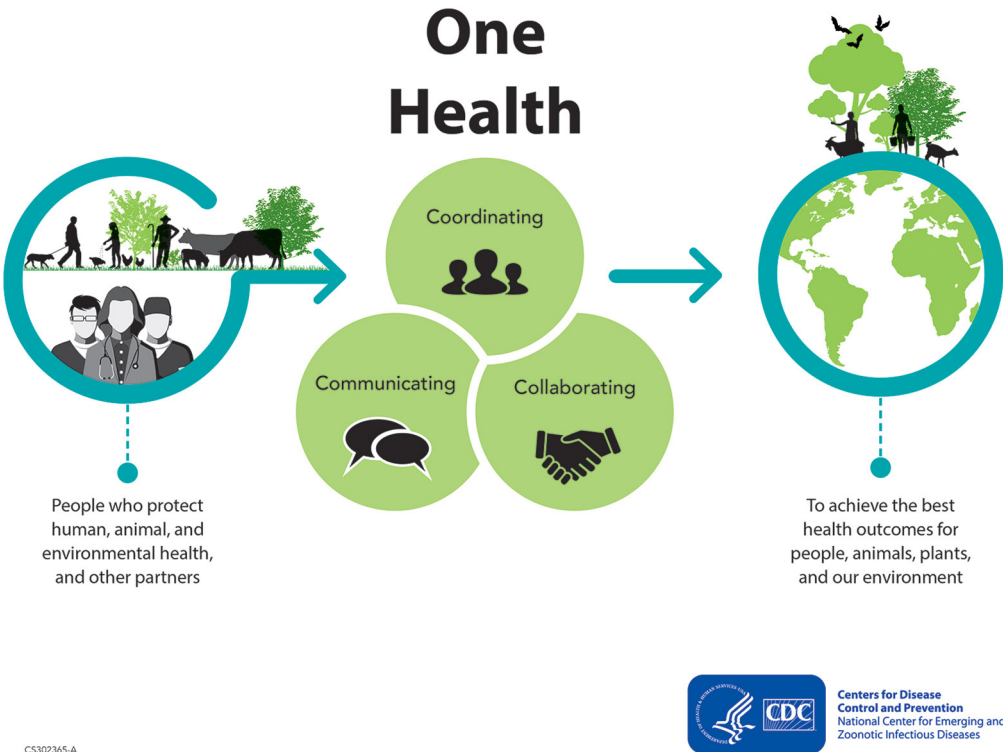

Figure 1.2 ***One Health.*** *(Adapted from CDC).*

the human, animal and their shared environment. Intriguingly, the problem of misuse of antibiotics originates from its utilization in livestock where ~80% of all the antibiotics produced are used as growth promoters and prophylactic agents in animals (nontherapeutic uses) worldwide [26]. These animals are often grown at places where they prone to infection due to unsanitary, filthy, and stressful conditions. The economic cost of maintaining a sanitary environment is a lot greater than that of addition of antibiotics as growth promoters. So addition of antibiotics to food and water for livestock makes them grow faster and prevent infections. This situation leads to incredible increase in AMR, and often these animals are home to multiple antibiotic-resistant organisms.

3.3 Introducing new chemical entities and managing current antibiotics

New chemical entities should be continuously introduced with a novel mechanism of action by incentivizing the research and development in drug discovery. But the introduction of new antibiotics is not the only solution to the problem. The solution to the problem is relying on our ability to manage current antimicrobial agents effectively. The problem is in the broken system, which we have developed over the years. We introduce our precious drugs into the broken system that gives millions of chances to bacteria to develop a resistance. Instead, antibiotics are the societal drugs and every person should bear the responsibility of using it appropriately [27]. Antibiotics are not the same as other drugs that we used to treat chronic diseases such as diabetes or cancer. For example, if a person takes paracetamol and accidentally gets overdosed, it can lead to the liver damage and kidney failure. But that does not change or affect anybody else's ability to take paracetamol. If the same person is going to misuse antibiotics, it creates drug-resistant bacteria that spread to the other people in society and prevent them from being treated with that same antibiotic. We should embrace the antibiotics like a precious treasure and save them for future generation.

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