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Introductory Chapter: Stepping into the Post-Antibiotic Era – Challenges and Solutions

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<http://dx.doi.org/10.5772/intechopen.84486>

1. Antibiotics and antibiotic resistance in the pre-antibiotic era

Antibiotics are known to exist in the history of mankind since ancient times. They can be traced back to as early as 350–550 CE, when scientists found traces of tetracycline in human skeletal remains of ancient Sudanese Nuba [1]. This has led to the speculation that the diet of this population contained tetracycline. Even the red soils of Jordan which have been used since time immemorial to treat wounds have been shown to contain *Actinomyces* bacteria which produced actinomycin [2]. Antimicrobial activity is also present in many of the herbs used in traditional Indian Ayurvedic and Chinese medicines.

Antibiotics have saved countless lives, and at one point of time, we imagined that infectious diseases were conquered. Most of the advances of modern medicine including state of art surgeries and management of neutropenic, transplant and cancer patients are based on the use of effective broad-spectrum antibiotics. Thanks to the way we have handled these precious resources for treatment of variety of infectious diseases. However, we found to our dismay subsequently that we are stepping into the post-antibiotic era.

Antibiotic resistance genes have been present in nature long before the modern antibiotic era began. Some of the serine and metallo-beta-lactamases originated more than 2 million years ago [3]. It seems prudent to assume that the ancient bacteria had defence mechanisms (such as antibiotic altering enzymes or efflux pumps) to protect themselves from high antibiotic concentrations. Hence, the biosynthetic gene cluster that makes the “antibiotic” must also contain genes which confer “resistance” to these antibiotics, and many aspects of the resistome (collection of all AMR genes in a specific bacteria or ecological niche) might have developed much before these antibiotics became prevalent in clinical practice.

2. Modern antibiotic era

Modern antibiotic era began in 1904–1910 with Paul Ehrlich and Alexander Fleming [4, 5]. Initially, it was limited to the discovery of chemicals like inorganic mercury salts and organo-arsenic compounds to treat syphilis. It was Paul Ehrlich who introduced the systemic screening approach that is the cornerstone of modern drug research trials [4]. Paul Ehrlich and his team synthesised hundreds of organo-arsenic derivatives of a very toxic drug Atoxyl and tested them in rabbits infected with syphilis. This approach led to the discovery of Salvarsan and later to a sulfa drug (Prontosil). The serendipitous discovery of penicillin by Alexander Fleming in 1928 changed the history of infectious diseases [5]. It was Florey and Chain who led the pathway for purification of penicillin and later to its mass production [6]. Interestingly enough, Fleming was the one who sounded the warning bells regarding the development of resistance to the penicillin, if not used properly. So, in a nutshell, discovery of the first three antimicrobials, Salvarsan, Prontosil and penicillin paved the pathway for the discovery of newer antibiotics in future.

The golden era of discovery of newer antibiotics continued and lasted till 1970s when most of the major classes like tetracyclines, methicillin, gentamicin, etc. were discovered [7]. This was followed by apparent absence of newer drug discovery with occasional antibiotic making an appearance here and there. Simultaneously, we made each newly discovered antibiotic ineffective after its launch by extensive use and misuse for trivial illnesses. The prime example of this is the fluoroquinolone, ciprofloxacin [8]. It was one of the most active, broad-spectrum antibiotics which had minimum side effects and a very good bioavailability upon oral use and soon became a drug of choice for many infections. Its extensive usage for gastroenteritis and respiratory infections, which were mostly viral in origin, led to the development of high level of resistance especially in developing countries.

3. Antibiotic resistance: origin and current status

The first concern regarding antimicrobial resistance appeared with the observation of penicillin resistant *Staphylococcus* in 1940 [7]. Initial few observations suggested that bacteria could destroy the drug by enzymatic degradation. Shortly thereafter, penicillin resistance became a substantial clinical problem. The first case of methicillin-resistant *Staphylococcus aureus* (MRSA) was identified in the United Kingdom in 1962 and in the United States in 1968 [9, 10]. In reality, this is true for many other pathogenic bacteria, including the *Enterobacteriaceae*, which have become resistant not only to the original penicillin but also to semisynthetic penicillins, cephalosporins and newer carbapenems [11]. Details about the development of the resistance in different classes of antibiotics are shown in the timeline (**Figure 1**) [7]. Antimicrobial resistance often occurs through various mechanisms such as inhibition of cell wall synthesis, nucleic acid synthesis, ribosome function, protein synthesis, folate metabolism and cell membrane function. The target can be (i) modified, as in the case of acetylation of aminoglycosides, (ii) destroyed (as the β -lactam antibiotics by the

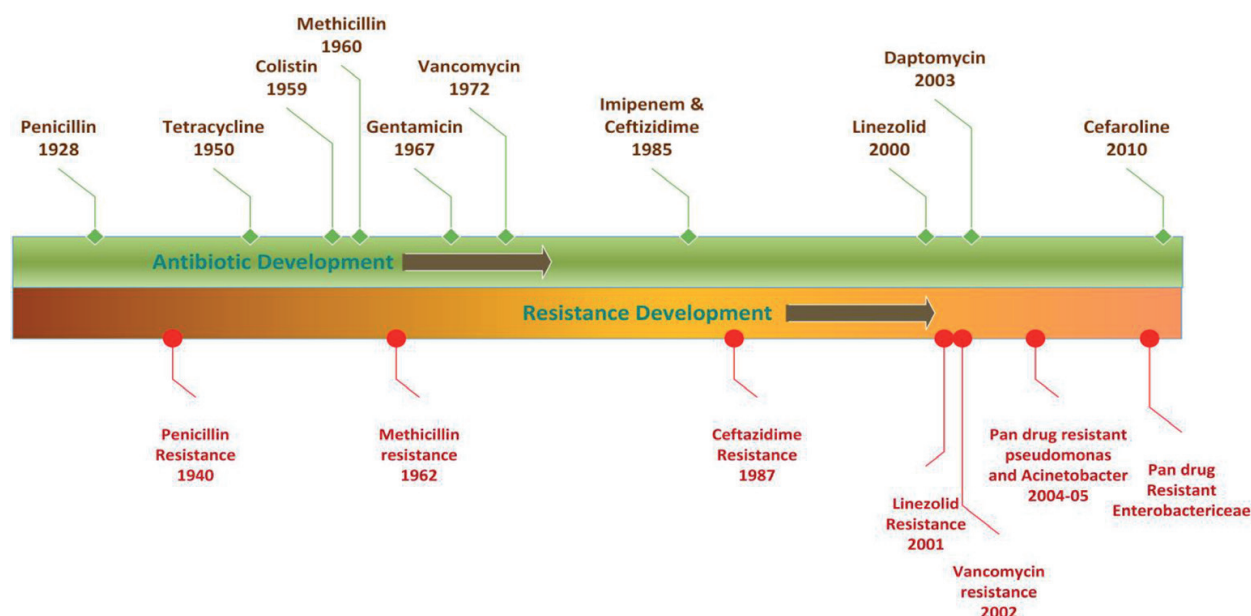


Figure 1. Timeline showing antibiotic development and antimicrobial resistance.

action of β -lactamases) and (iii) pumped out from the cell as in efflux pump mechanisms of resistance [12].

Unfortunately, true burden of antimicrobial resistance (AMR) remains unknown. There are many hindrances in estimating the burden of AMR. Incongruent data is available from public and private sectors; data are often not collected properly and contain little information of patient follow up. These problems are intensified in low- and middle-socioeconomic countries due to problems of inadequate surveillance, poor laboratory infrastructure and limited access to the crucial antimicrobials. According to a study from Vietnam and Thailand, prevalence of stool carriage of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* was 51.0 and 69.3%, respectively [13]. There is also an increasing prevalence of MDR Gram-positive bacteria. Another study in Thailand and Indonesia showed that prevalence of MRSA carriage is around 8% in admitted patients [14, 15]. Similar or worse situation exists in other Asian countries including China, Pakistan, Bangladesh and India. Antimicrobial resistance is a global issue. Resistance genes spread throughout the world as recent database lists the existence of more than 20,000 potential resistance genes (r genes) of nearly 400 different types, predicted from available sequences [16]. It is difficult to estimate the exact AMR burden due to the lack of comprehensive and uniform data. Gram-negative bacteria possessing the capabilities of producing extended-spectrum beta-lactamases (ESBL), AmpC beta-lactamases and carbapenemases have emerged as a therapeutic challenge for medical fraternity [17]. *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species have been classified into a group known as “ESKAPE” due to their ability to escape the action of antimicrobials [18]. Multiple mechanisms of antimicrobial resistance have been acquired by carbapenem-resistant *Enterobacteriaceae* (CRE), *P. aeruginosa* and *A. Baumannii* resulting in enhanced morbidity and mortality [19–23]. In the 1990s,

emergence of ESBLs among different microorganisms on global level led to widespread and increased use of carbapenems giving rise to emergence of pandemic CRE [24]. The Centers for Disease Control and Prevention has categorised CRE as *urgent* and ESBL-producing Gram-negative bacteria as *serious* antibiotic threats in the USA [10].

4. The scare and complexity of antibiotic resistance

The scale, to which antibiotic resistance has become a challenge in the treatment of the modern medicine, is scary to say the least. Every year, around 25,000 patients die of the infection with multidrug-resistant bacteria alone in the European Union [25]. In the United States alone, nearly 90,000 people die of hospital-acquired infections [26]. According to Jim O'Neill, >700,000 people die across the globe every year due to infections caused by multidrug-resistant organisms [27]. In this study, it was predicted that by 2050, more than 10 million people will die because of multidrug-resistant bugs. Huge economic losses are also expected, leading to reduction of 2–3.5% in GDP; livestock production will fall by 3–8%, costing the world up to \$100 trillion [27]. Developing countries in Africa and South Asia will be the worst affected.

AMR is not only a problem of human medicine but also an ecological problem. Microbes have proved not only smarter than humans in developing new arsenal but also have armies in the form of biofilms. It looks like humans may be losing the arms race to bacteria, and the advent of the post-antibiotic era is imminent.

5. Causes of the antibiotic resistance crisis

5.1. Overuse

Antibiotic consumption is the single most important risk factor for emergence and spread of resistant bacterial strains. In many countries including India, antibiotics are easily available over the counter even without a prescription [28]. Moreover, antibiotics are plentiful and cheap also. This non-prescription use of drugs varies from 19 to 90% in various countries outside the United States and Europe, which is a matter of serious concern [29]. The problem has been compounded by the online purchase of these products, which further facilitate the self-medication. Some surveys reported that patients often do not know that they were prescribed an antimicrobial and the true proportion of patients using antimicrobials is probably higher than the reported [30, 31]. On the other hand, there are instances where patients demand antibiotics from their clinicians.

5.2. Inappropriate prescriptions

Incorrectly prescribed antibiotics contribute majorly to the burden of resistant bacteria. Several studies have observed that indication, choice of the antibiotics and duration of

treatment are incorrect in almost 30–50% of cases [32, 33]. Extensive usage occurs in ICUs and high-dependency units, and there too approximately, 30–60% of the usage is unnecessary or incorrect [33]. Studies from pharmacies of Vietnam show that 90% of antimicrobials are sold without a proper prescription [34]. Upper respiratory tract infections (URTI) are good example, for which antimicrobial are commonly prescribed over the counter. This illustrates the overuse of antimicrobials for a condition that is often self-limiting and generally of viral aetiology. Suboptimal doses of any antibiotic further promote the genetic alterations as well as mutagenesis in the bacteria which lead to the development of multi-drug resistance in them.

5.3. Extensive use in livestock sector

Antibiotics are widely used as growth promoters and to prevent infections in the livestock sector. In the United States alone, an estimated 80% of the sold antibiotics are used in farm animals [7]. In 2010, India was one of the world's largest consumers of antibiotics in the veterinary sector [35]. The resistant bacteria reach the consumers through food animal products, mainly meat. These bacteria constitute large pools of AMR genes that can be transferred to humans and pathogenic bacteria by natural horizontal gene transfer mechanisms. These bacteria, although some may only be transient and do not colonise the intestinal tract, reside long enough to interact with the host microbiota and may possibly acquire or release genes. They can also act as opportunistic pathogens in susceptible hosts and probably play a key role in the evolution and dissemination of AMR. The use of antibiotics in food not only leads to the emergence and spread of resistant bacteria but also can be hazardous to many types of nontargeted environmental microorganisms. High concentrations of therapeutic antibiotics tend to be lethal to most bacterial strains leaving little opportunity for selection of subpopulations that have low or intermediate resistant traits. On the other hand, low levels of antibiotics in environment like soil, water and sewage become grounds for the selection of resistant microorganisms leading to the development of resistant gene pool or resistome [7, 12].

5.4. Availability of few new antibiotics

Investment in antibiotic development research is no longer considered as an economically wise decision for pharmaceutical companies [36]. According to a study conducted in London, it was calculated that the net present value (NPV) of new antibiotics is only about \$50 million, compared to approximately \$1 billion for a drug used to treat a neuromuscular disease [37].

Other reasons include low cost of antibiotics, regulatory barriers and tendency to save the new drug for serious infections. In spite of global warnings issued by many agencies, very few new drug discoveries fail to keep pace with worsening resistance scenario. As declared by the CDC in 2013, the human race is moving into a new era of infectious disease: the post-antibiotic period [38]. Here are few examples of the MDR organisms which are considered a substantial threat to the humankind. They have been divided as “urgent,” “serious” or “concerning” by CDC [24, 39] (Figure 2).

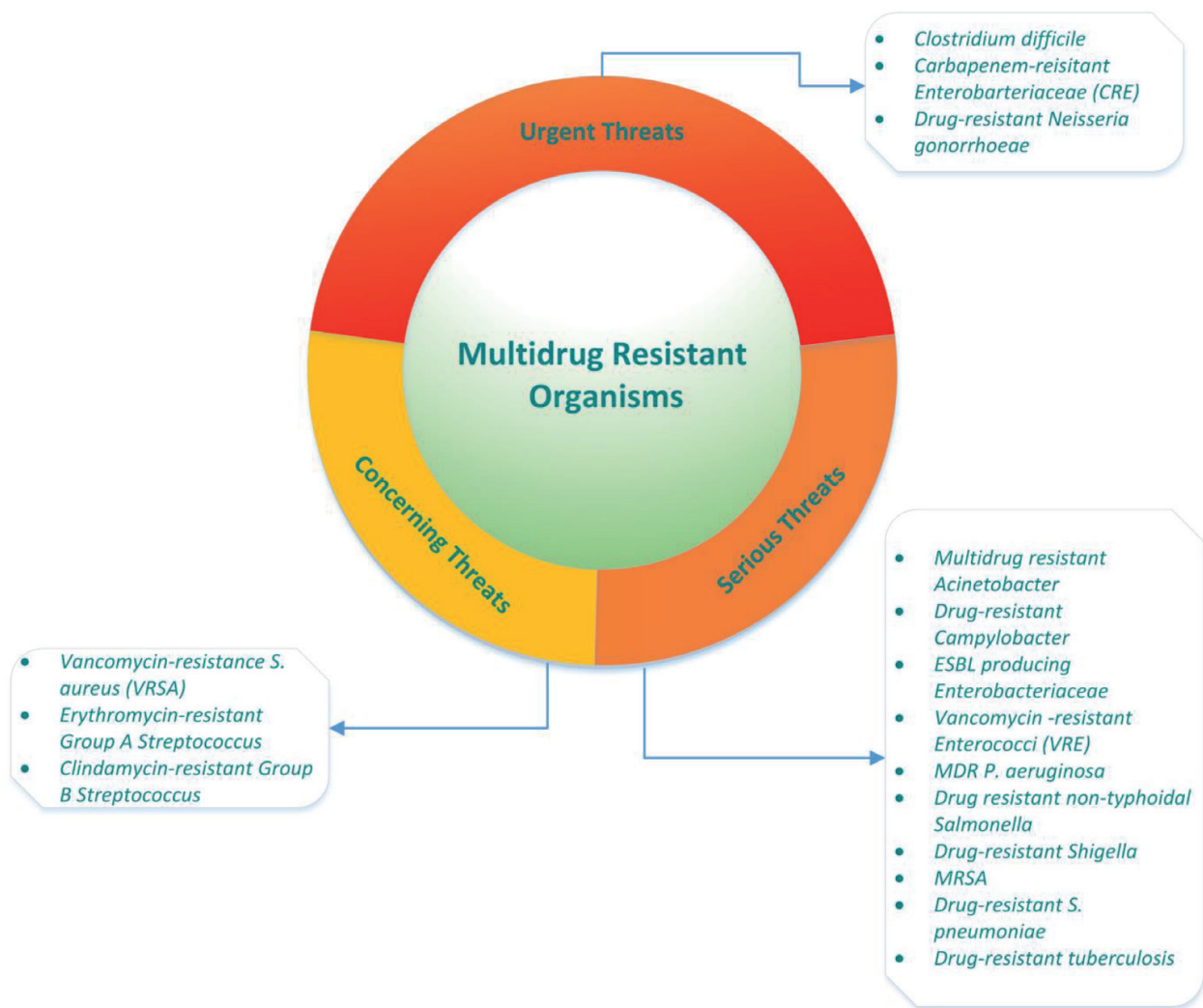


Figure 2. Urgent, concerning and serious threats with respect to development of antimicrobial resistance.

6. Solutions: do we have any?

There is an urgent need to strategize to save the existing antimicrobials. We can perform that by following means to improve the existing ones, discover novel antibiotics, dig up the old so-called toxic compounds, scale up antibiotic stewardship, use inter-sectorial multidisciplinary approaches, educate the public and clinician's alike and reduce the antibiotics in livestock and agriculture to name a few [12].

6.1. New targets/approaches

Soil and marine environments appear to be rich ecological niches to discover new agents and so do the plants and animals. Co-trimoxazole was a perfect example of targeting two enzymes in a metabolic pathway producing synergism. Compounds can be synthesised artificially to target more than one mechanism. There is important role of whole genome sequencing and metagenomics to find the new targets.

We hope that novel hitherto unknown mechanisms of antibiotic resistance will be revealed which can be exploited to find new targets. The drugs targeting anti-virulence mechanisms are an attractive strategy and have shown some promising results. Other interesting approach may be to target/alter untapped metabolic pathways like fatty acid synthesis, proton motive force, quorum sensing, signal transduction, efflux pumps, etc. [12]. Many of such compounds are currently in experimental stages.

6.2. Repurposing of compounds

Some of the compounds are already approved by FDA for treatment of metabolic disorders and cancers also have antimicrobial properties and can be repurposed, e.g., the compound BPH-652 that inhibits squalene synthase involved in cholesterol biosynthesis and also inhibits dehydrosqualene synthase involved in virulence in *Staphylococcus aureus*, hence a good candidate for Methicillin-resistant *Staphylococcus aureus* (MRSA) [12].

6.3. Considering conventional drugs

The drugs used in the past, which have been revived and now are used to treat the infections caused by Gram-negative bacteria, include colistin, fosfomycin, temocillin and rifampicin [17].

6.4. Combination therapy

Finding a suitable antimicrobial treatment option for some of the highly drug-resistant bacteria can be really daunting, and many times, clinicians resort to using combinations without data pertaining to their efficacy. The main drugs in these combinations are polymyxins and tigecycline; however, additional drugs comprise carbapenems, tigecycline, fosfomycin, aminoglycosides, and rifampicin [17] where data on randomised control trials of these drugs is also lacking. The factors which need to be taken into account before an appropriate combination is used includes the targeted organism and its susceptibility profile, co-morbidities present in the patient and the site of the infection. More studies including pharmacokinetic and pharmacodynamics studies are required to find the ideal combinations [40].

6.5. Phage therapy

Phages have the advantage of high specificity for their hosts without any notable adverse effects. They were historically in use in Europe for treatment of bacterial infections such as skin/wound infections, urinary tract infections, ear infections and even osteomyelitis [41]. New interest has been generated in phage therapy, and it may turn out to be a useful adjunct to antibiotics. Coupling antibiotics with phages or inhibitors of enzymes appears to be an attractive strategy which may succeed in many cases [41].

7. Prevention of further spread of AMR

The extent to which AMR has spread is due to the selective pressure provided by extensive antibiotic consumption and usage. Strategies to curtail the human use of antibiotic include antibiotic

stewardship, public awareness to avoid self-medication, use of antibiotics in therapeutic doses and for appropriate length of time and education and counselling to patients not to pressurise the clinician into prescribing antibiotics for trivial illnesses. Development of new rapid diagnostic point of care tests will inform the clinician not to use antibiotics in the viral infections.

7.1. Regulation in human as well livestock sector

Though a sticky and complex issue, regulation of unprescribed antibiotics is essential especially in developing countries. There should be the rule of “prescription-only medicines” similar to various international guidelines [42]. In the veterinary and agriculture set-up, antibiotic usage is linked to economic gains. Scandinavian countries set up a good example to follow by not using antibiotics as growth promoters, and they do have the least AMR issues [43].

7.2. Antibiotic stewardship

Antimicrobial stewardship refers to “The optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance” [44]. Hence, antimicrobial stewardship basically aims at helping each patient receive the appropriate treatment without adverse effects of antibiotic use. These programmes are beneficial in reducing treatment failures, decreasing health-care associated infections and also reducing antibiotic resistance while proving economically beneficial to the hospital.

7.3. Connecting human, animal and environmental health: One Health Approach

In 2003, in an interview, a journalist used the word “One Health” by saying that “Human or livestock or wildlife health can’t be discussed in isolation anymore-there is just one health” [45]. Since then “One Health” concept has gained more recognition in the public health and animal health communities. “One Health” is a collaborative approach among various sectors and disciplines to achieve optimal health outcomes emphasising the relation between humans, animals, plants and environment shared by them [46]. This is the need of the hour because many diseases are zoonotic in nature, and microbes harbouring drug-resistant genes have no barriers. Now the WHO and CDC have also adopted this approach.

8. Conclusions

The AMR is marching globally and threatens to undo the extraordinary advancements achieved in human medicine. Coordinated efforts are required across the globe to manage this great crisis. It is time we learn from our mistakes and gather our act together to outsmart the bacteria. All said and done, microbes do have an evolutionary advantage of nearly 4 billion years and have learnt to survive the onslaught of antibiotics. We can learn from them by using the sophisticated molecular approaches we have. Antimicrobial resistance is not only a

human health problem but is an ecological challenge as well. It is up to the human race to take up this challenge and save the world from this menace.

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