A REVIEW ON ANTIBIOTICS: HISTORY AND PRESENT

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ABSTRACT

"In my first publication I might have claimed that I had come to the conclusion, as a result of serious study of the literature and deep thought, that valuable antibacterial substances were made by moulds and that I set out to investigate the problem. That would have been untrue and I preferred to tell the truth that penicillin started as a chance observation. My only merit is that I did not neglect the observation and that I pursued the subject as a bacteriologist. My publication in 1929 was the starting-point of the work of others who developed penicillin especially in the chemical field."
-Alexander Fleming

Antibiotics, which were discovered more than 90 years ago, have dramatically transformed the healthcare system and have become an essential element of contemporary medicine. The discovery of the antibiotic penicillin in 1928 marked the beginning of a golden period of natural product antibiotic discovery, which peaked in the mid-1950s. Penicillin-resistant Staphylococcus aureus was discovered in 1942, and since then, numerous antibiotic-resistant bacteria have been wreaking havoc. When bacteria acquire resistance to available antibiotics, antibiotic resistance occurs. Many medical advances, such as joint replacements, organ transplants, cancer therapy, and the treatment of chronic diseases such as diabetes, asthma, and rheumatoid arthritis, are dependent on the ability to fight infections with antibiotics, and the emergence of AMR can cause serious health issues in such patients. According to different studies, AMR is believed to be the cause of 50,000 fatalities each year in the United States and Europe, with many more instances dying in other areas of the world. In this article, we will look at the history of antibiotics, antibiotic resistance, and the societal variables that influence the spread of antibiotic-resistant bacteria into various populations.

Keywords: - *Antibiotics, Bacteria, Resistance, Antimicrobial resistance*

1. INTRODUCTION:

Since their discovery more than 90 years ago antibiotics have drastically changed the healthcare system and has become an integral part of modern medicine. The discovery of antibiotic penicillin in 1928 started the golden age of natural product antibiotic discovery that peaked in the mid-1950s. In 1942 Penicillin resistant *Staphylococcus aureus* was identified and since then various antibiotic-resistant bacteria's have been creating havoc.
Penicillin, the first true antibiotic was discovered in 1928 accidentally by Alexander Fleming. He noticed that the mould contaminated culture plate prevented the growth of staphylococci. This observation led to the discovery of the first true antibiotic and since then many more antibiotics of different nature against different diseases have been discovered.
Antibiotics are chemicals that kill or inhibit the growth of bacteria and are used to treat bacterial infections. They are produced in nature by soil bacteria and fungi [1]. However ever since their discovery, there has been a significant growth in Antimicrobial resistance (AMR) which threaten the health benefits achieved by antibiotics and this phenomenon is a matter of global concern. It has been predicted that in the upcoming future AMR is going be a major public health concern and be the major cause of deaths around the world. *Klebsiella pneumoniae* infection and *Escherichia coli* infections have shown a significant increase in AMR [1]. According to various studies it has been estimated that AMR is the cause of 50,000 deaths annually across the US and Europe, with many other cases dying in other parts of the world [2]. This review article will be discussing the history of antibiotic discovery, AMR, strategies deployed by microbes to protect themself against antibiotics and social factors affecting the occurrence of AMR in different populations.

2. THE PRE-ANTIBIOTIC ERA:

Antimicrobials are one of the most successful and useful invention ever made in the human history, it has been employed to control infectious disease that was the leading cause of human morbidity. According to research, it has been proved that traces of antibiotics were found in the human skeleton hence, proving the fact wrong that antibiotics were confined to the modern "antibiotic era". After the study and analysis traces of tetracycline was found in the skeleton remains from ancient Sudanese Nubia [3],[4]. The presence of tetracycline in bones indicates the presence of tetracycline containing materials in the diet of these ancient people. A different study of femoral mid shafts in a late roman period sample from the Dakhleh Oasis, Egypt, showed discrete fluorochrome labelling [5]. Comparisons were made with the patterns of fluorescent labelling from this population and patients treated with interval and continuous dosage of tetracycline. The results indicated that the fluorochrome is most probably tetracycline that made its way into the bone [5]. The labelling was differential, similar to that of the patient on tetracycline interval dosages, thus it is claimed that the tetracycline was taken infrequently, most likely on a seasonal basis. The suggested consumption of tetracycline by these populations provided them with protection against infectious illnesses since the prevalence of such disease in the Sudanese Nubian population was low, and no indications of bone infection were identified in Dakhleh Oasis samples.

Tetracycline is an essential antibiotic for research because it is a powerful chelator that is incorporated into the hydroxyapatite mineral component of the bones as well as tooth enamel, providing persistent markers of metabolically active regions after tetracycline exposure. Data of additional antibiotic exposure in ancient societies is difficult to find, with only surviving customs and anecdotal evidence pointing to these occurrences. Another source of antimicrobial exposure during the pre-antibiotic era might have been millennia-old therapies used in traditional/alternative medicine, notably traditional Chinese medicine (TCM). The most well-known example is the discovery of qinghaosu (artemisinin), a strong anti-malarial medicine discovered in the 1970s from Artemisia plants that had been used for thousands of years as a treatment for a range of diseases by Chinese herbalists[6]. Phylogenetic reconstruction may reveal the natural history of antibiotic resistance genes, and this type of research shows that genes conferring resistance to various types of antibiotics were present in nature long before the antibiotic era [7].

3. THE ANTIBIOTIC ERA:

Paul Ehrlich and Alexander Fleming are commonly linked with the modern antibiotic era. Paul Ehrlich developed the concept of a "magic bullet" that selectively targets only disease-causing microorganisms based on the discovery that aniline and other synthetic dyes may stain particular bacteria but not others. In 1904 he launched a large-scale systematic screening effort to discover a cure for syphilis, which was an endemic incurable illness at the time. Ehrlich thought that such chemical compounds might be created that could exert their full effect solely on the parasite housed within the host. Inorganic mercury salts were used to treat syphilis, a sexually transmitted illness caused by *Treponema pallidiu*, but the therapy produced significant adverse effects and was ineffective. He produced hundreds of organoarsenic variants of the very deadly drug Atoxyl in his laboratory, along with chemist Alfred Bertheim and bacteriologist Sahachiro Hata, and tested them on syphilis-infected rabbits. They discovered the sixth chemical of the 600th series examined, therefore numbered 606, in 1909, which cured syphilis-infected rabbits and showed great promise for the treatment of people with this venereal illness in limited human trials[8]. Despite the difficult injection process and adverse effects, the medicine, sold by Hoechst as Salvarsan, was a huge success and, together with a more soluble and less toxic Neosalvarsan, was the most often prescribed treatment until it was replaced by penicillin in the 1940s [9].

Paul Ehrlich's systematic screening technique was utilised in the discovery of sulfa medicines, namely sulfonamidochrysoidine (KI-730, Prontosil), which was produced by Bayer chemists Josef Klarer and Fritz Mietzsch and evaluated for antibacterial activity in a variety of illnesses by Gerhard Domagk [10]. Protonsil were further investigated, and it was discovered that they were the precursors of active drugs, the active component of which being sulfanilamide. Because sulfanilamide was non-patentable and inexpensive to make, and the sulfanilamide molecule was easy to alter, several companies began mass manufacturing of sulfonamide derivates. The legacy of this oldest antibiotic on the market may be represented in one of the most widely distributed examples of drug resistance: sulfa drug resistance, which is usually always associated with class 1 integron.

Penicillin an antibiotic that was accidentally discovered by Alexander Fleming had saved millions of lives. Before the discovery of Penicillin Alexander Fleming discovered lysozyme in the mucus and later in tears, saliva, skin, hair and fingernails. Later, he extracted a bigger amount of lysozyme from egg white, but later studies revealed that this enzyme was only efficient against a small number of non-harmful bacteria. Nonetheless, this laid the basis for Fleming's next big breakthrough. In 1928 Fleming carried a series of experiments involving staphylococcal bacteria.

An uncovered Petri dish from the experiment became contaminated with mould spore. Fleming observed that the bacteria in proximity to the mould colonies were dying. He was able to isolate the mould and identified it as a member of the *Penicillium* genus [11]. He discovered that it was effective against all Gram-positive bacteria, which cause illnesses including scarlet fever, pneumonia, gonorrhoea, meningitis, and diphtheria. He deduced that it was not the mould itself that had killed the germs, but whatever 'juice' it had generated. He dubbed the 'mould juice' penicillin. Although Fleming published his study in the British Journal of Experimental Pathology in 1929, it was not widely recognised at the time. He also found it difficult to isolate the juice secreted by mould in large quantities. However, in 1940 two scientists Howard Florey and Ernst Chain began researching penicillin and were able to mass-produce it for use during World War II [11].

3. ANTIBIOTIC RESISTANCE:

Based on the observation that: "Syphilis has now been treated with arsenicals for about 40 years without any indications of an increased incidence of arsenic-resistant infections, and this work gives grounds for hoping that the widespread use of penicillin will equally not result in an increased incidence of infections resistant to penicillin" [13]. This observation still holds for Treponema pallidum but not for other pathogenic bacteria, such as Enterobacteriaceae, which have developed resistance not only to the original penicillin but also to semi-synthetic penicillin, cephalosporins, and newer carbapenems [14]. According to certain observations, it was suggested that bacteria could destroy penicillin by enzymatic degradation, even before the extensive use of penicillin [12].

The major four molecular mechanisms by which bacteria can withstand the effects of bacteria include alteration of the target site, modification or destruction of the antibiotic, antibiotic efflux via efflux transporters, and reduced antibiotic inflow through decreased membrane permeability [15]. Bacteria can show a high level of resistance to multiple antibiotic compounds due to different combinations of these resistance mechanisms.

A gut bacterium that can cause potentially fatal infections. *K. pneumoniae* resistance to last-resort therapy (carbapenem antibiotics) has developed throughout the world. *K. pneumoniae* is a leading source of hospital-acquired infections such as pneumonia, bloodstream infections, neonatal infections, and intensive-care unit infections. Because of resistance, carbapenem medicines do not function in more than half of the patients treated for *K. pneumoniae* infections in various countries.

Penicillin as an antibiotic was released in 1941 and the very next year in 1942 *Staphylococcus aureus* a bacteria which is resistant to penicillin was discovered and since then various strains of bacteria resistant against penicillin has been identifies.

4. SOCIAL FACTORS CONTRIBUTING TOWARD OCCURRENCE OF AMR AMONG DIFFERENT POPULATION:

While numbers vary by country, the overall tendency is that poorer nations face far greater levels of resistance. This is most likely owing to a combination of variables, including the increased availability of second-and third-line therapies in 'First World' nations vs their 'Third World' counterparts. Furthermore, with the advent of quick transcontinental travel facilitating the spread of resistant bacterial strains internationally, localised examples of increased resistance levels can have a global influence. It has been proposed that regional resistance levels may have an impact on international travel and trade, with individuals less likely to want to go to places where they may contract dangerous bacterial illnesses. The fact that AMR levels continue to rise despite the deployment of more healthcare measures in the world's most economically developed countries emphasises the need for new methods to addressing the AMR problem.

Most antibiotic resistance methods are hampered by a lack of resources. According to World Bank data, developing countries spent $41 per person on health in 1990, compared to $1,500 per person in developed countries. Disease prevalence, as assessed by disability-adjusted life years, is significantly higher in underdeveloped nations than in industrialised countries [16,17,18]. As a result of such massive underfunding, medication delivery in many nations, including Nigeria, is chronically insufficient or, at best, irregular [18,19].

Armed wars have recently resulted in the breakdown of health systems and sanitation, as well as the fast spread of resistant diseases, notably in Sub-Saharan Africa and Asia [20,21]. Resistance to several first-line antibiotics in clinical isolates of Vibrio cholerae and Shigella dysenteriae led to increased mortality rates during a cholera and bacillary dysentery outbreak among Rwandan refugees [21].

Even in non-conflict developing nations, governmental corruption and mishandling of finances, staff, and development projects have resulted in vast populations living in abject poverty and at high risk of infection [22]. Medical bills ,lost workdays, and transportation costs account for a substantial economic loss. Many people are

unable to afford medical treatment, even when it is subsidised. Patients' payments are occasionally extorted by underpaid health personnel [22]. As a result, those with contagious illnesses who cannot afford medical treatment risk infecting others. Poverty also impairs patient compliance, which encourages the emergence of antibiotic resistance during the short-term treatment of acute illnesses and long-term treatment of chronic diseases such as TB [22].

5. CONCLUSION:

Drug-resistant bacteria are one of the biggest global health challenges that the world will confront, making even the treatment of simple ailments difficult and perhaps fatal. The emergence of superbugs, which are strains of viruses, bacteria, parasites, and fungi that are resistant to the majority of available antibiotics, cannot be ignored given their high pace of transmission. Due to overexploitation, a discovery that was once regarded as one of the greatest of all time became a source of concern. The rate of development of new resistant strains of bacteria outpaces the rate of discovery of newer antimicrobial treatments. According to WHO, 32 antibiotics in clinical development might be employed against diseases on the WHO priority pathogen list in 2019, with just six categorised as innovative [23]. The availability of medicines against new infections will always be a source of concern since AMR not only impacts an individual's health but may also have a severe impact on national economies and health systems by reducing population productivity.

Overuse of medicines and failure to complete a course of therapy is still a major cause of the development of drug-resistant bacteria. Without effective prevention of overprescribing and proper treatment of drug-resistant illness, as well as the rapid discovery of new medications and simple access to them, the number of individuals for whom therapy may not work or who die from infections will rise. International research institutes should encourage and finance additional research. The Global Antibiotic Research and Development Partnership (GARDP), which was launched by WHO and the Drugs for Neglected Diseases Initiative, supports research and development through public-private collaborations. By 2025, the collaboration hopes to have developed and delivered five novel medicines that target drug-resistant bacteria recognised by WHO as the most dangerous [23].

It is also the responsibility of the government as well as practising medical personnel to regulate the over prescription of pharmaceuticals, whilst the general population should focus more on controlled medication usage and taking medications according to the prescription issued to them.

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