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Historiography of Antibiotics: A Paradigm Shift in Healthcare during the Twentieth-Century

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Abstract

The introduction of antibiotics since the 1940's has played a pivotal role in impeding the spread of several infectious diseases. Antibiotics can be natural (produced by bacteria and fungi), semi-synthetic (chemically altered for improving effectiveness) or synthetic in nature. Penicillin can be called as a pioneer miracle drug that revolutionized healthcare post World War II and opened a door for researchers to discover an armamentarium of antibacterial agents. In spite of this, antibiotics in the primary phase of development were not only expensive but also scarce. In due course of time, the process of manufacturing was modified and new formulations were developed. Apart from penicillin, streptomycin, chloramphenicol and tetracyclines were the antibiotics that were developed with collaboration among researchers, industry and policy makers. These were distributed in the form of coated-pills or embedded in ampoules and flasks. In parallel to their usefulness in treating diseases, there was a rise of a clinical phenomenon known as antibiotic resistance (being non-sensitive) among different bacteria. In the twenty-first century, the primary focus of the researchers is in finding ways to combat antibiotic resistance and ironically many pharmaceutical firms have severely limited investments for discovering new antibiotics owing to negative returns of investments.

Keywords: Antibiotics; Historiography; Penicillin; Antibiotic resistance

Introduction

Bacteria are a group of single celled microorganisms possessing cell wall but lacking an organized nucleus and organelles. Some bacteria are widely known to cause diseases (such as cholera, typhoid, tuberculosis, diphtheria and tetanus) in humans. Antibiotics, also known as antibacterials, are antimicrobial drugs which are used for treating as well as preventing bacterial infections [1]. These can be natural (produced by bacteria and fungi), semi-synthetic (chemically altered for improving effectiveness) or synthetic in nature. These might inhibit or kill growth of bacterial species. Additionally, a limited number of antibiotics also possess antiprotozoal (single celled microorganisms having nucleus and organelles). In general, antibiotics are not particularly effective against viruses (such as influenza or common cold) and drugs that inhibit viruses are called antivirals or antiviral drugs rather than being called as antibiotics. History of the twentieth-century medical drugs

is a wide research subject in which large contributions were made not only from the history of science and medicine but also from the history of industry [2]. Antibiotics shifted the paradigm of medicine in the twentieth century. In collaboration with vaccination, antibiotics proved beneficial in almost eradication of many diseases (particularly tuberculosis) in the developed countries. Penicillin not only proved important to scientists, government and industry but also to engineers, doctors and patients, expressing a history which is pretty complicated than public would remember. Historiography of antibiotics has majorly underlined the essential role of penicillin (an antibiotic produced in nature by few blue moulds but in present generally prepared in a synthetic way) as a pioneer miracle.

Only a few would deny that introduction of antibiotics around the 1940's brought a revolution in treating many infectious diseases. The maladies which had played an essential role in morbidity and mortality of humans in the previous millennia were suddenly diminished by these drugs. The widespread impact of these drugs in healthcare around the world constitutes a rich stuff of historiography for historians to recall. During and post World War 2 (WWII) era, the Americans triumphantly started the well known production program of penicillin. However, the history of a strenuous pre-war work of pioneers in the deep fermentation (a process for increasing the amount of antibiotics) is generally overlooked. Penicillin is famously known as the first wonder drug of the post-WWII years as its discovery and production including distribution was rejoiced for the coming half a century years. This was also historically important keeping in the view of pharmaceutical industries because these were dominant in Germany during the pre-WWII years but after the war dominancy shifted to the United States. The pioneer work in antibiotic discovery started with the research paper published in 1929 by Sir Alexander Fleming in which he described penicillin along with its antimicrobial effect leading to the exploratory trials [3]. Around a decade later Ernst Chain, Howard Florey along with their colleagues at the Oxford University (in United Kingdom) developed penicillin (although in small amounts) that allowed testing on humans [4]. During the WWII, an efficient method of production of this drug was developed in the Northern Research Laboratory (United States Department of Agriculture) in Peoria (Illinois). From this pilot plant, production moved to the manufacturing plants with the involvement of pharmaceutical companies such as Pfizer, Lilly, Merck and Squibb. In the following years apart from penicillin, streptomycin, chloramphenicol and tetracyclines were the antibiotics that were developed with collaboration among researchers, industry and policy makers. In 1947, protocols for treating and evaluating of the antibiotic streptomycin (an antibiotic produced by a soil bacterium *Streptomyces griseus*) were successfully standardized. The brief timeline of the historiography of antibiotics is shown in Figure 1. From 1940 to around 1960, successive antibiotics followed a distinctive, not only repeatable but also predictable pattern of first discovery and afterwards development into a marketable chemical therapeutic agent. These steps led to widespread easy accessible and economically feasible antibiotics for the public.

Nevertheless, the easy access as well as effectiveness of antibiotics also resulted in their overuse, which prompted bacteria to develop resistance against these miraculous drugs. This has been the leading cause of widespread problems in the twenty-first century. The World Health Organization (WHO) has classified the resistance against antibiotics as a

serious threat which is not just a prediction for the future time but is happening at present in every part of the earth, with the potential to affect any individual throughout the world [5]. As seen commonly in nature, many bacteria have already evolved ways of evading antibiotics, among which methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* species deserve a mention. In spite of this, as almost all bacterial infections can be adequately treated by antibiotics which are widely available and cheap, true coordinated efforts for addressing the rise of these extensively drug-resistant bacteria and multi-drug resistant have not been executed. The ways for slowing the spread and development of resistant bacteria (mainly by restricting the unnecessary use of antibiotics in humans as well as animals and improving hygiene) can be of a vital impact for treating these so-called superbugs [6]. This review tries to provide comprehensive information on the historiography (in particular of early antibiotics), basic classification of antibiotics and a brief overview of the present day viewpoint on antibiotics.

Discovery of penicillin and its circulation

Penicillin's discovery (among the world's first antibiotics) is a changing point in the human history. The doctors among the world ultimately had a tool which could be used for complete cure of patients suffering from deadly infectious diseases. It was discovered in September of 1928 (in London) for the first time. The common though among the masses is that Dr. Alexander Fleming (bacteriologist at St. Mary's Hospital) (Figure 2a) came back from a summer trip in Scotland and found a messy lab bench and plenty more. After examining some colonies of *Staphylococcus aureus*, he noted that a mold named *Penicillium notatum* had contaminated the Petri dishes he was working on before the trip (Figure 2b). After a careful examination of the dishes with a microscope, he was surprised to figure out that this mold had prevented the normal growth of the *Staphylococci* colony [7]. It took Fleming around a few weeks in order to grow enough of the mold for confirming the findings he got. His deductions proved to be remarkable because there was something in the *Penicillium* mold which was able to inhibit the growth of the bacteria and more importantly could be put to use for combating infectious diseases. Sir Fleming popularly wrote that he when he had woken up on the dawn on September 28, 1928; he nowhere planned to channelize all medicine by discovering the world's first bacteria killer or antibiotic. However, that was something he just did. In actuality, Fleming did not have a chemistry background and only a few laboratory resources at St. Mary's hospital for taking the next big step of isolating the essential component from the juice of *penicillium* mold. He also neither had the resources as well as the knowledge of how to purify it nor find out which pathogens it was effective against. This task fell on the shoulders of Dr. Howard Florey (a professor in the subject of pathology), who was the director of Sir William Dunn School of Pathology (at Oxford University, United Kingdom). He was proficient in the extraction of research grants from parsimonious bureaucrats and was versatile at administering a large research laboratory which was filled with talented but unconventional researchers. The landmark breakthrough came in 1938 when Florey (who was interested in devising the ways by which bacteria and mold kill each other naturally) had a chance to read Fleming's paper on the *penicillium* mold, while going through few back issues from a British journal on pathology. Just few days after, Florey and his colleagues gathered in his well built

laboratory with all the necessary stocks. They started to figure out the science of what Fleming called as antibacterial action of *penicillium.* Dr. Ernst Chain (a biochemist) was one of Florey's brightest researcher, along with Florey were able to produce a series of crude mold *penicillium* from the culture fluid extracts.

In the summer of 1940, the experiments of Florey and Chain were primarily on a group of fifty mice which had been infected with deadly *Streptococcus* bacterial strains. Half of these mice died from the sepsis which was overwhelming. The remaining ones, that were administered with the injections of penicillin survived. This was the point at which Florey had understood that he was having enough optimistic information for testing the drug on humans. However, the problem still remained, which was how to produce abundant pure penicillin for treating people. Although they tried hard to increase the yield of penicillin from the mold cultures but it took around 2000 L of mold culture for obtaining enough pure penicillin for treating a single case of sepsis in an individual. In the September of 1940, Albert Alexander (an Oxford police constable) became the first test case of this antibiotic. He had nicked his face while working in his rose garden and the scratch from the wound became infected with *Staphylococci* and *Streptococci,* soon spread to his scalp and eyes. Although he was admitted to the infirmary in Radcliffe and was treated with sulfa drugs, yet the infection worsened, resulting into abscesses in the lungs, shoulder and eye. Florey and Chain after hearing this, decided to intervene as they were asked by physicians if they may try their penicillin in a purified form. After around a week of injections, Alexander had begun to recover. However, Florey and Chain did not have enough amounts of pure penicillin for eradicating the infection, which led to Alexander's death.

Another prominent figure in the lab was Dr. Norman Heatley (a biochemist) who had used every available bottle, container and bedpan for growing the vats of penicillin mold and thereafter suctioning off the fluid along with developing the ways to purify the antibiotic [7]. He was able to build a makeshift mold factory which laid the foundation for constructing the big fermentation tanks as well as the sophisticated chemical engineering used nowadays. In the summer of 1941, just before the United States entered WWII, Heatley along with Florey visited the United States, where they collaborated with American scientists in Peoria (Illinois) (as described briefly in the introduction section) for developing a means for the mass production of penicillin which later was called as the wonder drug [8]. There was an addition of corn-steep liquor to the medium and the cultures were of submerged type. Florey and Heatley still knew that the fungus *Penicillium notatum* could never ever yield abundant penicillin to treat human population reliably. They tried to search for a more productive species which could yield abundant amounts of this drug. One hot summer day in 1941, Mary Hunt (Florey's laboratory assistant), entered the lab with a cantaloupe that she had found at the market, covered with a mold of golden color. Accidentally, this mold emerged to be a fungus named *Penicillium chrysogeum*, which yielded about 200 times the amount of penicillin as compared to *Penicillium notatum* which Fleming had discovered. In spite of this, this species required amplification with a mutation (an abundant genetic change) by X-rays and along with filtration process, ultimately the production of penicillin grew to about 1,000 times in comparison with the first batches of *Penicillium notatum*. In March of 1942, Anne Miller turned out to be the first civilian patient who was successfully

treated with the help of penicillin. When given the treatment, she was lying near death at the New Haven Hospital (in Connecticut, USA) after a miscarriage and had developed an infection which had caused blood poisoning. Figure 2(c) shows a child named Jean-Claude Fide being treated with penicillin by his mother.

In need of the hour during the WWII, penicillin successfully proved its mettle. While surveying all of the history of wars, the major killer was the infection caused by pathogens rather than the injuries from the battle. In the World War 1 (WWI), the death rate from pneumonia caused by bacteria was about 18%, but in WWII this fell to an astonishing less than 1%. During January to May in 1942, 400 million units of penicillin in purified form were developed in the United States itself. At the end of WWII, the pharmaceutical companies in America were producing large quantities, around 650 billion units, in a month. Alfred Newton Richards (the vice president at the office of scientific research and development) also encouraged the production of penicillin as part of the WWII effort in the States. Therefore, from a pilot plant, the production of penicillin shifted to the manufacturing plants with the involvement of pharmaceutical companies such as Pfizer, Squibb, Lilly and Merck. It is still ironic that Fleming did only a little research on penicillin after his first observation about it in 1928. In the Beginning of 1941, after the media began to unfold the early trials of penicillin on humans, the usually unpresentable and considerate Fleming was glorified as the discoverer of the antibiotic penicillin. It was a quiet dismay for Florey and his Oxford researchers whose contributions were basically ignored. However, this problem was partially rectified in the year 1945, when Florey, Chain and Fleming (but not Heatley) were awarded with the Nobel Prize in Medicine. It might be remembered that Fleming in his Nobel Prize acceptance speech, warned the public that overuse of penicillin may lead to resistance in bacteria (on which it was pretty effective by then). It is still pleasing that in 1990, Oxford was able to make up for the Nobel committee's inaccuracy by awarding Heatley with the first honorary doctorate in medicine (in its entire 800 year history).

Penicillin, in its early years, was injected eight times a day in the patients but with time it was chemically reconstructed. Moreover, its absorption in the body was slowed in order for allowing it to last for 8 hours rather than 3 hours in high concentrations within the blood. Furthermore, it was made sufficiently stable to be taken orally (Figure 2d) or as an ointment (Figure 2e). It was also to stand up for the challenge against aggressive pathogenic resistant bacteria that were able to exude penicillinase (a destructive enzyme that breaks penicillin rendering it ineffective). The manufacturing technology used in penicillin production was also applied to other drugs (mostly other antibiotics) and surprisingly to steroids which are chemically as well as therapeutically very different from antibiotics. As the time passed, the centers of penicillin production moved from the United Sates: firstly to the United Kingdom, then to Austria and finally to the Japan, China and Netherlands. However, it must be said that there was not a standard way of trajectory of penicillin antibiotic. Almost every developed or some developing countries were manufacturing large amounts of penicillin in factories. There is also a controversy over whether penicillin production actually moved from United States to the United Kingdom. In recent texts it has been stated that it was mass produced concurrently in the United Kingdom and United States [9]. In France, trips of the researchers to the United States made penicillin possible in the country. However, in

Germany (country on the losing side in WWII) pharmaceutical firms such as Bayer (pioneers of sulfa drugs) struggled to cope up with the worldwide developments related with antibiotics produced from fungi (such as penicillin). While internationalization and standardization were essential for producing and evaluating antibiotics, the viewpoint on their circulation served to emphasize the national policies of the United States that were involved in the era of post-WWII. These policies were able to shape early production of penicillin in labs and factories [8]. The national policies of this country propagated that penicillin was like a transnational object. News of its therapeutic capacities against infectious diseases travelled firstly in the form of publications. Later on, the antibiotic itself, filled in ampoules assembled in boxes, travelled worldwide along with methods of usage. Additionally, the types of infections and doses required for combating them circulated across the world along with the methods of industrial production.

History of other prominent antibiotics

The resistance of bacteria against antibiotics has mainly contributed to shape research and the medical practices not only in the present but also in the past. This phenomenon has primarily contributed to the increased knowledge of the action mechanisms of antibiotics in the body at a cellular level, along with setting the basis for further research into newer antibiotics. Penicillin was the first among the long series of antibiotics, followed by streptomycin's successful use in treating tuberculosis and later by tetracyclines and chloramphenicol.

Streptomycin was an antibiotic which was first isolated in 1943 and was the first antibiotic effectively used against tuberculosis disease. Additionally, it opened the gate for developing advanced clinical research in the field of antibiotics other than penicillin. In fact, it was the first antibiotic drug that was used for conducting a randomized control trial for treating pulmonary tuberculosis in the year 1946 by the Medical Research Council in the United Kingdom [10]. All around the nineteenth century tuberculosis was the major cause of death in youngsters. All the previous attempts to cure *Mycobacterium tuberculosis* (bacterium that causes this disease) infections were unsuccessful. The patients were mainly isolated in rooms and provided rest in sanitary conditions, so that the infection could not spread. After the initial discovery of penicillin drug and its successful treatment of bacterial diseases, the drug firm Merck tried to sustain research at Rutgers University in New Jersey (United States). Selman Waksman (a soil microbiologist in this place) expanded the information known about soil bacteriology such as the way different species of microorganisms influence one another. He had established that about 50% of actinomyces (a type of soil bacterium) found in the soil were able to have an inhibitory effect on the growth of various microorganisms. He also introduced the antimicrobial activity concept and described the effect by which small molecules made by microorganisms were able to antagonize the growth of other ones. From 1940 to 1952, Waksman had isolated as well as reported more than ten different chemicals having antimicrobial activity [11]. The most popular as well as influential among these chemicals was streptomycin. In the autumn of 1943, the diligent work of one of his collaborators, Albert Schatz was able to isolate streptomycin antibiotic from a *Streptomyces griseus* culture [12]. In lesser than a month, a streptomycin sample was sent

to a Mayo Clinic for allowing William Feldman to do toxicology experiments in animal models. Eventually, the collaborative works between Hinshaw and Feldman led to first clinical trials on patients suffering from tuberculosis, just lesser than a year after streptomycin's discovery. Nonetheless, the effects of streptomycin on some sever cases of diffuse tuberculosis was impaired by serious side effects along with quick isolation of resistant *M. tuberculosis* strains. The scarcity of economic funds as well as the necessary promising cure of tuberculosis influenced the British Medical Research Council, which was mentored by Sir Geoffrey Marshal, to perform the first double-blind, randomized, placebo-controlled, multicenter clinical trials throughout the United Kingdom. In 1952, the results of these trials were published. Luckily, soon afterwards, in 1944, the para-amino salt of salicylic acid was chemically synthesized by Lehman, while in 1952, rapidly followed by isonicotinic acid hydrazide. This was kind of triple therapy which resulted in the comprehensive cures for approximately 95% of the patients suffering with tuberculosis.

Chloramphenicol was firstly isolated from a soil bacterium *Streptomyces venezuelae* in a sample of soil and compost. The efficacy of this new antibiotic was proved with quite dramatic results. It was able to combat two typhus outbreaks in Malaysia and Bolivia in the year 1948. In 1949, this antibiotic was approved to be safely used by the United States Food and Drug Administration and was said to be the first antibiotic which had quite a broad-spectrum (able kill plenty of pathogenic bacteria) [13]. It was soon used rapidly, spreading worldwide and was used widely in treating many infections that ranged from bronchitis to bacterial meningitis to acne. However in the 1960's, this antibiotic's popularity started to wane off as its usage was kind of linked with the fatalities that resulted from its toxic effects in the human bone marrow (such as aplastic anemia). It is noteworthy that chloramphenicol was the first antibiotic which was synthesized chemically in a very efficient process. Nowadays, it is rarely used owing to its toxicity as well as readily available alternate and effective antibiotics.

Other important group of antibiotics include tetracyclines which involve the collaborative works of thousands of dedicated scientists, researchers, business executives and clinicians in the course of around 70 years. These drugs were discovered as compounds produced by actinomycetes (soil bacteria) and were first reported in 1948 in the scientific literature [14]. These drugs were remarkable as they had an antibacterial activity which was broad spectrum. They were commercialized with a lot of success that began in late 1940's to early 1950's. American Cyanamid was one of the pharmaceutical companies in the United States which was committed to research as well as development of antibiotics. It had built new laboratories in Pearl River (New Jersey, United States) under the guidance of Yellapragada Subbarow (head of research) and Wilbur Malcolm (the general manager). They started a search for an antibiotic which they felt could be able to rival Waksman's streptomycin and had enlisted Benjamin Minge Duggar (a retired professor from the University of Wisconsin having expertise in economic botany and plant physiology) as the head of their department related with soil screening. Duggar was very famous worldwide for his wide knowledge on soil fungi. He had collected soil samples from worldwide usually that were sent to him by his friends from sites that he was sure would be able to yield actinomycetes. These samples were firstly subjected to culture broth dilution assays (which were performed by technicians

in his laboratory), where the microorganisms were plated on Petri dishes and the observed colonies were assayed for antibiotic activities against bacteria. Many soil microbe species produced antibiotics but most were toxic in nature or had many undesirable properties, which led the team to encounter many false leads in experiments. However, one sample was able to draw their early attention. It was labeled as A-377 and was sent by William Albrecht from the campus of University of Missouri (Columbia, United States). This sample had yielded a very different yellow-colored colony which was able to inhibit the growth of all the other strains of initial bacteria in the plate and produced a very large zone of inhibition in the agar medium. In comparison, other few antibiotics known at that time were nowhere near this sample. They were further able to find that even the crude extracts of the colony were able to retain great antibacterial activity against lethal rickettsias (an infection whose cure was unknown at that time) and scrub typhus. This unknown substance was called as broad spectrum antibiotic and it became one of the first in entire history of medical sciences for attaining this title. Duggar named this drug as aureomycin, which was in reference to the yellow color and gold colored strain of *Streptomyces*. He was able to publish the results in 1948 and called the bacterium as *Streptomyces aureofaciens.* Within a short period of time, other pharmaceutical companies announced their own discoveries of newer antibiotics and by around 1950, Alexander Finlay and his colleagues at Pfizer Corporation isolated the soil bacterium named *Streptomyces rimosus.* Their organism was able to produce a compound having same yellow color as that of Aureomycin but it had better bioactivity as well as slightly more solubility in water providing not only medical but also competitive edge over Aureomycin for treating infectious diseases. This antibiotic was named as terramycin and was approved by the United States Food and Drug Administration in 1950, competed directly with Aureomycin, gradually gained success in treating a broad spectrum of infectious diseases. Its 2nd generation semisynthetic analogs and more recently 3rd generation compounds showed the continuing evolution of tetracycline scaffolds towards derivatives having increased efficacy and potency against tetracycline resistant bacteria.

Some other antibiotics that deserve a brief mention are the cephalosporins which are structurally similar to penicillin. In the July of 1945, Giuseppe Brotzu was able to isolate a fungus named *Cephalosporium acremonium* present in the sewer water in Cagliari (Italy). His research had commenced with the observation of the prevalence of typhoid fever in the Cagliari city which was pretty less than that of other parts of Europe. Since that time, other cephalosporins found in nature have been isolated from soil bacteria species. However, he himself was unable to proceed in further studies in by himself Italy. In 1948, Edward Abraham (a student of Fleming) started research into the products of microorganism isolated by Brotzu (another scientist). The first compound isolated by him was cephalosporin P (in 1949) and it was called so owing to the only compound which was effective against Gram positive bacteria (these get stained in purple color by Gram stain because of the presence of a thick cell wall made up of peptidoglycan) [15]. After this, the second compound isolated was firstly named cephalosporin N because of its effectiveness against both Gram positive and Gram negative bacteria (colored pink with Gram staining). As the chemical structure of cephalosporin N resembled penicillin, it was renamed as penicillin N [16]. Subsequently, another compound was separated after fractionation known to

have antibacterial activity, which was called as cephalosporin C. Additionally, further industrial developments led to the formation of semi-synthetic cephalosporins having the modification of the α-aminoadipoyl side chain of cephalosporin C structure which confers the advantageous antimicrobial activity to them.

Present knowledge on antibiotics (classification, biochemical activities and the growing phenomenon of antibiotic resistance)

The present day information on the classes (along with examples) and biochemical structures of antibiotics is shown in Table 1, while Figure 3 illustrates their chemical structures. This topic can be explained with a lot of detail but as this would be out of the scope of this review (considering the primary focus is on the historiography aspect), only brief yet comprehensive information is given.

Bacterial antibiotic resistance is a worldwide challenge which is associated with high mortality as well as morbidity. Many of both Gram positive and negative bacteria have evolved multidrug resistant patterns which has resulted in untreatable and more likely very difficult to treat infections with the help of conventional antibiotics. There is a general lack of the early identification of microorganisms causing diseases in patients (in most healthcare systems worldwide) and usually broad spectrum antibiotics are very unnecessarily and liberally used [17]. Increasing number of multidrug resistant bacteria present a challenge and it is a herculean task to develop alternative or novel treatments for coping them [18]. MRSA is a gram-positive bacterium responsible for many difficult to treat infections in people, generally causing small red bumps resembling pimples or boils in early stage and in later stages these become deep as well as pus filled boils. Besides, MRSA other resistant bacteria include Vancomycin resistant *Enterococcus* species (resistant to vancomycin antibiotic) that cause severe intestinal infections. The challenges which are associated with the infections due to resistant bacteria are mostly because of the lack or shortage of successful preventive/curative measures and most importantly owing to the lack of new antibiotics. Therefore, need of the hour not only requires a joint effort among all the pharmaceutical companies developing newer antibiotics but also from the general public (mainly to use drugs rationally). However, ironically these companies have severely limited investments for discovering new antibiotics owing to the negative returns of investments.

Conclusions

The development of antibiotics in the past has been a very fascinating expedition not only for the history of medical research but also for the development of modernized society. It is perhaps ironical that antibiotics were mostly seen historically as medicines successfully discovered or invented by just a few scientists than as technologies which exemplified the complicated processes of innovation around the world. We presented the detailed historiography of early antibiotics developed for combating major bacterial infections. This has been a tough journey but it is bound to get tougher in the twenty-first century due to the increasing incidences of antibiotic resistant bacteria.

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Tables

Table 1: Various antibiotic classes with their biochemical activities and examples

Antibiotic class	Discovery/Introduction years	Biochemical activity	Examples
β-lactams	Late 1920's	Inhibit bacteria cell wall biosynthesis	Penicillins, cephalosporins
Sulfonamides	Early 1930's	Do not kill bacteria but prevent their growth and multiplication. These might also cause allergic reactions in some patients.	Prontosil, sulfanilamide, Sulfadiazine, sulfisoxazole
Aminoglycosides	1940's	Inhibit the synthesis of proteins by bacteria; leading to cell death	Streptomycin, neomycin, Kanamycin , paramomycin
Tetracyclines	Late 1940's	Inhibit synthesis of proteins by bacteria, preventing growth	Tetracycline, doxycycline, limecycline, oxytetracycline
Chloramphenicol	Late 1940's	Inhibits synthesis of proteins, preventing growth	Chloramphenicol
Macrolides	1950's	Inhibit protein synthesis by bacteria occasionally leading to cell death	Erytromycin, clarithromycin, azithromycin
Glycopeptides	Late 1950's	Inhibit bacteria cell wall biosynthesis	Vancomycin, teicoplanin
Quinolones	Early 1960's	Interfere with bacterial DNA replication and transcription	Ciprofloxacin, levofloxacin, trovafloxacin
Ansamycins	1960's	Inhibit the synthesis of RNA by bacteria, leading to cell death	Geldanamycin, rifamycin, napthomycin
Oxazolidinones	Early 1980's	Inhibit synthesis of proteins by bacteria, preventing growth	Linezoid, posizolid, tedizolid, cycloserine
Streptogramins	1960's	Inhibit the synthesis of proteins by bacteria, leadinf to cell death	Pristinamycin IIA, pristinamycin IA
Lipopeptides	Late 1980's	Disrupt multiple cell membrane functions, leading to cell death	Daptomycin, surfactin

[Source: www.compoundchem.com]

Figures

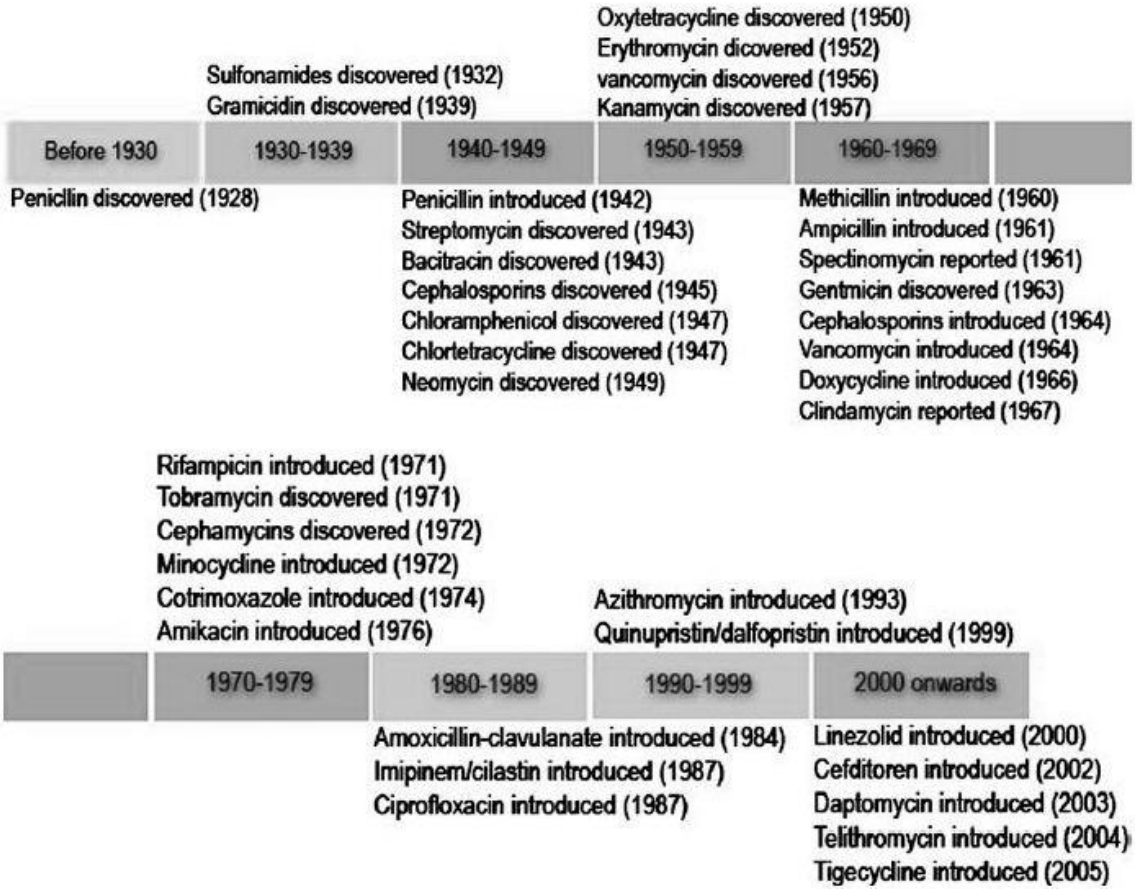

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Figure 1: A brief timeline showing the discovery/introduction of different important antibiotics **[Source: cvm.msu.edu, 2011]**

Figure 2: A brief description related with penicillin; **a)** Sir Alexander Fleming (6 August 1881 – 11 March 1955); **b)** A Petri dish showing inhibition (growth prevented) of bacteria by a Penicillium colony **(Pearson Education, Inc. 2004)**; **c)** Young Jean-Claude Fide is being treated with penicillin by his mother in 1948 in the French village of Mont-pres-Chambord **(Photo by Bert Hardy/Picture Post)**; **d)** A modern day oral solution of penicillin; **e)** A modern day commercial ointment of penicillin

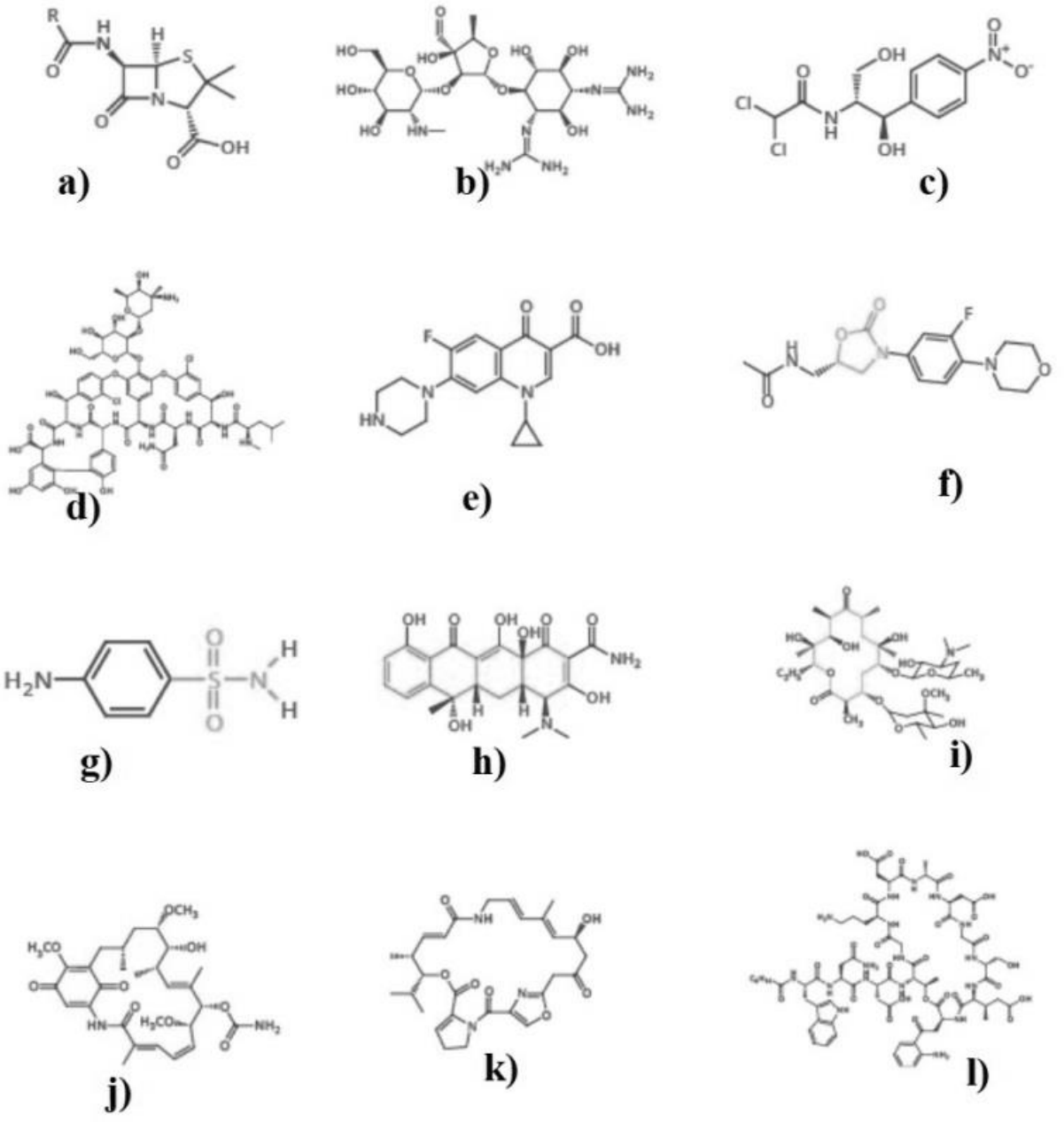

Figure 3: Chemical structures of different classes of antibiotics: **a)** β-lactams having a β-lactam ring (penicillins (shown)); **b)** aminoglycosides containing aminosugar substructures (streptomycin (shown)); **c)** chloramphenicol; **d)** glycopeptides consisting of a carbohydrate linked to peptide formed of amino acids (vancomycin (shown)); **e)** quinolones containing fused aromatic rings with a carboxylic acid attached (ciprofloxacin (shown)), **f)**

oxazolidinones (linezolid (shown)); **g)** sulfonamides containing a sulfonamide group (sulfanilamide (shown)); **h)** tetracyclines containing 4 adjacent cyclic hydrocarbon rings (tetracycline (shown)); **i)** macrolides containing a 14 to 16 membered macrolide ring (erythromycin (shown)); **j)** ansamycins containing an aromatic ring bridged by an aliphatic chain (geldanamycin (shown)); **k)** streptogramins (pristinamycin IIA (shown)); **l)** lipopeptides containing a lipid bonded to a peptide (daptomycin (shown)) **[Source: Compound interest, 2014: www.compoundchem.com]**