



How a medical miracle evolved into a human hazard: The history of antibiotics

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SUMMARY

Antibiotics have saved millions of lives but the rapid development of antibiotic resistant bacteria is inevitably becoming the most dangerous public health threat. These miracle drugs are widely used in agriculture, medicine and common everyday products; however, the overuse of antibiotics is correlated with the development of drug resistance. This growing medical concern invokes fear in the public as it eliminates the ability to effectively treat infectious diseases. Starting from the serendipitous discovery of penicillin in 1928, scientific advancements and government policies have led to controversies between scientists and industries on the use of antibiotics as the development of resistance has accelerated. This review discusses significant events, people and causes involved and identifies the time in history when antibiotic resistance became a serious public health problem.

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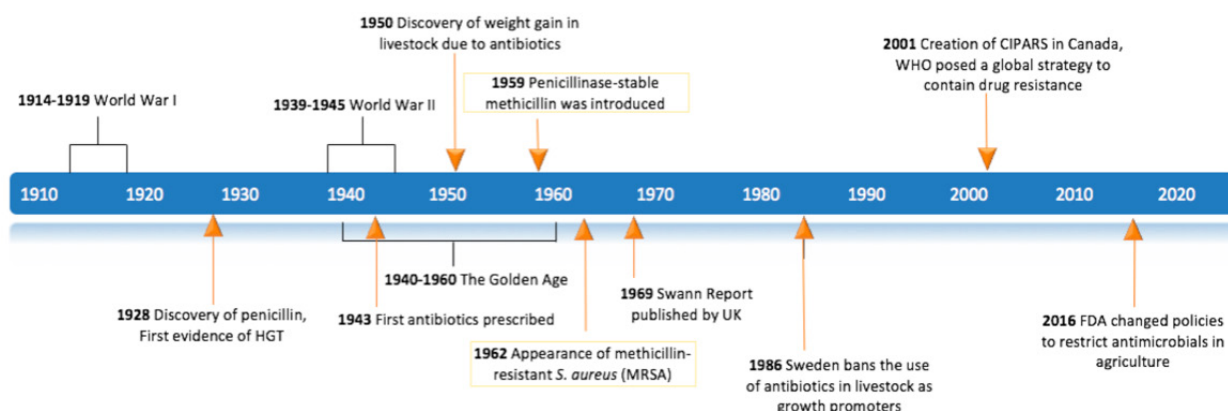


Figure 1: A brief timeline focusing on the significant events and contributions of the antibiotic era, which ranges from 1910 to the present.

INTRODUCTION

The use of antibiotics has been a controversial topic in recent years due to its ability to acquire resistance. However, resistance may not be a newly introduced phenomenon. It has been estimated that bacteria have been present on Earth for at least 3.5 billion years, thus it has been theorized that bacteria naturally developed genes that confer resistance to antibiotics billions of years ago, through their ability to evolve. Although re-

sistance may not be news to the environment, this has been a popular topic in the media for over a decade and has become a global threat to human health.

In 1941, Selman Waksman, a Ukrainian microbiologist, coined the term antibiotics and described these compounds to be molecules created by microorganisms that inhibit the growth of other microorganisms (Clardy, Fischbach and Walsh, 2006). Antibiotics are used to treat a variety of bacterial infections, and can

be created through either the modification of natural products with antibiotic properties or through the creation of synthetic compounds (Clardy, Fischbach and Walsh, 2006). Although most antibiotics currently prescribed have been isolated from microbes, there has been an overall decrease in the discovery of new antibiotics from natural sources (Peláez, 2006). This is partially due to the fact that less than 1% of bacteria can be cultured in the lab, which makes it difficult to investigate naturally occurring antibiotic compounds (Clardy, Fischbach and Walsh, 2006). Despite this difficulty, it is estimated that there is still a vast number of compounds with antibiotic properties from uncultured bacterial sources yet to be discovered. Thus, natural sources remain a promising area for the development of new antimicrobial drugs.

Antibiotic resistance occurs when a strain of bacteria can no longer be eliminated by a class of antibiotics that were previously successful in treating it. This means that if an individual is infected with a mutant bacterial strain, the bacteria may be multi-resistant and a required treatment no longer exists, which poses a serious public health threat. It has been determined that society has contributed to resistance through the misuse of antibacterial products. Scientists are in constant race between the discovery and development of novel antibiotics, versus the emergence of new resistant bacteria. If consumers continue to use antibiotics at the rate in which they are currently used, bacterial infections will cause more deaths than cancer by 2050 (Nothias, Knight and Dorrestein, 2016). It is crucial that governments, organizations, and hospitals address this issue to ensure that antibiotics are being used appropriately.

BEHOLD THE MOULD

Dr. Alexander Fleming, a Scottish bacteriologist, worked on treating wound infections during World War I. During this time, he recognized the role of white blood cells in healing lacerations through its ability to kill bacteria (Bottcher, 1959). Astonished by his observations, Fleming performed further studies to identify the active substance in white blood cells (Bottcher, 1959). In 1922, he discovered that the substance was an enzyme, which he named lysozyme. Six years later, while working at St. Mary's Hospital in England, he studied the nature of *Staphylococci aureus* (Fleming, 1929). One night, Fleming's assistant was putting away Petri dishes containing nutrient agar, however she neglected to cover the lids properly, allowing airborne fungal spores to contaminate the broth. The following day when Fleming observed the bacteria in the Petri dishes, he noticed that there was a fine lawn of grey-green mould and a transparent

halo, indicating an area of no growth (Fleming, 1929). This surprised Fleming as it appeared as though the bacteria had been dissolved by the fungus which had penetrated the broth. He identified the fungus to be *Penicillium notatum* and was intrigued by the idea of life inhibiting life, which motivated him to conduct further experiments over the next 10 years (Nicholas and Davies, 2012). Initially, he did not think of using penicillin to treat infections in humans, however reflecting on the research he conducted to identify lysozyme, Fleming proposed that the antimicrobial could be used against bacterial infections (Bottcher, 1959). Later, he proved the drug's ability to heal wounds in rabbits and its effectiveness in eliminating Gram positive pathogens (Page, 2012). However, ethical issues and Fleming's lack of biochemistry training presented him with challenges when attempting to isolate the active substance. Fleming eventually lost interest in penicillin and was reluctant to test it on humans (Page, 2012). Nevertheless, he published papers on his findings and hypotheses and allowed his fungal strains to be made available to the public.

Howard Florey, an Australian pathologist, and Ernst Chain, a German chemist, were fascinated by Fleming's work (Page, 2012). They expanded upon his research and successfully isolated penicillin from a related fungus, *Penicillium chrysogenum*, in 1939. This enabled them to conduct in vivo testing in mice to demonstrate how penicillin could treat bacterial infections (Page, 2012). Subsequently, they were granted the approval to conduct clinical trials in humans. After multiple failures leading to improvements of the flaws in their experiments, they were able to show that this miracle drug was effective in treating children who had severe streptococcal and staphylococcal infections (Page, 2012). To receive further funding and patents, they travelled from England to the United States in 1941 to produce the drug in large quantities, making it available as a medication in the early 1940s (Muniz, 2017). In 1945, Fleming, Florey and Chain received the Nobel Prize in Physiology or Medicine.

In Fleming's acceptance speech, he warned the public about something new and unheard of; antibiotic resistance. He cautioned the public to use antibiotics wisely as he understood that bacteria were able to develop resistance to these compounds (Fleming, 1945). Despite this, society disregarded his warning and the topic of antibiotic resistance was not investigated until decades later.

"There is danger that the ignorant man may easily underdose himself by exposing his microbes to non-lethal quantities of the drug to make them resistant...Moral: if you use penicillin, use enough." – Alexander Fleming

ANTIBACTERIAL ACTION

The development of penicillin antibiotics has allowed physicians to treat life-threatening infections, where patients show noticeable progress within hours after taking the drug. In the 1950s and 1960s, many scientists were dedicated to understanding the biochemical mode of action of penicillin (Nicholas and Davies, 2012). It was determined that beta-lactam antibiotics, such as penicillin, inhibit the synthesis of the bacterial cell wall, specifically peptidoglycan. Penicillin binding proteins (PBPs) are a group of proteins found in many types of bacteria that are essential for the cross-linking of peptidoglycan, which is necessary for the creation of a strong cell wall (Saga and Yamaguchi, 2009). The chemical structure of beta-lactam antibiotics resembles the C-terminus of peptidoglycan peptide chains; therefore, penicillin can bind to PBPs to form an enzyme complex (Page, 2012). Ultimately, this complex inhibits PBPs from performing cross-linking and the cell wall is not synthesized, which leads to the destruction of the bacterial cell.

Penicillinase is the enzyme responsible for inhibiting penicillin, thus contributing to the development of resistant bacteria (Ontario Medical Association, 2017). Resistant bacterial strains that produce penicillinase decrease the ability of penicillin to kill bacteria. These resistant bacterial strains were first discovered in the 1940s, but became more prevalent in the 1950s, signifying the spread of resistance (Saga and Yamaguchi, 2009). In response to this, another penicillin class antibiotic, penicillinase-stable methicillin, was developed in 1959. However, just three years after its introduction, methicillin-resistant *S. aureus* (MRSA) was discovered. The antibiotic streptomycin, another novel drug, was clinically introduced by Waksman in 1944 to treat tuberculosis (Davies and Davies, 2010). Similarly, resistant strains of *Mycobacterium tuberculosis* emerged rapidly after its use to treat the disease (Davies and Davies, 2010). Subsequently, the increased worldwide use of antibiotics after the 1940s acted as a selective pressure that led to the development of resistant bacteria (Read and Woods, 2014). This became regarded as an issue with the effectiveness of antibiotics and efforts were made to understand the spread of resistance. One mechanism was through spontaneous mutation and natural selection (Read and Woods, 2014). In 1928, British bacteriologist Frederick Griffith was conducting experiments using *Streptococcus pneumoniae* when he unknowingly discovered the process of horizontal gene transfer (HGT) (Arber, 2014). This was confirmed in the 1950s, when it was discovered that bacteria can transfer genetic material between individuals, including the genes coding for antibiotic resistance (Arber, 2014).

All in all, this trend of resistance was seen in all the an-

tibiotics introduced during this time period. To combat the mutant bacterial strains, other forms of antibiotics were needed to eliminate the resistant bacteria. However, the microorganisms continued to develop resistance to the new drugs, thus evolving into multi-resistant bacteria, or superbugs. Fortunately, many companies were on board with antibiotic discovery which advanced science into a triumphal period in antibiotic history.

GOLDEN AGE

Most of the antimicrobial classes that are still administered today, such as tetracyclines and vancomycin, were discovered between 1940 and 1960 (Davies and Davies, 2010). This time period was known as the Golden Age of Antibiotics. There are various factors that contributed to the success as well as the eventual downfall of the Golden Age. The discovery of penicillin was the forefront of medical breakthroughs during this time, satisfying the high clinical need for these therapeutics (Mills and Dougherty, 2012). There was a major need for penicillin during World War II as death caused by bacterial infections were more common than casualties in battle. As a result, many drug companies, such as Pfizer, invested in antibiotic drug discovery. Additionally, during this period, there were great decreases in the death rates caused by infections. Once antibiotics were made available as treatments, the human life expectancy increased by 8 years between 1944 and 1972, as these common infections were no longer a leading cause of death (Mills and Dougherty, 2012).

Unfortunately, the 1960s marked the end of the Golden Age, where many pharmaceutical companies abandoned the search for new antibacterial classes. Some scientists thought that they had completely cured all infectious diseases, so there was no need for more antibiotics. Others believed that antibiotic resistance was not a concern, and in fact, they considered drug resistance to be rare and the likelihood of bacteria developing resistance to be very low. Furthermore, in the 1980s, companies that continued antibiotic research shifted their objectives in drug discovery (Page, 2012). Alternatively, they focused on improving the biochemical activities and properties of existing antibiotics rather than developing new classes. Meanwhile, many other drug businesses abandoned research in antimicrobials and began moving towards other areas of other therapeutic needs, where they had the potential to make large profits.

Overall, the lack of new antibacterial compounds was a factor that contributed to the threat of drug resistant bacteria. Additionally, investing in an antibacterial product was unappealing as it was very expensive and challenging to get approval by the FDA, and the

profits for medications to treat chronic diseases were much greater. Apart from the pharmaceutical industry, antibiotic resistance has also affected other industries.

AGRICULTURE

Agriculture has been a necessary part of human survival and population growth for centuries, providing humans with food, clothing, heat and employment (Federico, 2005). As the global population has grown, there has been stress on the agricultural industry to produce greater amounts of food, and various technological advancements have allowed for more efficient production of food products (Federico, 2005). One of the advances in this sector was the discovery of antibiotics. In the late 1940s, Thomas Jukes and Robert Stokstad, two American scientists, were working at the University of California, attempting to find a source of vitamin B-12 (Wise, 2007). When studying chickens fed with a mix containing the fermentation products of *Streptomyces aureofaciens*, these scientists made an important discovery for the future of agriculture. They noticed that the poultry experienced a dramatic weight gain, which Jukes attributed this weight gain to the change of intestinal flora of the chickens (Stokstad and Jukes, 1950). Although its mechanism of action was not fully understood, the causative agent was determined to be a product of *S. aureofaciens*, called chlorotetracycline, which is an antibiotic of the class of tetracyclines (Wise, 2007). From this discovery, the benefits of antibiotics on livestock were realized and the worldwide agricultural industry began to change its practices.

The main purposes of adding antibiotics into animal feed include the promotion of growth and the prevention of infection in livestock populations, as this could have devastating effects on businesses (Khachatourians, 1998). In the 1950s, the recommended dose of antibiotics in animal feed was 10-20 ppm, however in the 1990s, this dosage had increased to 200-400 ppm (Khachatourians, 1998). With these increasing trends, the primary use of antibiotics became livestock feed. For instance, of the total production of antibiotics in the United States in 1998, 50% were used in the agricultural industry with only 5% being used to treat infectious disease (Khachatourians, 1998).

Although this discovery led to more efficient production of animal protein to sustain the ever-growing human population, problems with this new agricultural practice were soon discovered. The development of antibiotic resistance gradually became a concern in many different countries, especially in European countries. In 1969, the UK parliament created a committee to investigate the threat of antibiotic resistance in agriculture and provide recommendations for the future (Wise, 2007). This committee published the Swann

Report to advise the government and ease anxieties, which was then distributed to other countries in Europe and to the United States. Through their research, they concluded that the administration of antibiotics in agriculture posed a threat to human health due to the development of antibiotic resistance (Swann et al., 1969). They identified 1523 strains of bacteria that were resistant to certain antibiotics and concluded antibiotic use in agriculture was partially to blame (Swann et al., 1969). This committee recommended that antibiotics should be separated to be used either in feed or therapeutically and that drugs that are currently freely available should be limited so that they are only be available with a prescription.

Despite the recommendations of the Swann Report and further research on this emerging issue, the regulations and policies regarding antibiotic use in agriculture remained fairly unchanged. It wasn't until the 1990s when this issue became the subject of large debates, that more government action was taken (Wise, 2007). In 2001, the UK created a committee called the Specialist Advisory Committee on Antimicrobial Resistance that had representatives from human and veterinary medicine, public health, nursing, bacteriology, and virology (Wise, 2007). Similarly, a committee was created in Canada called the Canadian Integrated Program for Antimicrobial Resistance Surveillance (Government of Canada, 2007). The purpose of these committees is to monitor the development of resistant bacteria, including the contribution of resistance from antibiotic use in livestock (Government of Canada, 2007).

There are contrasting perspectives and lifestyles when it comes to antibiotic use between Western and European countries. Currently in Ontario, there are few regulations and little control regarding the types of antibiotics and dosage quantities that can be given to livestock (Ontario Medical Association, 2017). On the other hand, Sweden banned the administration of antibiotics to livestock as growth promoters in 1986 and Denmark followed their lead 9 years later (Ontario Medical Association, 2017). Antibiotic bans in Holland, Denmark, Germany and Sweden were shown to cause a decrease in resistance rates of one type of bacteria, called *Enterococcus* (Bogaard et al., 2000). As a result of these bans, the European economy has experienced deficits from the farming industry, which invoked fear in other countries and hesitations towards making drastic changes in their policies.

Currently, this overuse of antibiotics contributes to the development of resistance as the bacteria are exposed to the antibiotics more often. The drugs act as a selective pressure for resistance leading to increased development and spread of resistance genes through both HGT and random mutations, as previously mentioned

(Arber, 2014).

In the history of agriculture, the use of antibiotics is a fairly new development and the consequences of this practice are still being determined. Policies regarding the use of antibiotics as growth promoters are now being modified and implemented in many countries, yet agriculture is still considered a major contributor to antibiotic resistance.

HEALTHCARE

Although there have been large advances in the field of public health care, antimicrobials are still one of the most important and successful developments in medicine (Aminov, 2010). Evidence of the use of antibiotics has been found from ancient human skeletons dating back to approximately 350 CE, but the concerns regarding resistance only began in the antibiotic era, in the late 20th century (Aminov, 2010). Similar to the use of antibiotics in agriculture, the overuse and misuse of antibiotics in the healthcare industry also contribute to resistance.

Antibiotics are used in healthcare to control infectious diseases that were previously some of the leading causes of death; however, the misuse of antibiotics can decrease their efficacy (Kardas et al., 2005). Misuse includes the failure of patients to complete antibiotic therapy, skipping doses, reuse of antibiotics and over-prescription (Kardas et al., 2005). When antibiotics are used to treat an infection, the drug acts as a selective pressure which drives the selection of bacteria that are resistant and thus not killed by the drug (Kardas et al., 2005). In previous studies, it was determined that one third of patients did not comply with the therapy plan and one quarter had leftover antibiotics for later use (Kardas et al., 2005). The consequences of this misuse include the accelerated development of resistance.

Another practice in healthcare that contributes to antibiotic resistance occurs when physicians overprescribe these drugs. Antibacterial agents are commonly prescribed for respiratory tract infections which may be caused by viruses, instead of bacteria (Wang et al., 1999). A Canadian study that focused on data from preschool children from 1995 estimated that about half of the total cost of antibiotics in Canada was due to over prescribing the drugs (Wang et al., 1999). In Canada, it has been estimated that each year, there have been up to 26 million prescriptions from physicians that were unnecessary for treatment (Williams and Heymann, 1998). This means that the antibiotic acts more often as a selective pressure for bacterial evolution and does not actually treat the viral infection.

THE FUTURE IS NOW

“Antibiotic resistance is putting the achievements of modern medicine at risk.” – World Health Organization

Given that the consequences of antibiotic resistance were not understood when antimicrobials were introduced in the 1940s, regulations regarding the use and distribution of antibacterial products did not exist until recently. Since antibiotics are used on a global scale, the concern of antibiotic resistance is international. In 2001, the World Health Organization attempted to bring policies into action by posting recommendations and a global strategy on containment of drug resistance (WHO, 2017). Furthermore, federal governments have also tried to address the issue. The Canadian government intends on forming relations with animal agriculture providers by December 2019 to regulate the approval of veterinary medication and to ensure that these products are being used appropriately in animals and humans. Through these policies, they anticipate that there will be a decrease in the overall use of antibiotics. These are only a few examples of efforts that have been made by different organizations in recent years, however antibiotic resistance continues to be a large problem.

Aside from being an international issue, antibiotic resistance also involves affects different fields including but not limited to microbiology, healthcare, agriculture, ecology, education, legislative bodies, the pharmaceutical industry and the public (Aminov, 2010). Although efforts have been made to address this problem, more drastic global measures must be implemented, in order to prevent widespread resistance and loss of antibiotic efficacy. Since the spread of resistance is a naturally occurring process, it cannot be stopped, but the rate of this spread can be reduced.

Some recommendations to address this issue include changes in policies in both the agricultural and medicinal fields, which should be applied to many countries throughout the world. Prescription antibiotics should be used to treat bacterial infections and the use of these drugs for viral infections should be very limited as this misuse is a major driving force for bacterial evolution (Kardas et al., 2005). More recently in 2016, the FDA initiated a change in the marketing status of antibiotics used in livestock (Center for Veterinary Medicine, 2017). Antibiotics that were previously over-the-counter are now classified as either prescription or veterinary feed directive, which means that they can only be used under supervision of a licensed veterinarian. Since the majority of antibiotics are used in agriculture, a reduction or even an elimination of antibiotics in this industry would lead to a significant decrease in the spread of

resistance in bacteria. In addition to limiting use, the possibility of novel classes of antimicrobials should be explored as new technologies could lead to great discoveries (Aminov, 2010).

From the overview of the history of antibiotic era and studies regarding the spread of antibiotic resistance, we determined that antibiotic resistance first became a major concern in the 1970s (see Figure 1). When looking at the trends of antibiotic discovery, this time period was considered the end of the Golden Age and after this point, there have been few novel classes of antibiotics discovered. Additionally, there were few events promoting antibiotic discovery and few policies limiting antibiotic use in agriculture and healthcare as well as other products. With the combination of these factors as well as the increasing worldwide use of antibiotics, we propose that this marked the beginning of the antibiotic resistance crisis.

Ultimately, though antibiotics are considered relatively new in terms of human history, this revolutionary medicine could soon lose its value due to the spread and

further development of resistant bacteria. Compared to the billions of years of bacterial evolution, humans have only spent approximately the last 80 years in the antibiotic era. Although this time is only approximately equivalent to the current human life expectancy, these compounds have revolutionized human medicine with the ability to treat infectious diseases that were once considered leading causes of death and to produce enough food to support the growing worldwide population. Although resistance is inevitable, there are many measures that may be taken to slow this rate of resistance, some of which are stated in this article, however the fight against resistance requires global cooperation.

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