Antibiotic Discoveries and a Century of Creating Superbugs

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By

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INTRODUCTION

WHERE DID WE BEGIN, AND WHERE ARE WE GOING?

It's difficult for most people living today to imagine what life was like before the discovery of antibiotics. To determine just how often infections would result in death or morbidity without them, one would have to go back to the early 1900s or better yet, towards the end of the Dark Age of medicine just before Pasteur's germ theory of disease at the tail end of the 19th century. By that point, tuberculosis had killed approximately 1 in 7 people who had ever lived and those that it did not kill were often permanently affected, with long-term effects ranging from breathlessness to permanent lung damage (Ravimohan et al. 2018). Death rates from pneumonia during the Civil War hovered around 24%, with Sir William Osler whom many consider to be the father of modern medicine calling it "the most fatal of all acute diseases (Lively 2013)." In addition to this, surgical patients during the Civil War often developed Clostridia infections such as gas gangrene, up to 60% of which would be fatal (Reifler et al. 2015). Sexually transmitted infections such as syphilis and gonorrhea were prevalent, especially among soldiers. During WWI alone, the Army discharged approximately 10,000 soldiers due to these sexually transmitted infections (Rasnake et al. 2005). Not only was there no treatment but people often did not know when they were spreading it to others. Puerperal sepsis (also known as childbed fever) was caused by *Streptococcus pyogenes* and was most common in hospitals due to being spread by unknowing medical staff, killing around 5% of the women who contracted the bacterium during or after birth (Burch 2009). In the pre-antibiotic era, diseases such as scarlet fever and typhoid fever had a death rate of 15-20% (Sotoodian et al. 2020). Fortunately, the incidences of these infections have not only decreased due to improved hygiene, antisepsis, and in some cases vaccination, but mortality rates have also decreased due to the introduction of antibiotics during the golden age of antibiotic discovery, which took place between the 1930s and 1960s. From there, several decades passed before a new age of antibiotic discovery would begin, driven by an effort to stifle the emerging resistant bacteria resulting

from the first "wave" of antibiotic use. From the early 2000s to 2020 new antibiotic discovery has, despite not necessarily being a lucrative investment for pharmaceutical companies, been aimed at circumventing mechanisms of resistance used by difficult to treat pathogens. The path to get to this point was not only bumpy but also serendipitous in many ways. When reflecting on the antibiotic era, it is a prerequisite to consider the numerous steps history took to get there.

Historical use of antibiotics

It is difficult to say just how far back diverse cultures attempted to use natural means to contain infection and stave off death. According to Eber's Papyrus (Fig. I-1), which dates to 1550 B.C. Egypt and is considered the oldest preserved medical document, it was written that people used honey, lard, and lint to treat wounds. We now know that some of these treatments made sense since honey contains hydrogen peroxide and thus has some antibacterial properties. Similarly, in China, Greece, Serbia, and Egypt, moldy bread was pressed up against wounds to prevent infection (Haas 1999). It was not known why at the time, but now we know that the observed effectiveness of this practice was likely due to the antibiotics produced by the molds. Over the centuries, many other untested natural remedies were used including hypericum, oak sap, lady's mantle, and countless patented concoctions, all claiming to treat or cure illness (Forrest 1982).

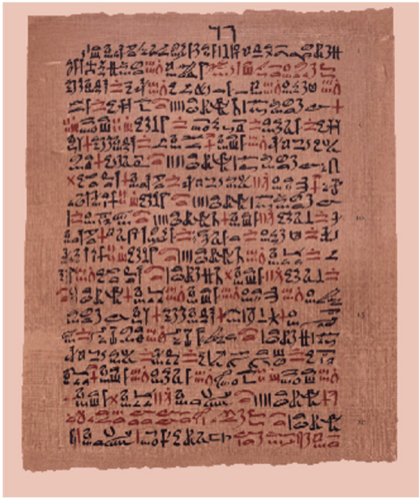

Fig. I-1. Eber's Papyrus circa Egypt 1550 B.C.
Credit: Wikimedia Commons

Fig. I-2 (left). John Parkinson, 1640.
Credit: Wikimedia commons

Fig. I-3 (right). Louis Pasteur. Credit: Wellcome Images

In the 1400s, treatments like mercury and bismuth were not uncommon, and mercury was used for syphilis until the end of the 1800s. The drawback of course would have been toxicity, and without the knowledge that microbes are responsible for infection, it would have been difficult to determine a therapeutic, non-toxic dose. Plants were often thought to be safe, however. In 1640, English apothecary John Parkinson, herbalist to King Charles I (Fig. I-2), wrote about mold's medicinal effects in his book on pharmacology which cataloged the medicinal utility of many plants and natural products (Parkinson 1640). For centuries, these natural products were what people used to treat their infections. It wasn't until the middle and end of the 19th century that research by Louis Pasteur (Fig. I-3) and Robert Koch led to breakthroughs in the young field of microbiology. In the 1860s, Pasteur conducted experiments describing fermentation and contamination, showing that this occurred due to germs in the air. In 1861, Pasteur would publish his germ theory of disease, which postulated that infections were caused by the activity of microorganisms (Pasteur 1861). Pasteur's germ theory would be further developed by surgeon Joseph Lister and German physiologist, Robert Koch. Lister was a British surgeon who

had read Pasteur's work and based on his observations regarding fractures that punctured the skin resulting in pus and subsequent mortality, Lister was interested in improving outcomes in his practice. Thus, he started using antiseptics including dilute carbolic acid in 1867 for compound fractures as well as on the skin before surgery. As a result, Lister started observing a significant reduction in morbidity and mortality.

Shortly after Lister's success with antisepsis, the first experiments of microbial antagonism were being observed in bacterial cultures at St. Mary's Hospital in London. In 1871, Sir John Scott Burdon-Sanderson observed an absence of bacterial growth in cultures covered with mold. Subsequently, Lister would observe the same thing in urine cultures covered with mold. Lister called the mold *Penicillium glaucum.* A few years later Welsh physician William Roberts also observed a lack of bacterial growth in *Penicillium glaucum* cultures, and in 1875 Irish physicist John Tyndall would present the antibacterial activity of *Penicillium* to the English Royal Society (Maddren 1946). Was this an early discovery of penicillin? Tyndall had solely observed the effect the mold had on bacterial growth; antibiosis was likely not to have been considered yet. Although likely, some of these early observations coupled with the knowledge of what causes infection were foundational for the idea of microbial antagonism by antibacterial compounds- it would still take several decades to get there.

Fortunately, Robert Koch would add further evidence that microbes were the cause of infectious diseases. In 1882 Koch announced at the Berlin Physiological Society meeting that he had discovered the etiological agent for tuberculosis. In 1884 he published Koch's postulates to suggest four criteria that he deemed necessary for determining the cause of infectious disease by a microorganism: 1. The microorganism should be found in the diseased individual but not in healthy individuals (a postulate that didn't quite hold up, as we know healthy individuals can be asymptomatic carriers of some infections); 2. The microorganism should be able to be cultured from the diseased individual; 3. Transfer of the microorganism to a healthy individual should cause the disease; and 4. The microorganism should be able to be re-isolated from the infected individual and match the original organism (Following Koch's example 2005, Koch 1882). The contributions of Koch and his students to the overall knowledge of microbial causes of infectious disease included the identification of the causative agents of syphilis, cholera, typhoid, pneumonia, diphtheria, meningitis, and gonorrhea amongst many others (Blevins and Bronze 2010). Armed with the knowledge of how microorganisms contribute to infectious disease, research started moving into the therapeutics arena. In Germany, E. de

Freudenreich studied the first recorded "antibacterial" in 1888, a blue pigment from the bacterium *Bacillus pyocyaneus* (now known as *Pseudomonas aeruginosa*), which was later called pyocyanase by fellow Germans Rudolf Emmerich and Oscar Löw. Emmerich and Löw performed clinical trials in 1889 and through these, pyocyanase was found to be effective in killing many disease-causing bacteria. The compound was toxic and unstable, however, which led to a decrease in its use (Levy 2002).

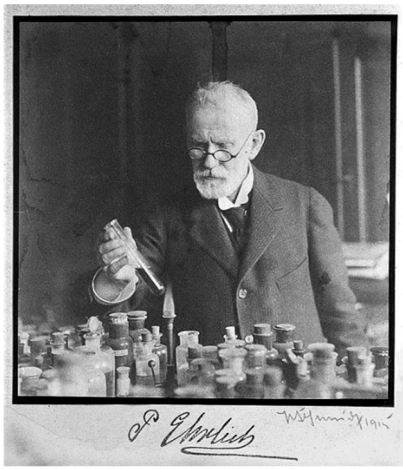

Fig. I-4. Paul Ehrlich, 1915.
Credit: Wellcome Collection gallery

After the failure of pyocyanase, German physician Paul Ehrlich was actively searching for a "magic bullet"—an agent which could kill microorganisms selectively, and not kill host cells. In 1908 Ehrlich was awarded the Nobel Prize jointly with Ilya Metchnikoff for their work on the immune system. In 1910, Ehrlich (Fig. I-4), in collaboration with his assistant Sahachiro Hata, discovered an arsenic-based dye that was effective against syphilis. This dye was known as salvarsan, the first of the "magic bullets" which, based on biological staining of cells, Ehrlich postulated could work as antibacterial chemotherapy. Salvarsan was the first compound to be used that cured a human infectious disease. In 1913 Ehrlich's address at the Seventeenth International Medical Congress in London predicted advances in the treatment of bacterial infections within five years. Without a doubt, Ehrlich's work helped to initiate further research into antibacterials that took place over the next two decades (Winau et al. 2004).

Inspired in part by Ehrlich's work, Alexander Fleming, a Scottish physician at St. Mary's Hospital in London would become a player in the burgeoning field of antimicrobials. In 1920, years before his discovery of penicillin, Fleming was researching antibacterials. His work involved studying a naturally occurring antibacterial enzyme known as lysozyme, which is found in human tears. While he learned that lysozyme causes lysis of some bacteria, he did not realize a clinical application since the work was done on non-pathogens (Hare 1983). In 1928, he made a serendipitous discovery on a discarded *Staphylococcus aureus* plate which contained the microbial antagonism that would change the way infectious diseases would be treated forever. The antibiotic resulting from this discovery—penicillin—would not be developed by Fleming alone, but would also include Oxford University scientists Howard Florey and Ernst Chain, among other important contributors, who are further described in Chapter 2. These three men would be awarded the Nobel prize for penicillin's discovery (Brown 2005).

During the decade between which penicillin was discovered and the time it would finally be developed for clinical use, the sulfonamide (sulfa) drugs were being developed by German physician Gerhard Domagk and colleagues. Prontosil and related sulfa drugs would be used in World War II for treating soldiers for gonorrhea as well as wounds and pneumonia (Lesch 2007). The discovery of Prontosil sparked a wave of development of newer and more efficacious sulfonamides. Prontosil and its analogs will be described further in Chapter 1. By 1942, penicillin was starting to replace the sulfa drugs and was in widespread use. As of 1943, eleven U.S. drug companies were making penicillin not only as part of the war effort to send overseas but also for use in civilians for which infectious diseases still desperately needed a cure. During World War II, the threat of biological weapons was a constant concern of the Allied intelligence; Germany and Japan could use bombs and shells filled with deadly bacteria such as typhoid, plague, cholera, or anthrax. Penicillin did not affect any of these. Thus, during the war and after, the desire for studying the utility of microbes for their potential antibacterial properties increased. Agricultural colleges with scientists who understood soil microbiology had the best chance of finding the next big antibiotic; these scientists were familiar with soil microbes that had microbial antagonistic effects such as producing chemical toxins that could kill harmful bacteria around them. Like Fleming's *Staphylococcus aureus* plate, these were demonstrated by zones of inhibition (Fig. I-5) which are seen when a microbe is producing a compound that inhibits the growth of other microbes around it.

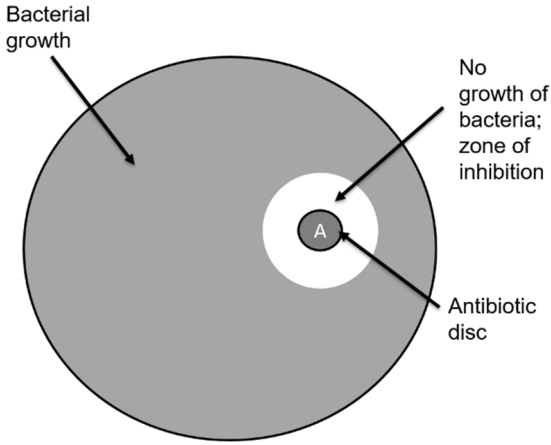

Fig. I-5. Bacterial zone of inhibition surrounding antibiotic placed in a culture plate of susceptible organisms

These efforts led to the discovery of streptomycin by Albert Schatz and his Ph.D. mentor Selman Waksman at Rutgers University in 1944, the next big antibiotic discovery which ended up being a game-changer for the treatment of tuberculosis (Pringle 2013). This discovery further solidified the idea that the soil is a microbial battlefield and probably rich with yet to be discovered antibiotics. This motivated pharmaceutical companies like Eli Lilly, Lederle, and Pfizer who were looking for the next antibiotic with improved spectrum activity to conduct massive screening programs; these searches subsequently resulted in chloramphenicol, tetracycline, erythromycin, and vancomycin (Rosen 2017).

Approximately a decade after the discovery of vancomycin, the first fluoroquinolone, nalidixic acid would be synthesized by George Lesher and colleagues at the Sterling Winthrop Research Institute in New York in 1962 (Dougherty and Pucci 2011). Almost as if the field had exhausted all possibilities for new antibiotics, four decades would go by before the world would see a new antibiotic drug class: the oxazolidinones, the first of which was approved by the FDA in 2002. The oxazolidinones, which would be used for infections resistant to already-existing treatments were the first of a new “wave” of antibiotic discovery: the investigation of new drugs aimed to circumvent bacterial mechanism of resistance. These new drugs, approved and coming to market in the new century, are often reserved for infections that cause a treatment conundrum due to resistance.

The problem of antibiotic resistance

The goal of an antibiotic is to act either as a bactericidal agent which kills the bacteria after having disrupted a step in its replication cycle or as a bacteriostatic agent, which hinders a step in its replication cycle, thereby slowing its growth. Bacteriostatic agents are still very useful since slowing down the pathogen's growth rate enables the host immune system to get a better hold on the pathogen and resolve the infection. However, when bacteria adapt to be able to overcome the inhibitory effects of the antibiotic, resistance occurs.

According to the CDC, over 250 million outpatient antibiotic prescriptions were written in 2019. Just over 54 million of those (approximately 20%) were for oral amoxicillin (CDC 2021). In the 2020s, the discovery of penicillin will approach its one-hundredth anniversary. Over the past century, countless compounds have been investigated for their potential antimicrobial properties. In revolutionizing medicine, antibiotics have become mainstays for anti-infective treatment and despite their important roles in treating human infectious diseases, their efficacy has diminished due to the selective pressure placed on the bacteria they are intended to treat. This selective pressure allows for bacteria who have gained antibiotic resistance genes through mutation or a gene transfer from other species, to become less susceptible to these drugs. This has created a quandary for the treatment of certain infections. According to the Center for Disease Control's 2019 Antibiotic Resistance Threats Report, a little more than 2.8 million cases of antibiotic-resistant infections occur in the United States every year, with more than 35,000 (1.25%) of those resulting in mortality. Additionally, approximately one in 31 hospital patients on any given day is ill with at least one hospital-associated infection, totaling 1.7 million cases of nosocomial infections per year in the US. Of these, catheter-associated urinary tract infections (UTIs) represent about 32%, surgical site infections 22%, ventilator-associated pneumonia (VAP) 15%, and central line-associated bloodstream infections 14% (CDC 2018). Without antibiotics for the treatment of these infections, far more of them would result in death. Since antibiotics are crucial for human and animal health, efforts to preserve their use to stem the development of antibiotic resistance must be taken seriously. Antibiotics should be used only when medically necessary and as called for by a medical practitioner.

After penicillin came into widespread use during World War II, resistance in some strains of bacteria appeared almost immediately. In the late 1940s, resistance to streptomycin, chloramphenicol, and tetracycline was described. In 1953, during a *Shigella dysenteriae* outbreak in Japan, isolates were

found to be multidrug-resistant to chloramphenicol, tetracycline, streptomycin, and sulfonamides (Levy and Marshall 2004). Evidence also began to accumulate that bacteria could pass genes for drug resistance between strains and even between species through the processes of horizontal gene transfer (HGT) (Davies 2006, Reygaert 2018). HGT can include the following types of gene transfer:

Conjugation: direct transfer of DNA from one bacterium to another
Transformation: bacteria take up DNA from the environment
Transduction: bacteriophages transfer DNA from one bacterium to another

For example, it was discovered that antibiotic resistance genes of staphylococci are carried on plasmids that can be exchanged with *Bacillus, Streptococcus*, and *Enterococcus,* providing the means for acquiring additional genes and gene combinations. Some resistance genes are carried on transposons, segments of DNA that can exist either in the chromosome or in plasmids. Misuse and overuse lead to exposure of bacteria to antibiotics, which leads to selective pressure and opportunities for bacteria to gain genes for resistance from each other. One opportunity for exposure is through the use of antibiotics in animal agriculture. It is astonishing to learn that approximately 70% of the antibiotics important to human medicine in the United States are used on farm animals (Pew Charitable Trusts 2016). In fact, in 2010, three agencies (FDA, CDC, USDA) testified in front of Congress that there is indeed a link between the use of antibiotics in food animal agriculture and the antibiotic resistance being seen in human infections (Antibiotic Resistance 2010). While there are many complex components by which antibiotic use on farms contributes to the resistance to antibiotics used by humans, various studies have shown that resistant bacteria emerge in animals who were given antibiotics and that these bacteria can pose a direct risk to humans through transmission in the environment, foodborne paths, as well as direct contact with animals who are infected (Pew Charitable Trusts 2017). Agricultural runoff also allows antibiotics to get into waterways. This, in turn, contributes to longer hospital stays, morbidity, mortality, and increased healthcare costs (Fig. I-6). The origins of antibiotic use in livestock will be discussed in more detail in Chapter 5. To paraphrase Julian Davies, a microbiologist world-renowned for his work on the mechanisms of antibiotic resistance, we are making the world a dilute solution of antibiotics selecting for antibiotic resistance (Shlaes 2010).

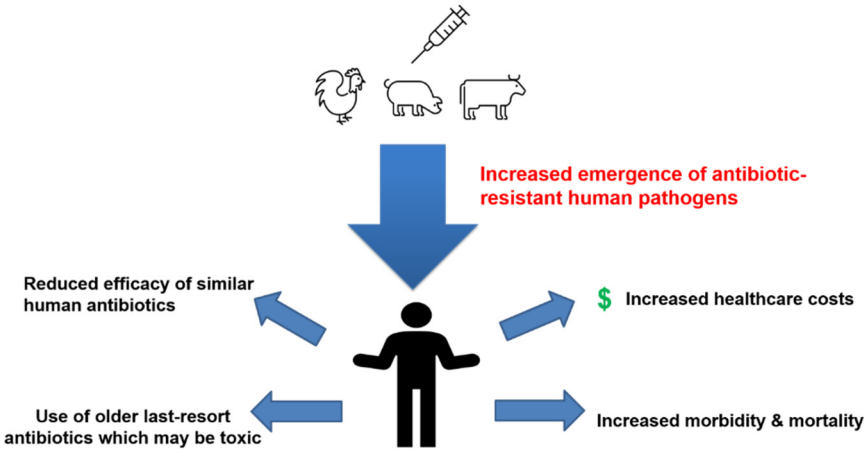

Fig. I-6. Antibiotic use in food animal agriculture contributes to the increased emergence of antibiotic-resistant pathogens in humans

To bring attention to problematic organisms with a penchant for the development of resistance the Infectious Disease Society of America (IDSA) released a report in 2004 called "Bad Bugs, No Drugs" to identify which pathogens are of critical importance, but also to illustrate the dire need for new antibiotics. According to the report, out of 89 new drugs that were approved that year, none of them were antibiotics (IDSA 2004). In 2009, the IDSA updated the report with a new publication by Boucher et al. called *Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America.* The paper outlines those pathogens of critical importance for which treatment options were (and still are) becoming dire. For these pathogens, we are re-approaching the pre-antibiotic era. "ESKAPE" stands for ***E****nterococcus faecium,* ***S****taphylococcus aureus,* ***K****lebsiella pneumoniae,* ***A****cinetobacter baumannii,* ***P****seudomonas aeruginosa,* and **E**nterobacter (Boucher et al. 2009).

***E. faecium* (VRE).** Vancomycin-resistant enterococci are the third most frequent cause of hospital-acquired bloodstream infections and resistance is increasing. Among *E. faecium* isolates, over half of them are vancomycin resistant.

***S. aureus* (MRSA).** More effective treatment options, particularly of the oral type for step-down therapy, are needed for MRSA.

K. pneumoniae. *K. pneumoniae* can express enzymes that break down beta-lactam antibiotics called extended-spectrum beta-lactamases (ESBLs) and carbapenemases, known as KPC (*Klebsiella pneumomoniae* carbapenemase) which break down the carbapenem antibiotics. This group also represents any carbapenem-resistant Enterobacterales (CRE) which can cause severe infection in long-term care residents and is not so easily detected in the lab.

A. baumannii. Carbapenem-resistant *A. baumanni* (CRAB) represents a difficult to treat infection which has an unmet need. There are only a few possible treatment options including tigecycline and colistin.

P. aeruginosa. Strains resistant to quinolones and carbapenems are increasing in incidence worldwide. Some have shown evidence of resistance to last-line options colistin and polymyxins.

Enterobacter. This pathogen often affects hospitalized, immunocompromised patients. Resistant Enterobacter strains often express ESBLs and carbapenemases. Few treatment options exist besides colistin and tigecycline.

One pathogen that is not technically part of "ESKAPE" but maybe should be is *Neisseria gonorrheae.* Currently, gonorrhea represents one of the most prevalent sexually transmitted infections in the United States, and yet, it has progressively developed resistance to every antibiotic used to treat it, including fluoroquinolones. This leaves the cephalosporins, more specifically, a single dose of ceftriaxone as the current recommended treatment for gonorrhea. Yet alarmingly, surveillance data is showing increasing resistance to cephalosporins. The CDC monitors resistance trends of *Neisseria gonorrheae* through the Gonorrhea Isolate Surveillance Project (GISP) which was established in 1986. Without new treatment options, there is not much that stands in the way of untreatable gonorrhea. Left untreated, gonorrhea can lead to ectopic pregnancy or infertility due to the scarring it causes in the female reproductive tract, or even bladder cancer in men (CDC 2021).

Mechanisms of bacterial resistance

Bacteria can utilize several mechanisms that enable them to "get around" the effects of antibiotics. It is important to remember that many antibiotic-producing organisms have these mechanisms in place to prevent themselves from being killed by their own antibiotic. Over time, other pathogens have either picked these up in the environment, through direct contact with microbes that have antibiotic resistance genes and/or have propagated

mutations yielding antibiotic resistance through selective pressure. The most common mechanisms by which bacteria are resistant to certain antibiotics are (Reygaert 2018):

1. Efflux pumps- membrane proteins that remove antimicrobial agents
2. Impaired permeation/preventing the drug from entering- downregulation of bacterial surface porin channels that would normally allow antimicrobial agents to enter
3. Target site modification- genetic change resulting in an altered protein on which the antimicrobial would normally bind
4. Enzymatic destruction of the drug- enzyme created by bacteria that chemically breaks down the antimicrobial agent, rendering it useless
5. Enzymatic modification of the drug- enzyme created by bacteria that chemically changes the antimicrobial agent, rendering it useless

Barriers to new antibiotic development

After the golden age of antibiotic discovery, no new antibiotic classes came on the market for nearly 40 years. In 2002, linezolid was the first new antibiotic to be approved by the FDA with a novel mechanism of action. Due to the emergence of resistance in several strains of bacteria representing difficult to treat infections, the identification of novel antibiotics has become more important than ever. Due to the cost of bringing a new drug to market, which usually tends to average between $1-2 billion dollars and 10-20 years, a low return on investment provides little incentive for pharmaceutical companies to spend money on a new drug that patients do not take for very long or which may become ineffective within a few years. Because the indications for these new drugs must be for antibiotic resistance, it is pretty much a given that they will be reserved, and once they come to market, they will sit on the shelf unless they're desperately needed (Shlaes 2010). Several pieces of legislation have been aimed at promoting antibiotic stewardship and prudent use as well as incentives for pharmaceutical companies to bring new antibiotics to market. Some of these have been successful and some have not.

One example of such legislation is The Food, Conservation, & Energy Act of 2008 which was part of the 2008 Farm bill passed into law by Congress on May 22, 2008. The act appropriates research and education grants for studying antibiotic-resistant bacteria in water, antibiotic use on farms, and appropriate use in both human and veterinary medicine (H.R. 2419). While a part of this bill aimed to study the problem of antibiotic resistance, it didn't promote the development of new antibiotics. This is an area of need in the

fight against antibiotic resistance that healthcare can't afford to let lapse. In 2010, the Infectious Diseases Society of America launched its 10x20 campaign, which aimed to help get ten new systemic antibiotics approved by the year 2020. By all accounts, the goal was met; during that timeframe, 20 new antibiotics were approved. Table I-1 lists antibiotics that have been approved for use since 2010. Several acts were intended to speed up antibiotic development and may have assisted in getting more than ten antibiotics to market during the 2010s. One of these was the Generating Antibiotic Incentives Now (GAIN) Act of 2012, signed into law by President Obama in July 2012. GAIN was a part of the FDA Safety & Innovation Act and created industry incentives for the development of new antimicrobials. These incentives included a fast-tracked FDA review as well as an additional five years of patent exclusivity for a "Qualified Infectious Disease Product" (QIDP). To aid in this, the FDA also must issue guidance on the development of pathogen-focused antibiotics and compile a list of "qualifying pathogens" that pose a serious threat to public health and update it every 5 years (FDA 2012).

Table I-1. Novel antibiotics approved by the FDA between 2010-2020

New antibiotic	Year approved
ceftaroline (Teflaro®)	2010
fidaxomicin (Dificid®)	2011
bedaquiline (Sirturo®)	2012
telavancin (Vibativ®)	2013
tedizolid (Sivextro®)	2014
dalbavancin (Dalvance®)	2014
oritavancin (Orbactiv®)	2014
ceftolozane/tazobactam (Zerbaxa®)	2014
ceftazidime/avibactam (Avycaz®)	2015
bezlotoxumab (Zinplava®)	2016
meropenem/vaborbactam (Vabomere®)	2017
delafloxacin (Baxdela®)	2017
secnidazole (Solosec®)	2017
plazomicin (Zemdri®)	2018
eravacycline (Xerava®)	2018
omadacycline (Nuzyra®)	2018
imipenem/cilastatin/relebactam (Recarbrio®)	2019
cefiderocol (Fetroja®)	2019
lefamulin (Xenleta®)	2019
pretomanid	2019

Some disagree that the GAIN Act worked to get more *new* antibiotics to market. Some argue the reason for this is that the required QIDP eligibility is too broad and not targeted to actual needs. For example, the list of qualifying pathogens, which contains resistant bacteria, includes some bacteria which are indeed resistant, but we currently do still have treatments for them. This removes the focus from resistant organisms for which we are truly running out of options. Additionally, the FDA labeled 147 experimental drugs in 2018 as QIDPs, half of which were novel, and the other half were new doses or indications for existing drugs. Of the Table I-1 list above, most of these are novel chemical entities, but most of them do not represent a truly novel mechanism of action. While some of these new drugs add to the antibiotic arsenal, some of them (lefamulin, cefiderocol, etc) were approved based on non-inferiority to existing comparison antibiotics, and do not necessarily add a clinical benefit. To improve the effectiveness of GAIN, infectious disease experts believe it should be, at minimum, modified to narrow the list of qualifying pathogens as well as to require QIDPs to demonstrate an improved clinical benefit over existing therapies. Other modifications could include removing exclusivity extensions for existing drugs that are simply modified and fall into the QIDP category (Darrow and Kesselheim 2020).

However, even before the GAIN Act and IDSA 10x20, issues existed within the FDA that hindered pharmaceutical companies from researching new antibiotics due to stringent clinical trial requirements. Dr. David Shlaes describes many of these issues with the FDA in his book *Antibiotics: The Perfect Storm*. To this end, the cost of research and development, as well as the FDA requirements for the clinical trial process, increased significantly, essentially setting potential antibiotics up for failure at the outset. This, coupled with the difficulty in recouping R&D costs acts as a deterrent for pharmaceutical companies who may have brought new drugs to market (Shlaes 2010).

It wasn't until after GAIN was passed that the CDC released the first AR Threats Report (2013) which brought attention to the growing problem of *specific* antibiotic-resistant infections. This included three urgent threats (*C. difficile,* Carbapenem-resistant Enterobacteriaceae, and drug-resistant *Neisseria gonorrheae)*, twelve serious threats, and three concerning threats (CDC 2013). To fight this problem, President Obama signed an Executive Order on September 18, 2014, called Combating Antibiotic Resistance (CARB) which established a Task Force to be co-chaired by the Secretaries of Defense, Agriculture, and Health and Human Services. It also established a Presidential Advisory Council on Combating Antibiotic-Resistant

Bacteria (PACCARB) with the main goals of improving antibiotic stewardship, strengthening national surveillance efforts for resistant bacteria, responding to outbreaks of antibiotic-resistant bacteria, and promoting the next generation of antibiotics and diagnostics. In 2015, a five-year action plan for combating antibiotic-resistant bacteria was released by the White House and was centered on 5 main goals: 1) to slow the emergence of resistant bacteria and prevent the spread of resistant infections; 2) to strengthen national one-health surveillance efforts to combat resistance; 3) advance the development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria; 4) accelerate basic and applied research and development for new antibiotics, other types of therapeutics, and vaccines; and 5) improve the international collaboration and capacities for antibiotic resistance prevention, surveillance, control, and antibiotic research and development. In addition to the establishment of the PACCARB in 2015, Congress also appropriated funds to support the goals outlined in the National Action Plan (The White House 2014).

In addition to this, there are several bills that have been and are still being proposed by both Democrats and Republicans in Congress to limit the use of antibiotics in agriculture. While many bills have been proposed, very few have made it to the Congress floor or have had a favorable outcome (Table I-2). Several versions of these bills have been introduced and reintroduced over the years, assigned different numbers, and have had various congressional sponsors. Unfortunately, politics often get in the way. According to GovTrack many of these bills have a 0-1% chance of being enacted. Problems arise when lobbyists side with the farming and pharmaceutical industries and campaign contributions are made to quash a bill. The American Farm Bureau is the biggest lobbying arm of agriculture and has roughly $3.3 mill worth of lobbying dollars. Some pharmaceutical companies have spent close to a million dollars lobbying against the Preservation of Antibiotics for Medical Treatment Act (PAMTA) alone. PAMTA aimed to amend the Food, Drugs, and Cosmetics Act to allow for research to prove that nontherapeutic uses of antibiotics **do not** contribute to resistance. The Act also phases out the use of antibiotics in healthy animals for nontherapeutic purposes. Opponents to limiting the use of antibiotics in farming say that “an effort both through legislation and regulations to limit the use of animal antibiotics is based on emotion and no credible peer-reviewed science (Conradis 2013).”

Table I-2. Yet to be successful bills proposed with the goal of reducing antibiotic resistance

Bill proposed	Year(s)	Sponsored by (sponsors may vary based on the year the bill was introduced or reintroduced)	Goal
Delivering Antimicrobial Transparency in Animals Act (DATA) (H.R. 820 2013)	2013, 2015	Congressman Henry Waxman (D-California) and Congresswoman Louise Slaughter (D-New York)	Require documentation of non-medical antibiotic use of farms and would preserve beneficial practices including treatment of sick animals
Preventing Antibiotic Resistance Act (S. 629 2017)	2013, 2015, 2017	Senator Dianne Feinstein (D-California)	Maintain that a veterinarian-client-patient relationship should ensure that medically important antimicrobials are used in food-producing animals in a manner consistent with best practices. Scrutinize new animal drug applications if the drug is a medically important antimicrobial used in humans
Preservation of Antibiotics for Medical Treatment Act (PAMTA) (H.R. 1587 2017)	1999, reintroduced every two years	Congresswomen Louise Slaughter (D-New York) and Rosa DeLauro (D-Connecticut)	Amend the Food, Drug, Cosmetic Act to research (and prove) that nontherapeutic use of antibiotics will NOT contribute to resistance. The act also phases out the non-therapeutic use of antibiotics in animal feed and for healthy animals. To use an antibiotic, a veterinarian must have a valid vet/farmer/animal relationship to prescribe antibiotics. There must be a significant risk of infection/transmission for the antibiotic to be used.

Strategies to Address Antibiotic Resistance Act (STAAR Act) (S. 3291 2021)	2007, 2009, 2013, 2016, 2018, 2019, 2021	Congressman Jim Matheson (D-Utah), Senator Sherrod Brown (D-Ohio)	Expands various initiatives to address antibiotic resistance & reestablishes the interagency Antimicrobial Resistance Task Force to coordinate and develop efforts addressing antibiotic resistance.
Reinvigorating Antibiotics and Diagnostic Innovation (READI) Act (H.R. 3539 2015)	2015, 2017	Congressmen Erik Paulsen (R-Minnesota) and Mike Thompson (D-California)	Allow for a tax credit to organizations that create new organizations or rapid diagnostic tests for treating or diagnosing life-threatening resistant infections.
Revaluing Antimicrobial Products Act (REVAMP) (H.R. 6294 2018)	2018	Congressmen John Shimkus (R-Illinois) and Tony Cardenas (D-California)	Encourage the development of priority antibiotics through offering an incentive of a transferable exclusivity period
Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) (S. 3787 2018)	2019	Congressmen Danny Davis (D-Illinois), Senators Orrin Hatch (R-Utah), Bob Casey (D-Pennsylvania), John Isakson (R-Georgia)	Increase hospital reimbursement for new antibiotics, require those hospitals to monitor their use, and report the data to the CDC. Establish stewardship programs
PASTEUR Act (Pioneering Antimicrobial Subscriptions To End Up Surging Resistance) (Kim 2020)	2020, 2021	Representatives Mike Doyle (D-Pennsylvania) and Drew Ferguson (R-Georgia), and Senators Michael Bennet (D-Colorado) and Todd Young (R-Indiana)	This Act aims to strengthen the antibiotic pipeline by allowing the government to enter into subscription contracts for new antibiotics that would be important to public health to spur the development of novel antibiotics that may not generate high sales.

One successful bill was the Pandemic and All-hazards Preparedness and Advancing Innovation (PAHPAI) Act which was both introduced and passed by the U.S. Congress in 2019. The Act was introduced by Richard Burr (R-North Carolina), Bob Casey (D-Pennsylvania), Lamar Alexander (R-Tennessee), and Patty Murray (D-Washington), and focuses on bioterrorism and antibiotic resistance, among other threats including pandemic preparedness. Regarding antibiotic resistance, the PAHPAI law allows the Secretary of Health and Human Services to continue the PACCARB. The Advisory Council can advise and recommend policies to the Secretary that would help to reduce antibiotic resistance. Some of these may include improving research on diagnostics and innovative methods or treatments for combating antibiotic resistance, as well as improving coordination of international efforts that inform the efforts of the United States to reduce antibiotic resistance. The bill was passed by Congress on June 24, 2019 and was signed by President Trump on the same day. PAHPAI became public law number 116-22 (S.1379 2019). In 2019, the CDC released the second AR Threats Report, which includes five urgent threats (the same three from the 2013 report, including *Candida auris* and carbapenem-resistant *Acinetobacter*), eleven serious threats, two concerning threats, and three new organisms on the watch list (CDC 2019). Many would agree that Europe is ahead of the U.S. when it comes to doing something about the spread of antibiotic resistance. It is important to note that the European Union banned the use of antibiotics for growth promotion in agriculture in 2006. This did not happen in the United States until more than a decade later. Legislative change by the FDA made it illegal to use sub-therapeutic doses of antibiotics in animal feeds for growth promotion. Drug manufacturers had to comply with relabeling their antibiotics to remove this as an indication. Regarding other uses of antibiotics in animals, the EU plans to ban the use of antibiotics that are used in human medicine for animals in 2022 (Ganzler 2018). For example, a veterinarian prescription will be required for antimicrobial use in livestock and antibiotics cannot be used as a substitute for poor animal husbandry and crowded conditions. These regulations also apply to meat imported into the EU, which doesn't import much U.S.-grown meat anyway, partly due to the EU's higher standards (European Commission 2005). Despite many pieces of legislation being proposed in the U.S. to do exactly what the EU is planning, there doesn't seem to be any hope that this will happen anytime soon. In 2017, the FDA Veterinary Feed Directive (VFD) asserted that antibiotics can only be used for the treatment and prevention of infections in food animals and not simply for growth enhancement. The VDR also requires that antibiotics must be prescribed within the context of a veterinarian/client/patient

relationship but allows for veterinarian oversight regarding the various types of circumstances that may be encountered (FDA 2022). While this is a step in the right direction, there is still work to be done to eliminate medically important antibiotics for human health from animal feeds.

Summary

In the grand scheme of this problem, this book merely scratches the surface. Researchers since the inception of antibiotic use have (and still are) attempting to isolate and identify the specific mechanisms that contribute to bacterial resistance. It is a complicated web that we are only just beginning to understand. And yet, there are still many unanswered questions and out-of-the-box ideas to combat this problem that have not been discovered. To that end, this book will discuss the main mechanisms of resistance utilized by some resistant organisms and provide an overview of some of the most concerning human pathogens that are becoming difficult to treat due to resistance.

Before the development of antibiotics as we know them now, bacterial infections were untreatable and sometimes resulted in death. Treatments consisted of dangerous surgical procedures or untested natural products with unknown side effects and questionable efficacy. The golden age of antibiotics beginning in the late 1920s and 1930s saw a flurry of activity and discovery. Further investigation into the mechanisms of microbial antagonism resulted in the development of several new drug classes, both synthetic and naturally produced. While these drugs have not quite been around for a century, it is already apparent that we have squandered many of them to the point where certain classes of antibiotics can no longer be used for certain types of infections- some of which are labeled as “Superbugs.” Efforts to quell the spread of antibiotic resistance are not much more than a couple of decades old; this results in having to reevaluate guidelines and choose other classes to treat the same infection, ultimately causing healthcare to run out of options. For certain multidrug-resistant strains, the problem isn’t a looming one, it’s already here.

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