Antibiotics: Abused and Expensive

How can the antibiotic resistance crisis be combatted when the economics do not support the discovery of new antibiotics.

Ethan T. Currin ’25

Discovery and Application of Zosurabalpin

In January of 2024 a group of scientists from Harvard University reported the discovery of a potentially groundbreaking new class of small molecule antibiotics[1]. After a screening of around 45,000 macrocyclic peptides, produced by the company Tranzyme Pharma, a cluster of compounds with antibacterial related activity were discovered[2]. One compound in particular, known as zosurabalpin, showed incredible potential in both computational models and *in vivo* studies of different animal models. Characteristically, zosurabalpin was shown to have an effect on Gram-negative bacteria, notoriously known for being difficult to kill because of their double membranous structure that allows them to block the entry of most antibiotics[1]; Gram-negative bacteria include *E. coli* and *K. pneumoniae,* as well as bacteria that cause salmonella, tuberculosis, and the black plague. What makes the discovery of this new potential antibiotic so unique is that it has the ability to block the transport of lipopolysaccharide, or LPS, from the inner membrane to its destination on the outermost membrane of a Gram-negative bacterial cell[2]. LPS is an endotoxin and structural component of the outer membrane that also acts as a permeability factor, allowing it to block the entry of most antibiotics into the cell[3]. Blocking the transport of LPS to the outer membrane of a Gram-negative bacteria would leave the bacteria both structurally compromised and more susceptible to antibiotics. A new class of antibiotics for Gram-negative bacteria had not been approved in over 50 years, so this discovery is certainly exciting[1].

Zosurabalpin and CRAB

Zosurabalpin was found to be particularly effective against an antibiotic-resistant bacteria known as carbapenem-resistant *Acinetobacter baumannii*, or CRAB[2]. CRAB is opportunistic in nature and typically a nosocomial-acquired infection. It causes severe infection in patients who are hospitalized and those with various critical illnesses, particularly those with blood infections or nosocomial acquired pneumonia[2]. These patients are likely immunocompromised as a result of fighting off their previous infection or taking other antibiotics, allowing a nosocomial infection like CRAB to easily infect the patient. The mortality rate of CRAB is around 40-60%, earning it a label as a priority 1 critical pathogen by the World Health Organization[4]; it is also listed as an urgent threat by the CDC in its 2019 Antibiotic Resistance Threat report[5]. This pathogen is responsible for anywhere between 50,000 to 100,000 deaths annually worldwide[6], with over 700 deaths annually in the U.S.[5] CRAB is deadly because it is resistant to the antibiotic carbapenem, which is a cell wall synthesis inhibitor typically prescribed to fight multi-drug resistant bacteria[2]. The mutated form of *A. baumannii* became resistant to carbapenem, leaving health care professionals with few treatment options for patients who contracted CRAB, which is attributed to the high mortality rate. Researchers hope that the breakthrough discovery of zosurabalpin and its’ effectiveness against CRAB *in vitro* will allow it to enter clinical trials and one day, hopefully soon, be used as a treatment for CRAB[1].

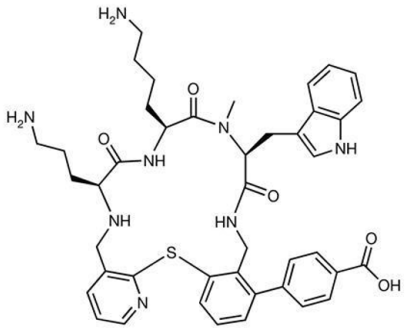

Figure 1: Chemical structure of zosurabalpin[2]

The Antibiotic-Resistance Crisis

Antibiotic resistance like that of *A. baumannii* is becoming an increasingly concerning problem in the medical community, largely due to the spread of other antibiotic resistant bacteria, or ARBs. Certain bacterial species have the ability to confer resistance to particular antibiotics after a series of exposures, leading to the formation of ARBs. Another family of bacteria that is resistant to carbapenem, known as Carbapenum-resistant *Enterobacterales,* or CRE, has been shown to survive and reproduce in sink drains; it has also been shown to spread via wastewater to other patients[5]. CRE is also on the CDC urgent list along with CRAB, as well as a drug resistant strand of *Neisseria gonorrhoeae*, the causative agent of the STD gonorrhea, that increases the risk of getting and giving HIV while also resulting in infertility and ectopic pregnancy[5]. Perhaps the most well-known ARB is MRSA, or methicillin-resistant *Staphylococcus aureus*, which causes a severe rash that can develop into gangrene if left untreated, as well as other serious complications[5]. There are thousands of other additional ARB species, as well as bacteria like

Clostridium difficile, of *C. diff*, that are not necessarily resistant to antibiotics but rather arise opportunistically as a result of continual antibiotic use[7].

Antibiotics: A Recent Discovery

The occurrence of these ARB arises from varying levels of exposure to antibiotics. Antibiotics, of course, are natural or synthetically produced biological agents with the ability to kill bacteria[8]. The discovery of natural antibiotics was a relatively recent event, occurring largely during the 1940s through the 1960s, known today as the Golden Age of antibiotics[8]. During this time, antibiotics that are still commonly used today were discovered, such as cillin-type drugs like penicillin, the sulfonamides, mycin-type drugs like streptomycin, the cephalosporins, and cycline-type drugs like tetracycline[8]. Other advances were made following the Golden Age of antibiotics that led to the creation of synthetic versions of discovered antibiotics such as amoxycillin and azithromycin, known commonly as a Z-Pak, as well as new kinds of antibiotics like carbapenems and lipopeptides[8]. To say that the discovery of antibiotics was the medical breakthrough of the century would be an extreme understatement; scientists estimate that the discovery and implementation of antibiotics extended the average lifespan by 23 years[8]. That being said, antibiotic discovery has slowed down significantly since the 1960s, while the emergence of ARBs has increased exponentially since that time. The threat of ARB was exacerbated by the COVID-19 pandemic, which saw the nosocomial infection levels of ARB rise nearly 15%; ARB infection numbers were trending down prior to COVID-19, but the strain of the pandemic on medical facilities led to an increase in infection rates in hospital settings[7].

Antibiotic Abuse and Misuse

To understand how to combat the threat of ARB, it is necessary to know how they came about. The over-prescribing of antibiotics is perhaps the biggest factor in the conferring of antibiotic resistance to certain bacteria. According to CDC statistics, approximately 211.1 million courses of antibiotics, equating to nearly 2 antibiotic prescriptions per every 3 persons living in the US, were dispensed by pharmacies in the US in 2021[9]. The number of antibiotic prescriptions varied by state, as shown in **Figure 2**, with Alaska representing the low end of antibiotic prescriptions with 354 prescriptions per 1000 people and Mississippi representing the high end of antibiotic prescriptions with 1083 prescriptions per 1000 people. In **Figure 2**, white represents 354-466 prescriptions, yellow 472-551 prescriptions, orange 555-619 prescriptions, red 635-675 prescriptions, burgundy 677-765 prescriptions, and dark-red 766-1,083 prescriptions. Of these totals, approximately 30% of the antibiotic courses that were prescribed were for infections that did not require the use of antibiotics[10]. During the first 8 months of the COVID-19 pandemic in 2020, 80% of people that were hospitalized with COVID-19 were given antibiotics, which was likely not appropriate in every circumstance[7].Quite simply, there appears to be a problem with the abuse of antibiotics because of over-prescribing by medical professionals. The problem of abusing antibiotics also stretches farther than just with humans; in order to cut animal losses to disease and increase profits, many farmers give their livestock and poultry excessive amounts of antibiotics, creating an environment in which bacteria can gain resistance to certain antibiotics easier[5]. The more contact a bacterium has with an antibiotic that is supposed to kill it, the more opportunities it has to develop ways to escape the mechanism of destruction of that antibiotic. The abuse of antibiotics, whether it be by people or in animals, allows for bacteria to become resistant to antibiotics faster.

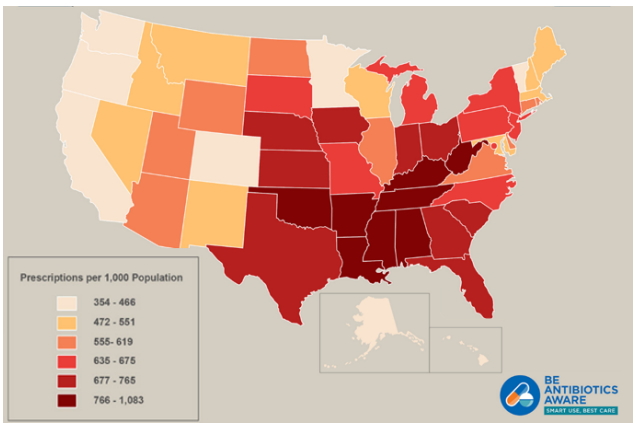

Figure 2: Antibiotic Prescriptions per 1,000 Population by State in 2021[9]

Antibiotic misuse is also a way in which bacteria can gain antibiotic resistance. Of the aforementioned 211.1 million doses of antibiotics administered in an outpatient setting in 2021, as much as 50% were prescribed inappropriately; this number represents not only the antibiotics that were unnecessarily used but also the prescribing of the wrong type of antibiotic, the wrong duration, and the wrong dosage[9]. Not taking antibiotics for their full duration will not kill all of the intended bacteria, giving it a chance to develop resistance from its near-death experience. Using the wrong antibiotic could also cause the intended bacterial target to mutate in order to confer resistance to that particular antibiotic. This

now mutated bacteria could then spread its acquired antibiotic resistance genes to other bacteria via conjugation, a process in which bacterial cells can spread genetic information. It could also spread through transduction, a process in which a bacterial virus known as a phage takes in the DNA of an antibiotic resistant bacteria and injects the DNA into a different bacterial cell, giving that cell the respected DNA for antibiotic resistance[5]. Misinformation about the uses of antibiotics also leads to misuse. A 2015 WHO survey of 12 different countries found that roughly 64% of participants believed that antibiotics could be used to treat viral diseases like colds and the flu[11]. Viruses are non-living pathogens, so antibiotics have no effect on them whatsoever. Overall, both the abuse and misuse of antibiotics can create resistance, but they also can harm the body; antibiotics work very well in that they are able to effectively kill bacteria, but they do not necessarily discriminate on the type of bacteria. This leads to the destruction of the gut microbiome with excessive or unnecessary antibiotic use; the gut microbiome is a term used to describe the community of "good" bacteria that live and function within the gut, which helps to digest food and protect against pathogens[12]. Over time, continual antibiotic use will weaken the gut microbiome, leaving a high risk of developing an opportunistic pathogen such as *C. diff* or developing other diseases that would have been destroyed by the body's good bacteria.

Antibiotics and Economics

A 2021 study found that the treatment for the six ARB listed as urgent by the CDC costs $4.6 billion annually, with the most expensive treatment being that for CRAB[13]. These numbers do not include the multitude of other ARB, which likely push the totals into the tens of billions annually. Scientists predict that in the next decade, if left unchecked, ARB could result in a GDP loss of $3.4 trillion dollars annually, while also pushing as many as 24 million people into poverty[14]. According to a study published in the Lancet, an estimated 1.27 million people worldwide were killed as a direct result of ARB in 2019, while an additional 5 million deaths were indirectly attributed to ARB[6]. In that same year in the United States, 2.8 million people contracted an ARB infection and over 35,000 people were killed as a result; when factoring in *C. diff* infections, these numbers rise to well over 3 million infections and nearly 50 thousand deaths[5]. In 2019, more people were killed by ARB than were killed in car accidents[15]. It is predicted that ARB will have created losses of roughly $100 trillion and caused more than 10 million deaths worldwide annually by 2050, which is equivalent to the number of people who died of cancer in 2020[14].

An Expensive Process

Now, knowing that CRAB is such a deadly and expensive ARB makes the discovery of zosurabalpin that much more important. If zosurabalpin could become implemented in the fight against CRAB, the infection numbers would likely go down and disease progression would yield better outcomes. The problem is that there is a long and expensive process for a potential antibiotic to become sold on a mass scale. It is estimated that the cost of developing an antibiotic into a product that is clinically approved is approximately $1.5 billion; of this, roughly 45% is spent solely in research and development[16]. The process of antibiotic discovery is extremely difficult while also being hit or miss, so there is a high likelihood that hundreds of millions of dollars in research and development would yield no antibiotic to show, leaving a massive cost behind to the developing company. The length of time it takes to develop an antibiotic is also a problem. After passing through the three phases of clinical trials, where it could be rejected at any step, it typically takes anywhere from 10 to 15 years for an antibiotic to gain regulatory approval[17]. After approval is gained, an antibiotic is then only expected to make roughly $46 million per year[16]. On top of this, the now marketable antibiotic is only given a 5–10-year exclusivity period where no generic varieties can be sold; after this time expires, however, other companies, who did not spend millions in research and development, could then begin to sell the antibiotic at often a much lower price[16]. Essentially, pharmaceutical companies are losing money by trying to develop new antibiotics.

Lack of Interest

To put it rather bluntly, pharmaceutical companies are not going to develop antibiotics out of the goodness of their hearts. The money has to be there for the process to be economically reasonable. According to the Pew Charitable Trust, only 43 new antibiotics were in development in 2021, which has only risen to around 50 in 2024. Only 13 of the 43 were in phase 3 clinical trials, with the expectation that only half would be regulatorily approved. As well, only two of the 38 pharmaceutical companies working to develop these antibiotics ranked in the top 50 pharmaceutical companies by annual sales[17]. Privately funded antibiotic discovery is not seen as profitable by the big pharmaceutical companies, leading many to shift their focus to developing cancer treatments or drugs for musculoskeletal conditions, which are on average 3 and 11 times more profitable respectively than antibiotics[16]. The numbers of cancer drugs in development compared to antibiotics is especially skewed, with over 1300 drugs in clinical trials according to a 2020 report[18]. **Figure 3** shows

the number of drugs approved between antibiotics and cancer treatments since the 1980s. The decline in antibiotic approvals compared to the overall increase in cancer drug approvals is likely a combination of the complexity in finding new antibiotics and the increased understanding about cancer and its methods of action.

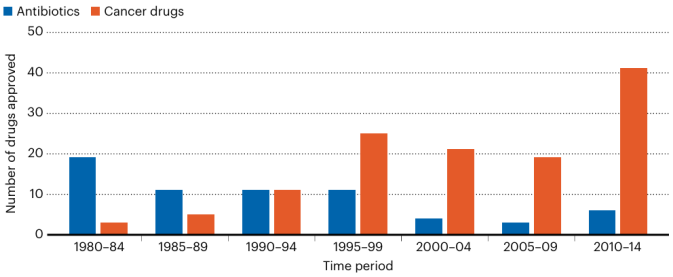

Figure 3: Drug Approvals between Antibiotics and Cancer Treatments[16]

Antibiotics and Cancer Funding

Still, there appears to be a rather large difference in interest between the treatment of the two diseases, which may boil down to levels of funding. The National Cancer Institute was allocated $7.3 billion in fiscal year 2023, with $216 million coming from funding from the Cancer Moonshot project that was established in 2016[19]. On the other hand, the CDC pledged more than $197 million to fight antibiotic resistance in 2023, with additional emergency supplemental funding in excess of $250 million to implement safer health measures in containing ARB outbreaks[20]. Cancer is the "big one" in that it is the second leading cause of death in the US, making every penny spent towards development of effective treatments worth it; however, there needs to be additional funding for the ARB crisis, perhaps in the form of government incentives. With the threat of 10 million deaths per year in two and a half decades, there is a valid argument for more research into antibiotic development. Several private programs and funds have committed nearly $2 billion for the discovery of new antibiotics, but there needs to be additional monetary input by the government, who largely funds prevention and safer health practices to combat the threat of ARB[16]. While prevention is important and will act to slow the spread, there needs to be more antibiotics in the pipeline when ARBs yield our common antibiotics useless. There also does not need to be a shift in focus from cancer research to strictly antibiotic research, but there certainly needs to be more interest into antibiotic discovery, which at the moment is not favorable because of the lack of funding and profits available.

Future Treatments and Outlook

As a result of the ARB crisis, there has been an exploration into alternative methods to treat these resistant bacteria, as well as new ways to discover antibiotics. New treatment techniques like that of phage therapy has been introduced as a possible method of treatment for ARB without the use of antibiotics. Using phage therapy, an ARB-specific bacteriophage is introduced into a patient, which will then act to, in theory, destroy all of the ARB within the patient[21]. Other new methods, like that of CRISPR-Cas9 systems and nanotechnology, are also being explored for selective targeting of ARB DNA and membrane structures[22]. Because of our recent innovations in the field of artificial intelligence, there has been increased interest into using deep learning models to create millions of compounds that could be used as antibiotics against ARB; in December of 2023, a deep learning model was able to discover an entirely new class of theoretical antibiotics[23]. "Antibiotic hunting" has also been used to discover natural antibiotics from unculturable bacterial species. Only around 1% of bacteria isolated from soil samples can be grown in a lab setting, largely because the bacteria can only thrive in their natural setting. Using a device called an iChip, which acts to grow and culture bacteria by leaving them in their natural environment, the percentage of bacteria that can then be grown in a lab setting increases to over 50%[24]. The iChip was used to discover a promising antibiotic called texiobactin from a bacteria known as *E. terrae*, which was shown to kill both MRSA and the bacteria that causes tuberculosis; it was isolated from a field in rural Maine[8]. Currently, the best method available to slow the spread of ARB is through safer health practices and monitoring for potential ARB outbreaks.

An Inescapable Outcome

Although research is being done to combat the crisis of ARB, they are not going anywhere; current efforts can only act to slow the eventual spread of these bacteria. The longer an antibiotic is on the market, the more opportunities bacteria have to become resistant to it. Penicillin was first made available for commercial use in 1941; penicillin-resistant bacteria were first identified in 1942[5]. Methicillin was first introduced in 1960, and MRSA was identified in that same year[5]. As Jeff Goldblum's character Dr. Malcolm said in Jurassic Park, "Life finds a way." The relative speed of antibiotic resistance in bacteria was demonstrated by a group of Harvard researchers in a 2016 study, where they introduced *E. coli* to a large agar plate containing the

antibiotic trimethoprim in various degrees of concentration. *E. coli* is unable to live on trimethoprim, which was originally shown after the initial introduction of the *E. coli*; however, after a few days a particular colony of bacteria had developed resistance to the antibiotic and was shown growing on a portion of the agar, eventually growing into the middle of the agar that contained 3000 times the lethal dose of trimethoprim after only 12 days[25]. In essence, the discovery of antibiotics also introduced the inevitable and unintended threat of eventual antibiotic resistance.

Future

Overall, the implementation of safer health practices and the reduction of prescribed antibiotics is a step in the right direction to combat the ARB crisis. Doctors are prescribing less antibiotics per year and are clearing up misconceptions and misunderstandings with their patients regarding antibiotics and their appropriate usage; prior to the medical crisis that was the COVID-19 pandemic, ARB infection numbers were trending down, and there is hope that these numbers will return to their descending pace now that the brunt of the pandemic is over[9]. Increasing information about antibiotics and resistant bacteria is also important to slow their spread. In the same WHO survey that found 64% of people believed that antibiotics could work against viral infections, 76% believed that antibiotic resistance occurred when the human body became resistant to antibiotics[11]. There certainly is misinformation concerning ARB and antibiotics, so more public awareness would help the cause of slowing the spread of these resistant bacteria. Unfortunately, the difficulty of finding new antibiotics combined with the lack of interest from large pharmaceutical companies has created a dire situation for this ever-present crisis; the economics must support the science, and until this becomes the case there is not likely to be any increased interest into the field of antibiotic development. The antibiotic resistance crisis was created by us, so it is up to us to attempt to solve it. If not, there may be a time in the not-so-distant future where common surgical operations will not be done because of the risk of ARB infection, or even a time where a once common bacterial infection will prove to be deadly. Until that time, the current repertoire of antibiotics will continue to be used with the hope that new antibiotics will come to save us from resistance.

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