Brainstorming Solutions for the Unintended Consequences of Antibiotics and the Development of Resistant Bacteria

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BRAINSTORMING SOLUTIONS FOR THE UNINTENDED CONSEQUENCES OF ANTIBIOTICS AND THE DEVELOPMENT OF RESISTANT BACTERIA

By

RAJNI D. RAMSUKH

A master’s thesis submitted to the Graduate Faculty in Liberal Studies in partial fulfillment of the requirements for the degree of Master of Arts, The City University of New York

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Rajini D. Ramsukh

This manuscript has been read and accepted for the Graduate Faculty in Liberal Studies in satisfaction of the thesis requirement for the degree of Master of Arts.

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ABSTRACT

Brainstorming Solutions for the Unintended Consequences of Antibiotics and the Development of Resistant Bacteria

By

Rajini D. Ramsukh

Advisor: Joseph W. Dauben

This thesis entails the study of bacteria that cause infections requiring antibiotic treatments and the development of antibiotic resistance as an unintended consequence. Antibiotics were originally formulated to remedy medical problems, but the consequence of inappropriate usage has created a serious setback: the development of drug-resistant bacteria. The objective of this thesis is to illuminate the misuse, over-prescription, and mis-monitoring of the dispensing of antibiotics that results in the development of antibiotic-resistant bacteria. However, the core of the thesis is to evaluate the solutions implemented thus far to remedy the already existing problem of resistant bacteria and to propose suggestions for developing new solutions. Resistant bacteria are non-responsive to any antimicrobial treatments, which ultimately limit medical therapeutics. For future implications, two studies are proposed that suggest interventions to enhance existing solutions. Investigating the effects of the suggested experiments will create other possible explanations to remedy the problem of resistant bacteria.

On a global scale, the development of resistant bacteria could lead to a pandemic. The purpose of highlighting that this is a problem is to urge government agencies to review policies implemented for medication management, and to rethink/restructure those rules currently in place to better manage the dispensing of medicines, specifically antibiotics. The main task of
writing this thesis is to focus on the solutions that are already established and to brainstorm and employ other innovative ways to remedy the problem of antibiotic-resistant bacteria.
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Chapter 1: Historical Overview: Experimental Processes Involved in Formulating Antibiotics and the Microbes Responsible For Those Formulations

The scientists who pursued the journey to invent and discover new and efficient chemotherapies encountered many adversaries. These difficulties are real for both the current and past attempts. It is a continuous struggle to develop an effective treatment with minimal side effects that is safe for human subjects. The struggles are even greater so when dealing with the treatment of infections that require antibiotics. Some of the factors that hinder the formulation of new antibiotics are the cost of resources to conduct experimental studies, the level of tolerable side effects from new drugs, and the lack of sufficient time to develop new antibiotics.

Hospitals used antibiotics most often leading to higher rates of drug-resistant strains. For example, in the 1930s, sulfonamide-resistant Streptococcus pyogenes was prevalent in military hospitals.\(^1\) In the 1940s, penicillin soon led to the emergence of penicillin-resistant Staphylococcus aureus in London civilian hospitals.\(^2\) Soon after antibiotics were discovered, similar observations were made for the advent of community-based streptomycin-resistant Mycobacterium tuberculosis.\(^3\) Therefore, there are many cases that exemplify the existence of antimicrobial resistance.

Davies and colleagues highlighted that the problems of antibiotic resistant bacteria were nothing new, despite the recurring times and places this type of news was being publicized. During 1952, when Japan was a war zone, the country was struck with outbreaks of dysentery. This gastrointestinal infection was caused by the bacteria Shigella dysenteriae. These bacteria were non-responsive to sulfonamides, yielding approximately 80% as sulfonamide-resistant. There were reports in Japan as early as 1955, where a strain of Shigella dysenteriae was

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\(^2\) Ibid., 122.

\(^3\) Ibid.
isolated and found to be resistant to four different antibiotics. In addition, the efficacy of streptomycin, tetracycline, and chloramphenicol, which were all relatively new antibiotics, was temporary. When the aforementioned antibiotic prophylaxes were used in a clinical setting, resistant strains caused the treatments to be ineffective.

The emergence of the resistance problem was not taken seriously until the 1970s. This period was when *Haemophilus influenzae* and *Neisseria gonorrhoeae* emerged. These were organisms that caused respiratory and genitourinary diseases, respectively. The problem was that they were both resistant to ampicillin, rendering the treatment for the bacteria ineffective. In addition, *Haemophilus influenzae* was also resistant to both chloramphenicol and tetracycline, resulting in difficulties to treat either one of the bacteria that cause the diseases mentioned above. As antimicrobial usage increased, the frequency of resistance accelerated in many different bacteria. Although there are other factors to consider, reckless use of antibiotics was more apparent in the developing countries where antibiotics were available without a prescription compared to countries that have strict guidelines to prescribe these drugs. Simultaneously, poor living conditions caused by unsanitary practices propelled the spread of infections. These infections were more likely to go untreated because healthcare industries were creating a barrier to obtaining medical services. Limited healthcare budgets resulted in reduced access to innovative treatments. As a result, effective prophylaxis was limited because they were expensive. These were all factors that indirectly facilitated the problem of resistant bacteria.

In general, some organisms become resistant to multiple antibiotics. These bacteria are more challenging and costly to treat. In some cases, treatments are unsuccessful, and patients may succumb to multi-drug resistant (MDR) infections because all antibiotics have failed to work. This problem is prevalent in the developing countries. For example, enteric disease-causing agents such
as *Salmonella enteritidis*, *Shigella flexneri*, and *Vibrio cholerae* “threaten and circumvent public health measures.”

In the United States and the United Kingdom, 40-60% of nosocomial *Staphylococcus aureus* strains are Methicillin-resistant. Vancomycin has been one of the only antibiotics that could effectively treat Methicillin-resistant *Staphylococcus aureus* (MRSA). However, there has been a steady increase in small portions of MRSA that show low-level resistance to this drug of choice. In some cases, there have been treatment failures. In addition, there have been cases of full vancomycin-resistant strains of *Staphylococcus aureus*. In parts of Southeast Asia and China, 60-70% of *Escherichia Coli* are resistant to fluoroquinolones. Pneumococci resistance continues to be an increasing global threat that limits treatment options for cases of pneumonia and ear infections.

Resistant genes become replicated quickly during the process of cell division. When a patient is taking antibiotic treatments and if a resistant gene is identified, that gene gets propagated throughout the host's body and to other cells during the DNA replication process. The resistant gene becomes amplified and extends the problem to other host cells and other locations within the patient's body. Bacteriophages, plasmids, naked DNA or transposons could transfer the resistant genes to other bacteria. If these portals are absent, then sequential chromosomal mutations are responsible for the emergence of resistant bacteria, as in the case of penicillin and tetracycline that are resistant to *Neisseria gonorrhoeae*.

All of the above statistics, observations, and trends in increasing treatment failures indicate that there is miscommunication among the discussion and use of antibiotics. Those indications also highlight the need to supplement current research on bacterial metabolism and

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5 Ibid., 124.
6 Ibid., 123.
its effects to facilitate the problem of resistant bacteria. Although Levy and colleagues are in support of the ecological and biological basis for the cause of resistance, it is also important to look at the social factors that influence bacteria alterations that result in antibiotic resistant bacteria.\(^7\) Such social factors include patient habits, provider prescribing patterns, likelihood to follow guidelines for prescribing antibiotics, and communication skills.

During the 1940s and earlier, the search for any therapy to combat the prevalence of tuberculosis (TB) was underway. The increase in war injuries that developed into infections, such as gas gangrene, propelled the mission to discover new treatment options. The bacterium, *Mycobacterium tuberculosis*, is responsible for the cause of tuberculosis. There are different types of TB: blood-borne (miliary) disease, exudative pulmonary TB, long-standing fibrotic TB, and meningitis TB. Tuberculosis infections can happen in two ways: by drinking and eating food that are products of infected animals or by inhaling particles that carry the bacteria. During this time, sixty percent of TB sufferers would die if gone untreated after five years since onset. The use of sanatoria to provide continuous bed rest and exposure to maximum fresh air were suggested treatments during this time. However, these measures were proved ineffective. Therefore, at the time, tuberculosis was viewed as a death sentence and considered to be the greatest killer in history.\(^8\)

Pneumococcus is the bacterium that causes pneumonia. The bacteria survived because our white blood cells (WBC) could not destroy the outer capsule composed of a polysaccharide. This capsule is a protective wall made of complicated sugar molecules. The capsule that

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surrounds the germ is similar to the structure of cellulose and is impervious to phagocytic cells.\(^9\) Phagocytic cells are known as maintenance cells that engulf bacteria to help fight infections. The discovery of the Cranberry Bog Bacillus bacteria destroyed the pneumococcal capsule. The experiment that discussed the effects of the Cranberry Bog Bacillus bacteria will be elaborated later on in this chapter.

A scientist, Gerhard Domagk, continued the process of formulating treatments for infections by testing synthesized compounds to observe the effects those compounds would have on infection-causing bacteria. He experimented during the 1940s in Germany. After entering a term of medical school, Gerhard Domagk joined the army in 1914. At the age of 18 years old, he and his friends volunteered to join Germany’s march, hoping for a glorious war and as a unit specializing in the use of the grenade. Domagk moved to Berlin after becoming injured during a battle to recuperate. Due to his injuries, he was unable to reenter the war, so he was recruited to provide first-aid services in a field hospital in the Ukraine.\(^10\) Gerhard Domagk utilized his volunteered experiences acquired during the time in the army and dedicated his life to finding a cure for infections that afflicted soldiers during wartime. He used a compound that had the appearance of a red dye which had a new chemical side group called the sulphanamide group. An experiment with mice that involved different groups exposed to none or varying amounts of this chemical showed that the mice given the red dye containing the sulphoanimide group all remained alive. The identification of this compound with characteristics of a red dye was a crystalline chemical labeled KI-730.\(^11\)

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The red dye experiment also reconfirmed the advantages of using dyes as a laboratory technique. When the experimenter examined the cells of microorganisms dyed with sulphonamide chemicals, only some became stained, and others did not. Although the importance of using dyes as a staining technique was widely known in the 19th century and was first utilized by Dutch biologist, Pieter Harting, in the 1840s, the experiments conducted by Domagk also concluded that some cell membranes have specific affinities. This finding could then be generalized to investigate cell membrane affinity to specific antibiotics.

The level of effectiveness a medicine has is not the only dilemma encountered when formulating antibiotics. Scientists also have to take into account the mode of administration and the solubility index of a drug. The mode of administration is the route—orally or by injection—by which a drug is administer. The solubility index of a particular compound indicates its ability to dissolve properly. For example, Prontosil is one of many chemotherapies (chemical therapies) to treat infections caused by bacteria but eventually either developed resistance or did not have an effective mode of administration. Rubrum-KI-730, also known as Prontosil, is a crystalline red dye that targets gram-positive bacteria. These are a particular type of bacteria that are often resistant and cause abdominal infections. These bacteria became resistant to Prontosil. However, Prontosil was effective to treat pneumococcus and streptococcus that caused infections, but not for other type of infections. The solubility properties of Prontosil determined that the route of administration is oral, not via injection. This discovery was a significant disadvantage for very sick patients because they were unable to take the medication by mouth. Prontosil was categorized as an oral therapy and therefore was not advantageous for treating very ill patients. This predicament is yet another indication of the difficulties involved in formulating new drugs, ones that are efficacious and have an efficient route of administration at the same time.
Testing drug interactions on human beings to learn their effectiveness is unethical. Therefore, animal testing is mostly done. However, the problem with animal testing is that if there is a significant finding of the experiment on animals, the results may not be broad enough to generalize to human subjects. In 1938, Johns Hopkins School of Medicine conducted an experiment involving fifty-nine guinea pigs as subjects. They were all injected with a virulent strain of human tuberculosis. The experimenter divided the subjects into four groups: a control group, a low-dose group, a high-dose group, and a highest-dose group. Thirty-one of the fifty-nine guinea pigs were treated with sulphanilamide. Researchers treated the low-dose group with a small dose of sulphanilamide. However, there was no change in the severity of the infection. The subject’s disease remained the same as the control group. Treatment for the high-dose group involved higher doses of the same drug sulphanilamide that showed less proliferation of the disease. Finally, the highest-dose group was treated with the maximum dose of sulphanilamide. In this group, there was an extreme reduction in the appearances of abscesses, and any other symptomatic presentation of the infection and a decreased spread of bacteria to the internal organs. The untreated or control group was still teeming with TB bacteria. The conclusion of the study was that sulphanilamide could stop the proliferation of TB but would not be useful to cure the infected subjects.\(^{12}\) As a result, the findings extrapolated from this study could not be generalized to human subjects. This is another synopsis of the difficulties in formulating effective antibiotic treatments to combat bacterial infections.

Another experiment conducted in the attempt to discover a treatment for bacterial infections involved “The Effects of Salicylate on the oxygen uptake of the tubercle bacillus.”\(^{13}\) These attempts could sometimes have promising effects and sometimes not. Nevertheless, any

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\(^{13}\) Ibid., 144.
experimental studies and their findings are important because information obtained from such studies will develop ideas to improve future research, thereby increasing the likelihood to formulate an effective treatment. In this experiment, 1mg of salicylic acid (aspirin) was added to a TB bacteria culture. After adding the acid, the observation was that the oxygen uptake is stimulated approximately 100% in its entirety.\textsuperscript{14} This finding illuminated specificity among bacteria and infections. By knowing the effects of salicylic acid on TB bacteria led to the discovery that specific bacteria are responsible for specific infections. The next step was to find any component in aspirin that would inhibit the bacteria. Scientist conducted an experiment that accomplished this next step.

Since finding a component in aspirin that functioned as an inhibitor to particular bacteria was pertinent, the following test was carried out. In the experiment, a substance (enzyme) that destroys the growth-inhibiting property of penicillin was found in the bacteria extract. In preparation for the experiment, scientists incubated a solution of 1 mg of penicillin and 0.8 c.c. water along with 0.2 c.c. of dialyzed and centrifuged bacteria extract. The incubation period for this solution lasted three hours at 37 degrees Celsius in ether. While keeping the concentrations, temperature, and time constant a control solution of penicillin was also prepared without the enzyme extracts. After the preparation, a quantitative analysis testing was conducted. Experimenters tested the growth-inhibiting activity of the penicillin solutions on agar plates against \textit{Staphylococcus aureus}. The findings were reported as follows: the incubated-penicillin solutions lost their growth-inhibiting activity compared to the control solution, which retained its growth-inhibiting ability. The research concluded that a particular enzyme was responsible for

\textsuperscript{14} Frank, R., \textit{The Forgotten Plague}, 144.
the loss of growth-inhibiting activity of penicillin.\textsuperscript{15} Further experiments supported the conclusion that heat, an acidic pH of 6, and non-solubility destroyed the substance. Since \textit{Micrococcus lysodeikticus} contained that particular enzyme, the presence or absence of the enzyme in a bacterium is not the only factor that determines its responsiveness to penicillin. This organism is responsive to the growth-inhibiting activity of penicillin but less so than \textit{Staphylococcus aureus}. This experiment provided evidence that supports the claim that antibiotic-resistant bacteria do exist. Also, the findings supply a reason why there might be resistance in bacteria. In other words, there has to be a component within the bacterium’s metabolism that contributes to the loss of growth-inhibiting activity.

Since specificity is a fundamental component to understanding the mechanism underlying bacteria that cause infections, the discovery of any chemical that inhibits their function will be promising findings. In 1941, Frederick Bernheim reported that the chemical derived from benzoic acid called 2,3,5 tri-iodobenzoate caused the inhibition of oxygen uptake by the germ. This compound was added to both of the bacterial cultures in the above mentioned experiment and that chemical inhibited the growth of the bacteria.\textsuperscript{16} If the tri-iodobenzoate-suppressed bacteria were transferred to a new culture medium, they multiplied; therefore, the chemical did not kill them. The tri-iodobenzoate treatment only prevented them from reproducing. This experiment uncovered the process of competitive inhibition. It is the phenomenon whereby molecules compete for a binding site that propels a particular response. A binding site is an area located in a cell where an enzyme can attach itself to the compound associated with that area.


\textsuperscript{16} Frank, R., \textit{The Forgotten Plague}, 146.
Binding sites are unique to the structures of the enzymes or compounds that bind to the site.\textsuperscript{17} This process is explained further on page 13 using the example of para-amino salicylic acid (PAS) by altering its chemical group to create an inhibitory molecule that obstructs the bacteria function. Although this experiment did not yield a valid treatment option, the findings revealed the mechanism by which the bacteria function. These results are useful for future experiments and to conceivably produce an active drug.

Physician’s prescribing patterns and patient’s usage is discussed further in chapter 3. Unlike \textit{Streptococcus pneumoniae}, \textit{staphylococcus} is a type of bacterium resistant to Prontosil. In time, \textit{Staphylococcus} would become resistant to penicillin too. In the attempt to further investigate this observation, a single type of microbe was prepared to grow in soil and was fed staphylococcus bacteria to survive. In other words, an isolated bacterium was nourished with the \textit{staphylococcus} bacteria creating an environment for the isolated microbe to develop adaptive properties and eventually producing medicinal effects. As a result of this manipulation, a new microbe—\textit{Bacillus brevis}—was created. When \textit{Bacillus brevis} was added to a suspension of \textit{staphylococci}, \textit{pneumococci}, and \textit{streptococcus}, the bacteria in the suspension were all killed and disappeared.\textsuperscript{18} This finding illustrated that antibiotics are derived from chemicals in the environment and soil microbes are the creators of those antibiotics. The underlying message is that intervention practices, such as prescribing patterns, utilizing antibiotics derived from soil microbes will impact the abundance of those bacteria. Increased use of antibiotics made with a particular microbe will eventually deplete the abundance of those existing microbes. Mis-using microbe-derived antibiotics could lead to those antibiotics becoming resistant.

\textsuperscript{17} “Biology online” Last modified June 3, 2015. 
\texttt{http://www.biology-online.org/dictionary/Binding_Site}

\textsuperscript{18} Frank, R., \textit{The Forgotten Plague}, 153.
The study also illustrated that TB germs survived in sterile soil but died in contaminated (with other microbes and fungi) soil indicating that microbes compete against and kill each other. There are many microbes and organisms in the ground that have antibacterial properties. From what [experimenters] knew about [antibiotics such as] sulphonamides, penicillin, and gramicidin, it was clear that [an unusually] large group of disease-causing bacteria were resistant to all of these recently-discovered drugs. As a result, antibiotics should be used judiciously.

The experiments summarized thus far have been done to show that antibiotics are derived from various bacteria themselves. This fact was apparent in an experimental technique called the “plate method” used to detect the presence of a microbe capable of killing gram-negative bacteria. To conduct the experiment, the researcher took a soil sample and diluted it with tap water and a small quantity was evenly dispersed on a culture plate. Another layer of agar, a gel-like substance found in a petri dish, consisting of a disease-causing germ was poured over the soil sample on the culture plate. This mixture was then incubated at body temperature overnight. Normally, the disease-causing germ would proliferate in the agar appearing as patches of cloudiness. The presence of a single or more microbes within the soil sample and water mixture appeared as a clear circle in the cloudiness. This appearance indicated that disease-causing bacteria had been destroyed. The soil sample began to create medicinal effects concluding that microbial cells formulate antibiotics.

The search for new interventions was a continuous process that does not always produce effective therapeutics. According to Ryan, the two microorganisms that were discovered, which had medicinal effects, are from the bacteria Pseudomonas aeruginosa and the actinomyces groups. Another antibacterial drug called actinomycin was too poisonous because it killed mice

20 Ibid., 179.
within twenty-four to forty-eight hours.\textsuperscript{21} Actinomycin was not used to treat human infections but years later was proven to be an ideal drug to suppress the rejection of organ transplantations.

In 1943, Albert Schatz, under Dr. Selman Wakman’s supervision, discovered new microbes called \textit{Streptomyces lavendulae}. After further testing, a new anti-bacterial drug was formulated from these microbes called streptothricin.\textsuperscript{22} This medication was more effective than actinomycin because streptothricin is soluble in water, unlike actinomycin. Streptothricin killed both gram-positive and gram-negative bacteria. An unrelated finding was observed with the bacterium called \textit{Brucellus abortus} which was responsible for abrupt and contagious abortions in cattle. There was no treatment at the time, so scientist Jones D. Metzger agreed to test streptothricin on the infected cattle. In 1945, he discovered that the treatment was effective and cured the animals. This discovery is an indication that continuous efforts and trials are needed to obtain an effective treatment. The treatment may not be the one scientist are seeking but may shed light on other medical problems.

The more prominent the need for newer antimicrobials became, the more time scientists at the Merck pharmaceutical industry spent brainstorming innovative techniques to test streptothricin in blood and body tissues. As the desire to invent new therapeutics increased, the methods to obtain new antibiotics improved as well. In 1943, the first chemical trials using streptothricin were conducted in humans.\textsuperscript{23} However, the administration of this new therapeutic intervention was instantly terminated due to delayed toxicity. The side effects were apparent when mice died due to poisonous effects to the kidneys. Demonstrated by the experiments mentioned earlier, it is clear that the search for antibacterial chemotherapy is gradually becoming

\begin{itemize}
\item \textsuperscript{21} Frank, R., \textit{The Forgotten Plague}, 180.
\item \textsuperscript{22} Ibid., 182.
\item \textsuperscript{23} Ibid., 183.
\end{itemize}
mainstream especially as techniques and methods are improving. Also, the practices during the investigative processes to develop new chemotherapies can add to the problem of developing antibiotic resistance. In fact, if not monitored continuously, resistance can develop due to depleting bacteria or the inability to discovering new ones with time.

The following discovery will prove promising but then showed tremendous negative side effects that rendered the medicine ineffective or unsafe to administer to sick patients. This uncertainty is a frustrating reality within the scientific world. When a new sulphonamide called sulphapyridine was produced the formulation resulted in another antibacterial intervention called Promin. In 1932, Gerhard Domagk was supervised by Heinrich Horlein to create a new antibiotic by manipulating sulphonamide molecules. Promin was shown to be more of a promising treatment than sulphapyridine.24

The experiment described below was conducted to investigate Promin’s effectiveness. In this experiment, the participants were thirty-six people suffering from pulmonary TB and were treated with Promin. Out of the thirty-six pulmonary TB suffers, eight showed improvements but still had symptoms after treatment and six showed “beneficial effects” that resulted in a cure. Promin was one of the first drug to show positive results toward treating TB.25 However, it was discovered that the drug had several side effects, including “haemolytic anaemia” or the rupture of red blood cells. Scientists, Corwin H. Hindshow, and William H. Feldman formulated another version of the drug called Promizole. This drug appeared to be promising because it was shown to cause fewer side effects when compared with Promin.

The next cases reported that the prevalence of antibiotic-resistant bacteria is a perpetuating medical dilemma that is becoming predominantly more frequent in the practice of

25 Ibid., 228.
infectious medicine. Waksman postulated that there was something in the soil that killed the germs that caused TB. In 1915, an experiment conducted by Waksman proved that this was true.\textsuperscript{26} The test that screens for any antimicrobial interventions is called the “streak-test.” If the cross-streaks, a pattern in which bacteria grow, of bacteria did not proliferate when they came next to the \textit{Actinomyces} growth culture, then the antibiotic-producing microbe is effective and is considered a useful finding. However, many confounding factors could explain the activity of growth vs. no growth of the bacteria: pH, nutrient, or whether or not they have antibiotic effects.\textsuperscript{27} Therefore, the experiment is manipulated further as described below.

The experimental procedures continued if there was no growth of bacteria near the actinomyces streak. The experimenter examined the sample further. If there were a larger quantity of bacterial growth in the living medium, then the sample would be tested with the modified plate test, which is another method to eliminate any contaminations. The scientist would inoculate the agar with disease-causing germs and pour that mixture onto the surface of the agar plate. Once the agar hardens, the actinomyces sample was inserted in the center of the agar plate. This sample was then incubated overnight. The results of growth versus no growth were measured by a technique called the zone of inhibition. The zone of inhibition is the area on the agar plate where there was no growth of TB bacteria. If the zone of inhibition had a measurement of 15-10 mm, that means \textit{actinomyces} bacteria were present and were effective against TB germs. This discovery encouraged further testing. There were two findings as a result of those replications. The first finding was that there were colonies of \textit{Actinomyces} known as \textit{Actinomyces griseus}.\textsuperscript{28} The second finding indicated that the Staphylococcus sample grew

\textsuperscript{26} Frank, R., \textit{The Forgotten Plague}, 214
\textsuperscript{27} Ibid., 216.
\textsuperscript{28} Frank, R., \textit{The Forgotten Plague}, 218.
cloudy and covered the entire medium. If the Actinomyces were working, the effect then should be a clear area around the Actinomyces agar plate.\textsuperscript{29} The conclusion is that there are various confounding variables to consider when conducting experiments. These can serve as variables that hinder the existing therapeutic effects of antibiotics.

Another experiment conducted using egg embryos revealed the effectiveness of the antibiotic called streptomycin against TB germs. Scientists injected a bacteria called Salmonella garllinarum into egg embryos and treated half of the batch with streptomycin. The ones treated with streptomycin survived whereas all of the egg embryos that were untreated died. The antibiotic streptomycin cured them.\textsuperscript{30} There were no bacteria in their blood or internal organs. To understand other effective properties of streptomycin, the researchers continued with the experiment. The mixtures were added to agar slants in various dilutions to conduct the experiment that proved the effectiveness of streptomycin against TB. The results indicate the “…meticulous adherence to effective drug combination—provided they were dealing with new patients, whose germs were not as yet resistant to any of the drugs—were able to cure every patient.”\textsuperscript{31} Thus far, we’ve seen continuous efforts to conduct experiments in anticipation of finding new and effective antibiotics. Streptomycin would be one of the first effective drugs that would be beneficial in treating TB but eventually develops cases of resistance over time.

Other experiments that attempted to test different methods to cure TB are also discussed. In 1956, Wallace Fox conducted an experiment called “The Madras Experiment” to test the drug’s ability to cure TB without using sanatoria. A Tuberculosis Chemotherapy Centre found in Madras, India, conducted “The Madras Experiment,” which consisted of two groups: a

\textsuperscript{29} Frank, R., The Forgotten Plague, 217.
\textsuperscript{30} Ibid., 220-221.
\textsuperscript{31} Ibid., 380.
treatment-at-home group and a treatment-in-a-sanatorium group. Both groups were given the
drugs in combination, PAS and Isoniazid, for one year. A follow-up was done after five years to
determine whether the patients were cured. The findings were as follows: 90% of patients treated
in their homes were cleared of the disease, 89% of patients treated in the sanatoriums were also
cured.\textsuperscript{32} Therefore, the location does not seem to make a difference in the successful treatment
and cure of the disease. The effects of PAS were studied further to understand these results.

Replicated experiments were conducted using PAS since it appeared to be an effective
drug. The administration of PAS and its effects on pulmonary TB was studied. The signs
indicating that the infection was spreading to patients’ intestines were examined. Twenty-two
patients with pulmonary TB and its spread to their intestines were given PAS. In nineteen out of
twenty-two patients, the symptoms of TB that spread to their intestines dissipated. The remaining
three cases showed improvements. The TB germs were also showing signs of resistance to PAS.
When streptomycin and PAS were administered in combination, streptomycin resistance proved
less likely. This type of treatment is called combination therapy.\textsuperscript{33} Although streptomycin was an
effective treatment the first time around, resistant germs were apparent in the sputum or saliva in
which TB germs could inhabit. In 1943, Waksman would discover the true potential of
streptomycin. Even if there was no allergic (adverse) reaction, the drug was not going to work
the second course of treatment. The problem was likely due to faulty duration and dosage
measurements. “If streptomycin was continued for four months, a staggering ninety percent of
patients were coughing up germs that were now resistant to streptomycin.”\textsuperscript{34} The limitations of
streptomycin had to be clearly understood. During the 1940s, the increasing cases of TB

\textsuperscript{32} Frank, R., \textit{The Forgotten Plague}, 383.
\textsuperscript{33} Ibid., 329-331.
\textsuperscript{34} Frank, R., \textit{The Forgotten Plague}, 326.
infections and the vast demand for an effective chemical intervention led physicians to administer these drugs without proper approvals. The urgency to treat and doing so without standardized dosage led to the development of streptomycin-resistant bacteria.

Another experiment to prove PAS was effective involves adding the medicine to a culture of TB germs. By adding aspirin to that TB culture increased the reuptake of oxygen. Since aspirin has an effect on the way oxygen is consumed by bacteria, altering the structural properties of aspirin will contribute to the inhibitory effect on bacteria. To change the chemical makeup of aspirin slightly requires adding a small chemical subgroup. To test the reuptake properties of the altered aspirin, add it to the TB culture medium. Tuberculosis germs consume this new compound as did before, but the molecule that altered the aspirin would block the germs respiration causing the bacteria to die. This process is known as competitive inhibition.35

While testing PAS against a culture of BCG bacteria, which are “live attenuated tuberculosis germ used in vaccination,” the results demonstrate that the drug blocked any bacterial growth. Animals such as rabbits and guinea pigs that were infected with TB were subjects for this experiment. The results indicated that there was no toxicity in rabbits that were listed. Other animals such as rats, mice, and guinea pigs were given the drug for several weeks. The guinea pigs were the ones who became ill, but if milk was added to the animals’ diet, they then became free of the TB symptoms.36 This case seems to illuminate positive effects of PAS when treating TB.

Another instance that further solidifies the positive effectiveness found in the advent of PAS involved females with a family history of TB, who had given birth. The prevalence of empyema TB was apparent among this population. This infection is a type of TB that affects the

35 Frank, R., *The Forgotten Plague*, 243-244.
36 Ibid., 246-247.
delicate membranes and fluids that surround the lungs. When PAS was injected into the chest wall of these patients, their chests became clear, more spacious, and the TB pus became smaller.

In this study, 2440 females who had given birth and had a family history of TB presented difficulties with breastfeeding. The symptoms included vomiting and a cough that produced muco-purulent phlegm. In addition, they presented weight loss but had no sweats or fever. When doctors x-rayed them at the onset of these symptoms, there were no apparent signs of TB in their lungs. As time progressed, a second x-ray showed cloudiness in both lung fields. A sample of the patient’s sputum showed TB germs present. The infection was so mild, signs of TB were not apparent on the first x-ray when compared to the subsequent ones. By the time the TB germs proliferated, it was overwhelming to the patient’s lungs, exposing them to serious infections. These cases emphasized the importance of standardized medical testing and acknowledged the influence of family history. Although these practices are well advanced in our current approach to administering efficient medical care, in some areas the meticulousness of providing care is lacking. For example, the inappropriate administration of antibiotics when treating bacterial versus viral infections is apparent in clinical settings.

Antibiotic doses continue to rise annually.\textsuperscript{37} The etiology of infectious disease should be confirmed to determine if it is viral or bacterial in nature. Effective administration is dependent on standardization of dosage and etiology of infection. An experiment below discussed the importance of these two factors by testing PAS treatments.

A patient was given PAS as an oral treatment. The treatment lasted two days: on the first day, 6g of PAS and the second day, 9g of PAS were administered. The dosage fluctuated if the aforementioned dosages were ineffective. Fluctuation in dosage could be another way bacteria

develop resistance. After the second day, the patient was observed without any treatment. Symptomologies such as fever decreased but after four days, these symptoms reverted to its abnormal state. Para-amino salicylic acid treatment was reintroduced with larger doses and for a longer duration of five consecutive days. The patient’s signs and symptoms of the illness decreased and disappeared during the last set of treatment. Her physical strength improved, but she reported feeling nauseous, and the researchers then realized those were the side effects of the drug. Her inflammation index (severity of flare-ups) was approaching normality, but TB germs were still traceable in her sputum suggesting that she might be a carrier. Over the next two months, the patient received more treatment of PAS and eventually there was no trace in her sputum. The patient continued to revert to lengthy courses of PAS treatment following a complete recovery.  

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Streptomycin would become an effective drug, but the TB bacteria developed resistance to the antibiotic after a certain amount of time has passed. In 1944, Dr. Waksman continued his experiments on the effects of streptomycin on TB. Fifty-five patients treated with streptomycin presented with acute pulmonary TB. Fifty-two patients treated with sanatoria care alone presented with similar degrees of pulmonary TB. The patients treated with streptomycin: showed that most of the TB in their chest x-rays disappeared. The patients with standard sanatoria care indicated that 8% had improvements. Within six months, fourteen patients treated with only the sanatoria regime were dead, and four patients treated with streptomycin were dead. Five years later, those patients who survived were reexamined. Out of fifty-two patients treated with conventional sanatoria treatments, thirty-five were dead. Out of fifty-five patients treated with

39 Ibid., 327.
streptomycin, thirty-two were dead.\textsuperscript{40} The conclusion drawn from this study is that few people used streptomycin, but it had reduced the severity of the infection temporarily. The germs developing resistance to streptomycin caused the deaths. Resistant bacteria only took eight weeks to develop and remained resistant once they had achieved that status. In addition, they proliferated rapidly creating a new colony of bacteria that had new adaptations, now resistant to streptomycin.

Streptomycin showed promising medicinal effects but eventually became resistant. The case discussed below will also illuminate the importance of letting the body's defenses heal itself. However, if the dosage and timing to administer is standardized, the medicine could become effective on a long-term base without the development of resistance. During the same time of the experiment above, a case of a 14-year-old Irish American female was admitted to the hospital with convulsions and a high fever, and she was given anesthetic drugs to suppress her convulsions. She presented with abnormalities such as difficulty breathing and pain on the left side of her chest indicating TB, which became progressively worse. She had a lumbar puncture to obtain a sample of cerebral spinal fluid (CSF) to be tested. The results stated that TB bacteria were present, and she was diagnosed with TB meningitis. Doctors treated the patient with streptomycin via intramuscular injections. The drug was administered every two hours and once daily directly into her brain via a hole in her skull.\textsuperscript{41} The patient recovered as a result of the treatment. She was then discharged from the sanatorium after a year and went on to live a normal and active life. At the end of the treatment course, her sputum still had TB germs present. Streptomycin had decreased the severity of the infection to allow her own body’s immunity defense to take over.

\textsuperscript{40} Frank, R., \textit{The Forgotten Plague}, 327.
\textsuperscript{41} Ibid., 239.
At the beginning of the century, scientists such as Gerhard Domagk, Selman Waksman, and Albert Schatz were chasing a cure for TB and pneumonia. In the process of formulating an effective chemotherapy free of toxicity and limited side effects to treat bacterial infections; a new battle of antibiotic resistance arises. There are numerous limitations but the work done thus far can only propel the ongoing research to discover new antibiotics. The next chapter discusses the unintended consequences of new technology; that is the development of resistant bacteria while using antibiotics to treat infections.
Inappropriate dispensing and use of antibiotics has led to the unintended consequence of antibiotic-resistant bacteria. We live in a world populated by a variety of living things, and bacteria are ubiquitous. When a bacterial infection arises, prophylaxes are sometimes prescribed using trial and error methods that may or may not produce desirable outcomes. There are countless ways a person can acquire a bacterial infection: developing a nosocomial infection during a hospital stay; being placed on extracorporeal membrane oxygenation (ECMO), i.e. life support; becoming infected after having any surgery; using unsanitary water and food; or by bacteria that infect the gastrointestinal tracts of humans.

A documentary, ‘Frontline-Hunting the Nightmare Bacteria,’ depicts circumstances that involve antibiotic-resistant bacteria. This documentary features three disconnected stories about cases of bacterial infections that continued to spread and in some cases became fatal. The first medical case is a female in Arizona exposed to community-based Methicillin-resistant \textit{Staphylococcus aureus} (MRSA) from a playground where she fell and bruised her knee. Her family took her to the hospital weeks later when she became ill with stomach pains. She was given antibiotics after her vital signs were becoming irregular indicating an infection. Physicians admitted her to the ICU after being diagnosed with pneumonia. The second case involved an adult male who traveled to Calcutta, India, to perform charity work. As he was walking one day to the site where he did his charity work, a train hit him. He became infected after having had surgery in India. The final case reported in the documentary occurred in New York City. The

\footnote{Hunting the Nightmare Bacteria.” pbs.org. Last modified October 22, 2013. \url{http://www.pbs.org/wgbh/pages/frontline/hunting-the-nightmare-bacteria/}}
point is that bacterial infections have no boundaries. There is no specific period, socioeconomic status (SES), educational level, or geographic locations that prevent the development of antibiotic-resistant microorganisms.

In the current discussion of harmful bacteria that develop resistance involves three different types of bacteria: *stenotrophomonas*, which is a gram-negative bacteria; NDM-1, which is an enzyme-like substance that is produced by an organism, but behaves like a bacteria; and *Klebsiella pneumoniae carbapenemase* (KPC), which resides in the gastrointestinal tracts of humans. The claim is that resistant bacteria develop over time. This progression from effective therapeutic index to complete resistance involves various contributing factors. A focus on two of those contributing factors is physician prescribing patterns and patient usage habits. These factors will be discussed further in chapter 3.

A current example, discussed in detail and will further solidify the claim above, is a bacterium called Methicillin-resistant *Staphylococcus aureus* (MRSA), which is currently resistant to an entire class of antibiotics. The spread of antibiotic-resistant bacteria is an urgent matter that could create a pandemic if it were to get out of control. It can wreak havoc on our nation’s public health. The reason antibiotics become ineffective and create resistant bacteria is that they are misused and overprescribed. Chapter 3 discusses these reasons with a public health perspective. Additionally, inappropriate use of antibiotics can lead to the reconfiguration of our individual microbiome. Also, the foods consumed could epigenetically change our level of susceptibility to antibiotics. If patients do not follow the instructions on how to take antibiotics precisely, the levels fluctuate, which in turn results in ineffective treatment for any bacterial infections. Alexander Fleming, the scientist who discovered penicillin, “warned as early as 1945
that, freely taken, an oral form of the drug could breed resistant strains that could then infect other people, especially if patients stopped treatment before all bacteria were destroyed.\textsuperscript{43} 

Some of the current topics on the cause of the unanticipated consequences of antibiotic involve patients’ and physicians’ behavior toward antibiotic use. These discussions promoted the awareness and severity of the problem of antibiotic resistance in addition to brainstorming ways to remedy the issue. Changes in physicians’ attitudes toward giving instructions to patients are evolving, placing an emphasis on the need to complete antibiotic treatments. Nevertheless, cases of resistant bacteria are still prevalent in high rates. It is imperative to complete the course of antibiotic treatments prescribed by doctors even if the patient’s symptoms have subsided. The consequence of not completely following the instructions is that some of the bacteria may still be alive and continue to multiply. As a result, bacteria with more adaptive mechanisms that become resistant to antibiotics are created. Suggestions to improve instructions and better monitoring are given in chapter 4.

The misuse of antibiotic treatments allow bacteria to adapt to the way those treatments work and develop barriers to circumvent their effects. Antibiotics become “wasting assets”\textsuperscript{44} because we diminish their usefulness slightly each time we use them.\textsuperscript{45} The bacteria build appropriate defenses to prevent their eradication, and this is how antibiotics become ineffective, and bacteria become resistant. Bacteria that build defenses contribute to the development of antibiotic resistance. They do so by building a capsule or a wall, preventing antibiotics from entering and targeting the bacteria itself. Refer to the illustration depicted in figure 1 one page

\textsuperscript{44} Ibid., 59.
\textsuperscript{45} Ibid.
The bacteria create “plasmids—minute, self-replicating pieces of DNA outside the chromosome—adding valuable capabilities to their hosts.” As a result, the bacterial infection can become pan-drug resistant (PDR), leading to antibiotic resistance. Finally, misusing antibiotics by taking them when they are not needed, will also promote antibiotic resistance, as in the case of MRSA.

Methicillin-resistant *Staphylococcus aureus* has become resistant to various antibiotics and is difficult to treat. Carbapenems are known as a broad-spectrum antibiotic, which treats both gram-positive and gram-negative organisms.

Until recently, carbapenems, such as imipenem, were almost uniformly active against resistant gram-negative organisms, but some strains have now developed very effective ways to deal with the carbapenems, including the production of β-lactamases (designated carbapenemases) that demolish the carbapenems; changes in outer-membrane porins that block the entry of these antibiotics; and active pumping of the antibiotic out of the cell using complex “efflux pumps.” The situation is further complicated by the fact that the “permeability” barrier and efflux mechanisms also affect other classes of antibiotics (e.g., quinolones, aminoglycosides, and tigecycline).

Methicillin-resistant *Staphylococcus aureus* is now resistant to this class of antibiotics. Among different side effects of antibiotics, one that is crucial to discuss is the fact that antibacterial can kill off the body’s natural defense bacteria, resulting in the growth of harmful bacteria.

Similarly to our fingerprint, which uniquely identifies individuals, humans have microorganisms that uniquely identify them as well. These organisms are part of a system called

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our microbiome. Bacteria live on our entire body, covering our epidermis and the walls of our intestines. Humans need these bacteria because “microorganisms often produce metabolic by-products, such as organic acids and alcohols that have an antibiotic effect, inhibiting the growth of other organisms.”\footnote{Rhodes, Rosamond, Nada Gligorov, and Abraham Paul Schwab, eds, \textit{The Human Microbiome. Ethical, Legal and Social Concerns}. New York: Oxford University Press, 2013.} This “symbiotic relationship” enables us to fight off minor bacterial infections on our own.\footnote{Ibid., 19.} Knowledge of this relationship is essential because it can address one of the factors—over-prescribing—that contributes to antibiotic-resistant bacteria. The continuous use of antibiotics can decrease the normal flora of bacteria, thereby obstructing the body’s natural defenses causing antibiotic-resistant bacteria to develop.
Figure 1: A Display on How Mutations Happen.\textsuperscript{51}

The harmful effects on our health by overusing antibiotics highlight that “antibiotic resistance is now a linked global problem” attributed to rising social and physical epidemics, such as obesity, asthma, diabetes, and cancers.\textsuperscript{52} According to Tenner, antibiotics took a problem of acute illnesses and turned it into one of chronic attention.\textsuperscript{53} One of the prominent reasons that bacteria develop resistance to antibiotic treatments is the way antibiotics are used. The overuse of antibiotics has harmful effects on our health. According to Blaser, there is a connection to current medical cases and antibiotic use. He also concluded that there is an association between the rise of social and physical epidemics and the use of antibiotics.\textsuperscript{54} The author discussed the symbiotic relationship human cells and bacteria once had, but discovers that bacteria are being damaged by what is supposed to be a major advancement in medicine—antibiotics—facilitating the extinctions of irreplaceable bacteria resulting in serious health consequences. The author also examines the measures that can be taken to prevent future health problems due to the cause of antibiotics. These occurrences describe the need to develop measures indispensable to avoid future health concerns due to drug-resistant antibiotics.

Humans and the environment interact on a daily basis. The foods we eat can impact the way we develop. Most humans are omnivores who consume both plant and animal products. Animals and plants are treated with antibiotics to enhance production; however, “the use of antibiotics in animals has raised controversies, particularly [relevant] to their use as feed


additives to promote the growth of livestock." Regular doses of antibiotics are used to treat a majority of the swine, poultry, cattle, and even fish farms in the United States. This medicine becomes a part of the animal’s genetic material. Animals with antibiotic-resistant bacteria then transfer those resistant genes to humans when they consume those modified products. As a result, “in the 1980s, the proportion of drug-resistant salmonella bacteria doubled from 16 to 32 percent.” This increase has raised concerns of developing bacterial infections and the compulsion to monitor antibiotics because “without prompt action, ‘the post-antimicrobial era may be rapidly approaching in which infectious disease wards housing untreatable conditions will be seen.’”

Since it is critical to complete the course of treatment, “the actions of every physician and every patient help determine the length of a medication’s useful life.” Antibiotics are given to treat bacterial infections, but if the treatment is interrupted and continued in a fragmented order, the bacteria will have time to develop a way to adapt to that antibiotic treatment. Antibiotics are grouped based on the way they work. They are unique to the type of bacteria or parasites that they are meant to treat. There are approximately nine main types of antibiotics that may be prescribed by a primary care physician, but there are others prescribed for rare infections, such as tuberculosis. Antibacterial has a bacteriostatic or a bactericidal effect on bacteria. They will either prevent the bacterial cells from dividing or kill them, respectively.

55 Soulsby, E.J., “Resistance to antimicrobials in humans and animals: Overusing antibiotics is not the only cause and reducing use is not the only solution,” British Medical Journal 331 (7527) (2005): 1219-20.
57 Ibid., 60.
58 Ibid.
59 Ibid., 59.
There are different ways antibiotics can function: by inhibiting synthesis of the cell wall to hinder cell division, intersect protein synthesis that is vital for bacterial growth or disrupt membrane potential that results in a lack of protein, DNA, and RNA production. Methicillin-resistant *Staphylococcus aureus* is especially a concern in hospital settings, prisons, and nursing homes where infected open wounds are abundant. As a result, there have been several preventative measures implemented to decrease the likelihood of spreading these bacteria. These preventative measures include sanitizing surfaces, hand-washing, proper disposal of hospitals materials, restricting antibiotic use, and community education.

In some cases, a person who becomes infected could develop resistance to all types of antibiotics. Doctors are sometimes out of options and thus, have to refer to older antibiotics, such as Clostrin. However, this antibiotic is extremely toxic, and treatments become truncated while having surgery to remove more of the bacteria becomes a solution for saving a patient’s life. For example, amputating a patient’s leg or other body parts to stop the bacteria from spreading is usually a final and drastic solution.

As in the case of Carbapenems, some advancements in medicine that should make patients feel better have counterintuitive effects. People utilize hospital services because they want to feel better, but hospitalized patients are at a higher risk of contracting a nosocomial or staph infection that may make them sicker. This occurrence is one of the many contradictions in modern medicine. At the time of hospital admissions, most patients’ immune systems are not functioning at their optimal levels, and thus, patients become easier targets for hospital-based bacterial infections.

As discussed in chapter one, when a person becomes infected, there is a probability that they will become resistant to all antibiotic treatments, which could lead to fatality. This
consequence is another troubling aspect or adverse effect of antibiotic-resistance known as the post-antibiotic crisis. Post-antibiotic crisis is when a patient is at the last stage of an infection, they are unable to respond to any antibiotic treatments, and thus the infection can fatally propagate throughout the body. The prognosis is not good for a patient at this stage of the infection, thus illuminating the reality that modern medicine is limited.

There are different types of infections: viral and bacterial. The etiology of bacterial infections is due to specific bacteria, and specific antibiotics are required to treat them. Also, viruses cause most infections, but viral infections will not respond to antibacterial treatments. However, most often the careful distinction between whether the etiology is viral or bacterial is not given enough attention, thus leading up to a disconnection between deciding the treatment type: antiviral or antibacterial. The Standard Operating Procedures (SOP) in hospital settings, especially in the emergency department, is to treat the presenting infection then confirm the source of it by laboratory tests. This is another example of how antibiotics are not used appropriately.

There are other indications that bacterial resistance is an emergent problem that needs attention. The findings in the following study conducted in different nursing homes explain the requisite for further investigation within this domain. Crinch et al. discussed a longitudinal study conducted from 2000 to 2004, which reported trends in antibiotic resistance. The participants in this study included residents in nursing homes. Researchers obtained data from them by handing

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out questionnaires. The study concluded that there is a demand for ongoing research on antibiotic use in these types of facilities.

Since microorganisms “exists in communities where they interact both with other microorganisms and with macroscopic organisms, such as plants and animals,” obtaining more knowledge of types of bacteria and the distinctions between them and viruses is essential for understanding when and how to prescribe antibiotic treatments. As the experiment described in chapter one also demonstrated, antibiotic resistant cases prevalent. The authors reported clear evidence why resistant bacteria developed. They suggest that there has to be a component within the bacterium that is part of its metabolism, which contribute to the loss of growth-inhibiting activity.

The connection between antibiotic consumption and the emergence of bacterial resistance is well documented. Another study highlights the problems of antibiotic-resistant bacteria even in remote areas of the world. An interesting observation is that even in areas of low antibiotic usage, there is still evidence of antibiotic resistance. What is the reason for this? The observation is worth examining further to understand the role cell mechanism, and structures play in this investigation of the emergence of antibiotic resistance. There were no significant differences between the antibiotic-exposed areas and those least exposed to antibiotics. The study involved a population sample of Angaiza inhabitants. As of 2002, the population count was 113 with 15 households. It is a remote community populated by humans known as Chayahuita

65 Ibid., 125.
Indians. These inhabitants are located in the Alto Amazonas Province of Peru. The living conditions are underdeveloped, no sanitation control and no electricity. Rainwater is a source of water. Activities are agriculture, hunting, and animal breeding, specifically poultry, pigs, and cows.

During the investigation, samples of urine and fecal matter were collected. Urine samples were added to two different agar plates: one with a *Staphylococcus aureus* sample labeled ATCC 29213 and the other inoculated with *Escherichia coli* labeled ATCC 25922. The agar plates were left overnight at 37 degree Celsius, and the samples were checked the next day for zones of growth inhibition. If bacterial growth was inhibited, then that means the urine sample have antibiotic activities.\(^{66}\) This study concludes that there is a presence of antibiotic-related activity within the participants’ systems.

There are no comparable studies to investigate further because the other studies were not in remote areas. Therefore, more research is needed, specifically in highly remote areas to explore this interesting presence of antibiotic resistance in areas with fewer exposures to antibiotic treatments. The author is suggesting that limited contact with urban areas that compose of livestock, sporadic travelers, and wild animals could be a good enough reason for the influx of resistant isolates and resistance genes within this community.\(^{67}\)

The cost effectiveness of formulating antibiotics is not favorable and does not promote economic stability. For this reason, many pharmaceutical companies are reluctant to produce antibiotics. GlaxoSmithKline (GSK) is one of a few large pharmaceutical companies that are still interested in doing research to develop new antibiotics. The financial support of Biomedical

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\(^{67}\) Ibid., 127.
Advanced Research and Development Authority (BARDA), a branch of the U.S. Department of Health and Human Services, would speed up the development of new compounds. These developments are still in phase 1 negotiations and thus may take years before the researchers receive approval for use of any antimicrobials. Currently, a committee composed of members from BARDA and GSK monitors and regulates the collaboration's progress from phase 1 negotiations to produce useful antibiotics. A $200 million developmental deal made between Washington and GSK pharmaceutical company was funded to work on threats of drug resistance.⁶⁸ There is an urgent need to promote further research dedicated to understanding antibiotic resistance.

According to the article, investors are reluctant to invest funds for the development of new antimicrobials because of their poor economic returns. In 1991, five new antimicrobials were approved for treatment and only two treatment options in 1990.⁶⁹ Decreased profits are because patients are taking antibiotics for a short period and only for acute infections; therefore, investing in the development of new antibiotics is not financially feasible because short-term use of medicine, such as antibiotics, minimizes continuous revenue. Industries are discovering “that new products, too, can have disappointingly short useful lives” and critics are deducing that “pharmaceutical companies have lost interest in developing new antibiotics even as old ones lose their power.”⁷⁰

These discussions among physicians, scientists, and businesspeople have certainly captured the idea that new technology can result in unintended consequences. These discussions have illuminated that there cannot be new technology without risks; however, the existence of

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⁷⁰ Ibid.
proper instruction and knowledge in using new technologies can assist to decrease possible unintended consequences.
Chapter 3: Examining the Practices of Prescribing and Taking Antibiotics among Physicians and Patients

Examining the doctor and patient relationship through the theoretical lens of the Health Belief Model (HBM) and the Theory of Planned Behavior (TPB) will suggest a further understanding of the behavioral patterns and can give insight to how bacterial resistance can develop. In addition, by developing programs using these theories to promote better practices will serve as a solution for remedying the problem of antibiotic resistance. The Health Belief Model looks at many factors including a patient’s perception of a disease as either severe or mild, and the way that knowledge affects patient’s actions to engage in specific health behaviors to eliminate the threat from that disease. The patient’s perception is one element that affects their willingness to adopt recommended physical and behavioral activities.71 The Theory of Planned Behavior discusses the perceptions of control people think they have over resources that influence their behavior. People’s awareness of having those resources affects their intentions to modify their behavior positively or negatively.72

The objective is to elucidate the misuse of antibiotics. This chapter will highlight the factors that influence the development of antibiotic resistance. Some factors include guidelines for prescribing antibiotics, providers’ prescribing patterns, patients’ usage patterns, and the communication styles that impact doctor-patient interactions. Finally, a proposal for new effective intervention practice designs that will benefit both patients and providers will be posited. This is discussed further in chapter 5. It is important to advocate the need for a review of

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72 Ibid., 97.
policies related to antibiotic prescriptions; and to rethink and restructure those systems to better manage the dispensing of medicines, specifically antibiotics.

Although there is an abundance of knowledge and information about bacteria and when a bacterial infection arises, treatments are sometimes ineffective and do not produce desirable outcomes. In addition, patients might not be aware of the importance of taking the full course of antibiotics. Here the doctor-patient relationship is vital to maintaining medication adherence. The rapport between patients and physicians will determine medication compliance among patients. Antibiotic compliance is an essential component to address the problem of antibiotic resistance.

Humans are social creatures, and building relationships is an important element within our diverse society. It requires people to develop effective communication skills to be able to converse and understand each other regardless of the vast number of different cultures, socioeconomic statuses (SES), levels of education, race, ethnicities, gender, and ages within our society. This social characteristic of human nature is a vital part of society, and it is especially important in the healthcare industry where maintaining the continuity of an established relationship, and also the interaction between doctor-patient encounters are necessary. Building a trusting doctor-patient relationship can result in a better diagnosis, treatment plans, and prognosis for the patient. Therefore, having an efficient doctor-patient relationship is vital to improving medical care for all individuals and better healthcare at the highest level.

There are some factors that hinder the doctor-patient relationship. In fact, unrealistic demands, such as time restraints, do not engender an emotionally intelligent provider or a compliant patient. Some of these factors that affect doctor-patient interactions are misunderstanding in communication, the gender of doctors and patients, class backgrounds, cultural differences, patient compliance, and advanced technology. These aspects are discussed

According to William C. Cockerham, there are three types of interactions. These interactions are the activity-passivity model, which is apparent in emergency cases, and doctors have complete control of the decision-making to render medical care. The guidance-cooperation model is seen when patients have an acute illness where the physician will choose the appropriate action to take via the medical decision rule, which is a guiding principle that monitors everyday practices while the patient agrees to comply. Finally, the mutual participation model occurs when patients are afflicted with chronic illnesses and the doctor and patient work together to control the condition.

Concerning misunderstandings in communication, there exists a barrier between patients and physicians because of status, authority, and training. These differences result in doctors prevaricating while giving diagnoses. The indirectness will alarm patients for no reason or fail to give a clear report of their medical condition. These miscommunications could lead to delayed treatments. If communication is done effectively, it should promote awareness, enhance proactive approaches to get well, and should result in a trusting and compliant relationship between the doctor and the patient. When examining class status, people who are of lower class and have no to the minimal educational background are more likely to receive less time spent in getting their medical questions answered. This situation results in a truncated doctor-patient encounter and may lead to misunderstanding and medication mismanagement. On the other hand, upper-class and upper-middle-class patients are more likely to have sufficient time with

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74 Ibid.,198-200.
75 Ibid.
76 Ibid.
their doctors to get answers to any questions they may have. Therefore, maintaining adequate communication during doctor-patient encounters will increase the likelihood for patient compliance. This, in turn, will address the inappropriate use of antibiotics and decrease the probability of antibiotic resistance.

As technology advances so do medical services. It appears that although there will still be a need for doctors' advice, advancing in technology are giving patients more self-controlled perspective of their health. This freedom includes retrieving medical information about their health via the Internet, receiving their patient records electronically, and having some doctor-patient encounters via teleconferencing.77

According to Shannon Brownlee, both patients and doctors agree that the relationship between them is amiss.78 The author discussed the need to have a good relationship with a physician because research has linked getting well with the type of relationships established with the provider and the patient. The writer reminisced about a television show, aired in the 1960’s, about an avuncular doctor named Marcus Welby, M.D. It expressed the physician’s familiarity with the patients and even their entire family. When compared to our contemporary society, continuity of care is not usual, and this results in a misaligned provision of adequate medical services. In worst-case scenarios, as in the case of Fred Holliday, whose death resulted from kidney cancer but his diagnosis was delayed because the doctor did not examine him completely; delays in arriving at an accurate diagnosis also delay appropriate treatments.

In addition, there is a higher probability of making mistakes when writing prescriptions, reading patients’ charts inaccurately, and ordering the incorrect lab workups when there is an

absence of good listening skills to understand a patient’s medical history. These are all vital components for efficient healthcare. However, all of these components may be compromised because of the limited time a physician may have to spend with his/her patients.

Chapter two highlighted some of the current factors surrounding the development of antibiotic resistance. This section explains guidelines to prevent antibiotic resistance by addressing those factors. Having guidelines can help physicians prescribe antibiotics appropriately. It is important to perform laboratory cultures to discern the correct infection-causing agents, such as fungal, bacterial or viral. This information will direct physicians to choose the correct antibiotic to treat the presenting infection because each drug is specific to its infection-causing agent. According to the Johns Hopkins Medicine Antibiotic Guidelines 2015-2016, there is a standardized list of information about each antibiotic. This list features the name of the antibiotic followed by a description of the medicine. The description highlights the drug class that particular antibiotic is classified in as well as activity or responsiveness to specific types of bacteria. For example, according to the aforementioned guidelines, Ceftaroline is active against staphylococci and many gram-negative bacteria but is not responsive to *Pseudomonas* or *Acinetobacter*.80

Subsequently, the terms for un/acceptable use of the particular antibiotic are also dictated. For example, the acceptable use for Colistin (Colistimethate) is utilized for a case-by-case base and for infections that are caused by multi-drug resistant *Acinetobacter* and *Pseudomonas*. The unacceptable use of this particular antibiotic is when used to treat gram-negative infections. Other pertinent information that is listed within this guideline are the strict dosage requirements,

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toxicity, and laboratory interactions.\textsuperscript{81}

The purpose of highlighting these details within the antibiotic guidelines is to reinforce the fact that there are established measures to prescribe correctly and appropriately. However, there are instances when antibiotics are not prescribed appropriately.\textsuperscript{82}

From the above description, it is evident that there are clear guidelines for an antibiotic prescription. However, it is also evident that there are instances when these guidelines are not followed. A possible solution to address this factor would be to evaluate the physicians who are responsible for following these guidelines.

Another factor that could aggravate the problem of antibiotic resistance is environmental forces.\textsuperscript{83} Agricultural use of antibiotics as a method to enhance animal growth was an element that led to the emerging problem of resistance. The authors observed a direct link between the development of drug-resistant infections and agricultural use of antibiotics. The use of antibiotic on animals and in agriculture results in the spread of strains such as vancomycin-resistant \textit{enterococci}. These strains are observed in farm animals that were exposed to antimicrobials. The spread of these strains was also seen in humans who came in contact with those animals. There is already extensive research being conducted on human pathogens.\textsuperscript{84} This approach limits the findings to just clinical mechanisms. The authors suggested widening the research and investigating environmental mechanisms or nonpathogenic organisms to find other reasons for


\textsuperscript{84} Ibid., 482.
the development of these strains.

The authors also reflected on the idea that it might be possible to predict resistance and avoid the problem before it becomes a clinical problem. Most antibiotics are natural product antibiotics. Over 80% of antibiotics that are being utilized in a clinic setting have been obtained from the soil. Apart from human actions that may contribute to the development of antibiotic-resistant bacteria, the natural processes of coexistence can also facilitate this evolution of resistant bacteria through the process of natural selection. Since natural products of antibiotics via the antibiotic-producing microbes occur in the soil, where the natural selection process is also occurring, this might be a way of allowing the existing bacteria to develop protection for themselves by becoming resistant as well. Therefore, understanding the soil resistome consisting of antibiotic-producing bacteria versus non-antibiotic-producing bacteria will reveal the diversity of the resistome and perhaps illuminate more information about resistance.

Given the difficulties to explore the unknown, mapping the existing bacteria in the soil to create an encyclopedia of these bacteria is necessary to continue the progression of research on resistance. The metagenomic approach is the creation of a library of soil activity yielding antibiotic-producing bacteria with a specific phenotype like antibiotic resistance.

Polymerase Chain Reaction (PCR)-based approaches involve testing the genomic make-up of the soil bacteria. This method yields various resistance genes. As D’Costa and colleagues discussed, it is necessary to build the knowledge base of the resistome to identify the different microbes and to distinguish the antibiotic producing from the non-antibiotic producing ones. This practice would eventually identify enzymes that mechanistically cause antibiotic inactivity or discovery of effective antibiotics such as telithromycin and daptomycin. There is a need to continue and develop the methods to show progress in this area of research to fight against
resistance. It is essential to enhance the knowledge of both the scientific, public health, and socio-cultural factors that are responsible for developing resistance and use that knowledge to build new program initiatives. Perhaps, a drug can be formulated to supplement other antibacterial chemotherapy as combination therapy to block the transfer of genetic information from cell to cell by applying the concept of competitive inhibition.

Horizontal gene transfer (HGT) allows for other developed metabolic abilities from the host to the recipient. This method allows the recipient to adapt other niches. Bacteria can acquire DNA in three different ways: transformation, conjugation, and transduction. After the DNA is acquired, two things occur: the DNA is replicated to form a different cell, or this new DNA gets integrated into the recipient’s chromosome. Not only are the actions of patients and physicians important but also the research processes. Information and databases about antibiotics exist in abundance; however if the efforts to utilize them become futile then it is unnecessary to have those databases. Nevertheless, research must proceed, and funding should be provided to facilitate this process.

In the very place where researchers are looking for the producer of new antibiotics lies the problem of antibiotic resistance. Ryan discussed the pneumococcal capsule test, which showed how the development of resistant bacteria to particular therapeutic interventions occurred. The ways in which antibiotics are prescribed and used contribute to the rate of bacteria becoming resistant.

Formulating antimicrobial prophylaxis from microbes that are already resistant is not going to help the matter, but rather exacerbate it. Researchers need to brainstorm alternative ways to formulate antibiotics chemically. This suggestion is one of the goals for combating the development of resistant drugs. In addition to D’Costa and Colleagues’ suggestion, research can
be done on specific drug and microbe to develop specific drugs that treat specific infections. Rather than treat infections with broad-spectrum antibiotics, the aim should be on formulating specific drug-to-bacteria chemotherapies.

There are enormous amounts of antibiotic resistance genes in the environment that are accessible to bacteria. They can use the different replicons, recombination systems, and gene transfer mechanism to produce resistant strains of bacteria. Monitoring the use of antibiotics can aid in controlling the unnecessary amount of antibiotics within this same environment of resistance genes so that the process of cell-to-cell gene transfer from resistant cells are less likely to occur. As seen in the experiments conducted, that antibiotics become inactive if the resistant genes are incubated with the antibiotic. *Methicillin-resistant S. aureus* was discovered in the 1960 and has an incidence rate of 80% in some hospitals.\(^8^5\)

Cell-to-cell contact was necessary for resistant genes to be transferred from a resistant bacterial gene to a sensitive bacterial gene and the process is known as conjugation. Acridine orange treatment could cure bacteria of the F plasmid. Resistance factors and F plasmids are functionally similar. Resistance factors are known as episomes. They have the resistant strain, which gets into cell-to-cell contact with other antibiotic-sensitive cells to have gene transfer. If that one cell or cluster of cells with the resistant strain could be identified via a laboratory test, it would be beneficial to prescribing appropriate antibiotics for the presenting infection.

Kissule and colleagues implemented a pilot program that to improve the antibiotic prescribing patterns among in-patients. The authors explored the effectiveness of transferring theory into practice. The behavioral change theory was utilized to develop the pilot program to

promote better prescribing patterns among hospital physicians for inpatients. The study was designed to produce pre and post-intervention evaluations of physicians.

Seventeen medical practitioners’ antibiotics-prescribing patterns were reviewed. Their evaluations included categorization of their treatment decisions according to whether the antibiotic treatments were effective. The categorizations were distinguished as appropriate, effective but inappropriate, or inappropriate. A profile of each practitioner was developed, and an academic detailing intervention session was scheduled. Their analysis of behavior change through the theoretical framework of behavior change theory indicated that behavior change is possible when initiatives are methodically planned and geared towards specific and targeted behaviors. The conclusion is that careful and methodical plan when implemented, could result in behavioral changes.  

Physicians have to modify their behavior—antibiotic-prescribing patterns—to promote efficacy and reduce the incidence of bacterial resistance. The behavioral change model dictates that learned behavior of antibiotic-prescribing patterns is the targeted behavior. Modifying physicians prescribing behaviors via the development of interventions will promote changes.

There are clinical guidelines for prescribing antibiotics, but the accuracy in which physicians appropriately adhere to these guidelines or not should also be questioned. Clinicians’ practice to adhere/non-adhere to the antibiotic-prescribing guidelines will result or propel the increase in the prevalence of antibiotic-resistant bacteria. Cost-effectiveness is another factor physicians should acknowledge when prescribing antibiotics. Patients’ compliance rate will

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87 Ibid., 68.
increase if the antibiotics are affordable. Implementing an antibiotic follow-up program will have far-reaching benefits.\textsuperscript{88}

One other research that was done by Meeker and colleagues suggested that decision-making about clinic practice could be influenced by cues that motivate appropriate behaviors.\textsuperscript{89} The authors defined motivators as “nudges” as an example of a type of cognitive mechanism. These “nudges” can be effective when implemented in different applications. One of the interventions utilized by the researchers in this study was to post commitment letters conspicuously in the examination rooms for twelve weeks. The letters incorporate a contract that stated the physician’s commitment to avoid inappropriate antibiotic prescription for acute respiratory infections (ARI). This commitment letter featured the physician’s signature and photograph. Although the researchers found that this method is effective in tailoring physicians’ prescribing behavior, there are few experiments to attempt the improvements in clinic practices. The objective of implementing the commitment letter was to urge judicious antibiotic usage.

The randomized study was conducted involving five outpatient primary care clinics. The participants were 954 patients who presented with ARIs. Physicians who were randomly chosen to utilize the rooms with posted commitment letters treated 449 patients and alternatively, physicians utilizing the standard practice control rooms treated 505 patients. Out of the cohort that underwent the conditions of the commitment letter, 335 were in the baseline period and 114 in the intervention period. The cohort that was a part of the standard practice control had 384

\textsuperscript{88} Kisuule, F., Wright, S., Barreto, J., Zenilman, J. “Improving antibiotic utilization among hospitalists: A pilot academic detailing project with a public health approach,” 69.
patients subjected to the baseline conditions while 121 patients underwent the intervention phase.\textsuperscript{90}

The baseline rates were 43.5\% and 42.8\% for the control group and the poster group, respectively. During the intervention period, inappropriate prescribing rates increased over 50\% for the control group but decreased to 33.7\% in the posted commitment letter group. The conclusion of this study illuminated that the presence of commitment letters motivated physicians to appropriately follow guidelines when prescribing antibiotics for patients presenting with ARIs. This intervention was by the cues to action theory; that is, if a reminder to motivate a person’s behavior is present, then that behavior is likely to be continued.\textsuperscript{91}

Another suggestion to address the development of antibiotic resistance is antibiotic cycling. This method involves alternating treatments on a timed scale. This is a strategy to slow the evolution of antibiotic resistance in hospitals. Bergstrom and colleagues discussed the mathematical model of antimicrobial cycling in a hospital setting.\textsuperscript{92} This model was used to explore the efficacy of the cycling programs. They found that cycling was less likely to have a reductive effect on the way antimicrobial resistance developed. Alternative drug-use strategies are deemed to be more efficient.

One of these strategies is mixing, where patients are treated with one of each drug classes simultaneously while in the hospital. These are other options that physicians can utilize to treat patients with bacterial infections. These are complex alternatives and require a good

\begin{itemize}
\item Ibid., 428.
\end{itemize}
understanding of the underlying reasons for choosing these options. Having information consolidated in a directional guide will force hospital physicians to consult these guides and administer antibiotics appropriately. According to the cues to action theory, physicians are more likely to administer medications by standardized guidelines if those guidelines are easily accessible. For example, having a pocket-size booklet with antibiotic guidelines that physicians can have access to at all times would be an ideal way to urge them to consult these guidelines and ensure they prescribe the correct antibiotic, its adequate dosage, and for an appropriate duration of time.93

Another factor that affects the development of antibiotic resistance is the financial cost to treat these cases. The economic cost of nosocomial infection is tremendous. If a person is resistant to antibiotics, treatment options become narrowed and mortality and morbidity increase. In the interim, their hospital stay becomes lengthier. All of these factors result in a higher economic cost of healthcare. It is necessary to continue formulating new drugs at a rapid pace as well as monitor and use current supplies of antibiotics judiciously to have strong control of antibiotic resistance.

The aim is to reduce the number of antibiotics prescribed. The way physicians accomplish this task will elucidate their prescribing patterns. Haggard observed a correlation between the amount of antibiotic prescriptions and the level of antibiotic resistance.94 There are guidelines and restrictions for prescribing antibiotics; however, factors such as having enough time impedes on whether these restrictive measures are followed closely. The explanation for

non-compliance raises skepticism because those reasons are not sufficient to justify why people do not comply with medication instructions.

Haggard proposed ways in which physicians could improve their skills: completing training modules and being apt with the guidelines for referring patients, and how to detect complicated infections. This article underpins the claim that antibiotics are prescribed for all infections but in some cases a fraction of those diagnoses are not bacterial and therefore should not be treated with antibiotics. This prescribing pattern reflects the physician’s skills and ability to determine the difference between viral and bacterial infections. The reluctance of ordering laboratory tests to confirm the source of the infection—viral or bacterial—prior to treatment is an oversight ultimately leading to an antibiotic prescription for all infections regardless if they originate from a bacterial cause.

A laboratory test, such as a paracentesis test is a way to extract fluids from a particular cavity—the origin of the infection—to undergo further laboratory testing. An advantage of this test will serve to reveal the specific bacteria that cause the infection. However, another argument is that conducting paracentesis is considered unethical. Until the ethical conundrum is tackled, hospital physicians should concentrate on their prescribing patterns.

One possible direction is to start prescribing antibiotics cautiously and with laboratory evidence prior to antibiotic treatments. Performing laboratory tests is the physician’s responsibility. Antibiotic resistance is a threat to public health because there is a connection between antibiotic consumption levels and the development of microbial resistance. This idea exemplified the findings in the European Surveillance of Antimicrobial

95 Haggard, M., “Poor adherence to antibiotic prescribing guidelines in acute otitis media-obstacles, implications, and possible solutions,” 330.
96 Ibid., 328.
Consumption. Programs or requirements that expect physicians to give supporting laboratory evidence for their antibiotic prescription to patients are shown to last only for a short-term duration.

This practice showed the “Hawthorn effects,” once the physicians know that their performance is being measured they are inclined to do what is expected of them; however, this is unlikely to continue on a long-term basis. There are many reasons for non-adherence to medications. These reasons are mostly surrounded by the physician’s skills and abilities. There are seven elements that impact patients’ non-adherence to antibiotics: cultural differences, physician inertia, lack of appropriate incentives, lack of detailed knowledge due to poor dissemination, conflict of interest, external pressures, insufficient use of appropriate analgesia, uncertain diagnosis, and concerns over possible complications from not treating infections. Physicians should be taught to de-medicalize or propose alternative treatments for their patients instead of adapting this robotic/monotonous behavior to continuously prescribe chemoprophylaxis such as antibiotics, especially when it has prospective detrimental implications to public health, such as antibiotic resistance.

According to Levy and colleagues, even a small increase in the “inhibitory concentration” to an antimicrobial should generate an alert to hospitalists and communities that an emergent problem of resistance is underway. This alert of an incipient problem should galvanize efforts towards altering the use of antibiotics in that environment.

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97 Haggard, M., “Poor adherence to antibiotic prescribing guidelines in acute otitis media-obstacles, implications, and possible solutions,” 323.
98 Ibid., 325.
99 Ibid., 326.
Levy and colleagues suggested some measures to take to manage and prevent antibiotic resistance. They proposed a local, national, and global surveillance system, which is necessary.\textsuperscript{101} Also to enhance the system, adding subcategories to these levels would be optimal. For example, on a local level, each hospital should have a follow-up call center, with nurses who contact patients to remind them of the antibiotic instructions as well as reiterate the importance of finishing the antibiotic course of treatment.

Additionally, new antibiotics are needed. New antibiotics should also have antagonistic effects, that is, those formulated should either block resistance mechanisms or those that attack new targets. Until this is possible, the dispensing of antibiotics should be closely monitored.

Levy and colleagues also suggested decreased antibiotic usage in intensive care units.\textsuperscript{102} This action will allow susceptible strains to repopulate and dominate their ecological niche. Decreasing antibiotic use is a good suggestion because some infections are not severe and are likely to heal on their own. Therefore, not all infections should be treated with antimicrobial agents.

In addition, rapid diagnostic laboratory tests will enable physicians to prescribe antibiotics more appropriately. For example, tests based on the procalcitonin levels distinguishes a viral from a bacterial infection are necessary. This test will decrease unnecessary antibiotic usage.\textsuperscript{103}

In order to control antibiotic usage and dispensary patterns, from patients and physicians, respectively, it is necessary to monitor the quantity changes. As demonstrated by the

\textsuperscript{102} Ibid., 128.
aforementioned experiments, it is apparent that the search for antibacterial chemotherapy is standardized. In fact, if not monitored continuously, resistance could develop. Therefore, it is necessary to keep continuous track of the usage, half-life, and dosage. Hence, the need for a program, such as a call center to track usage patterns by both patients and physicians, is apparent. A surveillance method should be used to track physician prescribing patterns. This approach would report the number of times the given drugs are prescribed, the reason, and whether if the reason is justified. Patients’ intake behavior should also be followed. All of these initiatives will promote accountability and permit close surveillance to observe any changes in effectiveness.

Bacterial infections proliferate to create new colonies, which require further research to understand the specific antimicrobial that targets specific bacteria. This information brings to mind that every type of disease/infection caused by TB could not be treated with one type of antibiotics. As a result, physicians need to know the type of infection and treat it with the specific type of antibiotics. In fact, currently, some infections may be treated and are curable with antibiotics.\textsuperscript{104}

Continuously prescribing antibiotics by trial and error allow the germs to develop resistance. Therefore, it is imperative to fine-tune the research to discover antibiotics that are infection-specific; rather than treating with broad-spectrum antibiotics. For example, in the case of treatment for blood-borne TB and tuberculosis meningitis, when streptomycin is given on a short-term basis, the effective dosage can cure these two types of TB without creating resistant bacteria. In other words, using the correct chemotherapy for a specific strain of TB is crucial.

\textsuperscript{104} Ryan, F. \textit{The Forgotten Plague}, 328.
This same line of thinking could be generalized to other bacterial infectious diseases requiring antimicrobial treatments.

Various extensive clinical studies should investigate different factors that are targets for resistant bacteria. In addition, surveys should be formulated to evaluate patients’ perception versus physicians’ perception in order to understand respective individual behaviors. This will shed more light on the matter of drug resistance. In addition, more funding is needed over longer periods of time for microbiologists who are interested in the area of microbes. Available funding will allow them to focus extensively on discovering microbes that we do not know exist, but might be potential candidates for formulating new and effective antibiotics. Those new antibiotics might have a higher probability of remaining effective while treating bacterial infections instead of developing resistant bacteria.
Chapter 4: Solutions: Remedies To Combat the Problem of Antibiotic-Resistant Bacteria

It is necessary to monitor patients after doctors prescribe antibiotics to them. This is one way to remedy the problem of antibiotic resistance. Although there is a standard policy dictating the appropriate dispensary of antibiotics within the United States, it is not entirely the case for developing countries. Globally, there is a vital need to track prescriptions and even change government policies allowing this practice because “in some countries, antibiotics are still sold legally over the counter to patients who may never get proper instructions.” \(^\text{105}\) Educating patients about the correct ways to take antibiotics when treating infections include: informing them of the consequences if not used appropriately, and to ensure that patients understand the use of antibiotics. This argument has been made multiple times, and suggestions to remedy the problem in multiple ways have been proposed but here is what should be done.

The following cases illustrate how the prevalence of antibiotic-resistant bacteria is an old issue that is becoming more frequent in the treatment of serious infections. Scientists, healthcare providers, and academics have come to the conclusion that there is an increase in cases of antibiotic-resistant bacteria. While examining the continuum of theory, research, and practice, theories have suggested that the problem of antibiotic-resistant bacteria is apparent. The next step is research. Researchers have done an ample amount of empirical investigation to discern that the development of antibiotic resistance is a problem. Now the next logical step is praxis; therefore, to use the theories and evidence obtained from different investigations to develop initiatives.

The bottom line is to take action, and that is what clinicians need to do. One of the logical actions to take is to systematically track antibiotic prescriptions by performing a post-follow up

inquiry to ensure the patient has adhered to the antibiotic instructions. Continuous research is needed to solidify further current theories and findings and to discover new information, but action now is also crucial. That is to find initiatives, maintain them, and conduct research that directly infuses solutions to the problem. Also in the words of John Dewey, “children learn best by doing.”\textsuperscript{106} We will only be able to discern the effectiveness of applied measures compared to the ones that are already implemented by brainstorming new ideas and putting them into practice. The development and execution of innovative remedies/programs to address the issues we are encountering with the rise of antibiotic-resistant bacteria will be advantageous.

One out of many recommendations for future biological/microbiological research is further investigation of the advantages of competitive inhibition. In chapter 1, the experiment involved groups of mice that were given treatment, which resulted in the survival of mice afflicted with pneumonia.\textsuperscript{107} Suggestions that will enhance the current studies on developing effective antibiotics are to employ the ideology that different drugs should be formulated to fit the different cell membranes. Developing a toxic chemical—toxic to the microbe that develops resistance to antibiotics and not toxic to patients—that competes with the antibiotic at the binding site will increase the likelihood of killing the bacteria. Therefore, the toxic chemical could become attached at the binding site killing the bacteria. Chemicals that mimic the function and structure of enzymes could be created. These modified chemicals could be manipulated to have a perfect lock and key fit to the binding site propagating cellular processes. This method will disrupt the life of the bacteria, preventing it from adapting to its environment and replicating.

\textsuperscript{106} Glanz, K., Rimer, B.K., Viswanath, K. Health Behavior and Health Education: Theory, Research and Practice, 4\textsuperscript{th} ed., Somerset, NJ: Jossey Bass, 2008.

\textsuperscript{107} Frank, R., The Forgotten Plague, 96.
more resistant strains. This toxic chemical has to be dependent on the type of microbe and be structurally compatible to the antibiotic.

Another recommendation is to choose a specific antibiotic chemotherapy and track its initial existence to the point of resistance. By evaluating ways in which the development of resistance could have been avoided or not and the prospects for future antibiotic chemotherapy can provide insight on how that antibiotic evolves. The task of tracking the lifespan of this particular antibiotic can enlighten revolutionary ways to change, maintain, and revise Standard Operating Procedures (SOP) when prescribing, dispensing and instructing patients about antibiotics and their usage. Standard Operating Procedures are a set of guidelines that give instructions on how to operate within a particular setting.

The following suggestions to gather information on people’s behavior with antibiotics are discussed as follows: the cell membrane’s affinity to absorb different dyes reveals that drugs are cell-membrane specific and should be formulated to fit a particular cell membrane.\textsuperscript{108} This knowledge will require providers to prescribe specific antibiotics for specific infections. More research is needed to develop an understanding of the different types of bacteria that cause infections and acquire specific details about the targeted bacteria. Ordering tests to discover specific details about the bacterial-causing agent that is responsible for a given infection should be an SOP. Ultimately more funding for research and capital to purchase specific equipment to carry out specific germ tests is necessary.

Thus far, there have been numerous studies about antibiotic-resistant bacteria. However, it is helpful also to have a Humanities perspective on the development of antibiotic-resistant bacteria. This point of view involves examining a community’s response and behavior toward

\textsuperscript{108} Ryan, F. \textit{The Forgotten Plague}, 88-90.
antibiotics from an individual to a systemic level. Suggestions about gathering information on people’s behavior with antibiotics are discussed below.

Alluding to chapter 1, the cell membrane’s affinity to absorb different dyes reveals that drugs are cell membrane-specific and should be formulated to fit its inherent cell membranes. This information suggests that providers should be prescribing specific antibiotics for specific infections, that is, antibiotics to treat bacterial infections and antivirals to treat viral infections. More research is indispensable to have a better understanding of the way bacteria function to cause infections. Specific details about those targeted bacteria will, in turn, illuminate the mechanism in which bacteria become resistant to antibiotics. Ordering laboratory tests to discover specific details about the bacterial-causing agent that is responsible for a given infection should be an SOP when diagnosing a presenting infection opposed to the current SOP to treat then confirm.

In chapter 1, the “Madras Experiment” discusses inpatient medical (sanatoria) treatment versus community-based therapy (at home). This study has raised various questions, such as, how does the administration and appropriate completion of antibiotics that were prescribed measured? Future experimental study to investigate the rate at which such group completes their antibiotic treatments is crucial. Based on the findings, it can be proposed that this method of treatment be implemented as a possible remedy/solution for reducing/preventing/eliminating the development of antibiotic-resistant microbes. If this study is not executed, then we might exhaust our existing soil bacteria. Researchers may not discover new ones within a reasonable amount of time to formulate newer chemotherapies against infectious diseases.

As seen in chapter 1, to control usage and dispensary patterns, from patients and

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110 Ibid., 383.
physicians, respectively, it is essential to monitor the changes in the quantity of antibiotics prescribed overall. As demonstrated by the aforementioned experiment, it is apparent that the search for new antibacterial chemotherapy is systematic without prospect for changes. In fact, if not monitored continuously, resistance could develop. Therefore, it is imperative to keep trace continuously of the quantity prescribed, half-life, and dosage. Hence, the need for a program such as a call center to track usage patterns for both patients and physicians is apparent.

As mentioned in chapter 1, infection-causing bacteria multiply to create new colonies. Further research to develop specific types of antibiotics that target those bacteria is necessary. This information reveals that every type of infections caused by bacteria cannot be treated with one type of antibiotic. A list of current bacteria and their treatments can be found in the antibiotic guidelines created by Johns Hopkins School of Medicine. Therefore, it is pertinent that physicians know exactly the type of infection-causing bacteria and treat it with a specific type of antibiotic. Currently, some infections may be treated that are not curable with antibiotics.

As mentioned in chapter 2, there exists is a disconnection between the treatment type for viral versus bacterial infections. Infections should be confirmed by laboratory tests to ensure they are bacterial rather than viral before treating with antibiotics. A precise knowledge of the differences between viruses and bacteria is paramount to maintaining the value of these blood tests. Obtaining specific blood tests is one method to prescribe antibiotics appropriately.

In fact, the human body’s innate immune system can respond to and cure mild bacterial infections on its own. Thus, not all infections caused by bacteria need to be treated with full

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113 Frank, R., The Forgotten Plague, 328.
doses of antibiotics. The body has a built-in defense against mild infections. The prescription of antibiotics for serious cases, such as meningitis or pneumonia, is not been overlooked in this claim, but medical practitioners should be more vigilant and prescribe for only serious cases. Tests are needed to identify the severity of bacterial infections.

The rise in antibiotic-resistant bacteria establishes the need to monitor antibiotic usage. In 1996, the Centers for Disease Control established new public health departments, such as The National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) to provide “national public health surveillance system to track changes in the antimicrobial susceptibility of certain enteric bacteria….” However, this does not specifically target the misuse or over-prescribed use of medicines that can result in antibiotic resistance. In other words, the data is collected, and cases are tracked after a reported case of bacterial resistance, which is not a preventative approach. Since research has linked misuse/over-prescribing to the cause of antimicrobial resistance, these connections that should be addressed prior to an emergent case of resistance. Thus, it is necessary to apply a bottom-up approach to closely monitor and regulate the dispensing of antibiotics on a hospital-to-hospital scale. Close monitoring will assist to eliminate at least one factor, such as over-prescribing antibiotics.

Physicians need to be educated more on the etiology and appropriate use of antibiotics. Objective tests are required to confirm these decisions. A database or a tag should be created to track every time antibiotics are prescribed. Perhaps we need a more advanced technological equipment to discover early/first signs of infections before it gets life threatening. Innovative equipment that screen for infections type might be one way to combat the misuse of antibiotics.

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A suggestion for combatting continuous exposures to bacteria that develops into fatal infections include educating people but also making an effort to understand the relationship between physicians and their patients. On a global scale, populations worldwide need to be educated about the risks of certain lifestyles that can be a threat to public health. In addition, people should be updated periodically and not when there is an outbreak about the link to bacteria and the causes of infections. These warnings should be given in languages that people can understand. People should be aware of the actual risks and take individual responsibility for their wellbeing and be conscientious of others. In addition, the World Health Organization (WHO) should issue strict mandatory rules for proper sanitation and living conditions. These ideas should be generalized over the community, the country, and worldwide.

Future studies should include surveys and investigative studies. To conduct surveys, see figure 2 for a sample of possible questions to ask on the questionnaire. The rationale for the following questions is to obtain information about usage patterns, prescribing, and existing datasets on quantities of antibiotics being dispensed. Proposed studies are described in chapter 5 utilizing the sample surveys.

For an investigative study of Emergency Rooms (ER), control groups and experimental groups are needed. The locations should include Veterans Hospital Centers since they are already teaching hospitals. In a pilot program, creating a Telehealth station in one of the two locations should implement a call center consisting of representatives (ideally nurses) to manage and collect all prescribed antibiotics from the ER, then initiate follow-up calls to obtain data on patterns of usage. This study is proposed in detail in chapter 5.

Such studies would create jobs and function as a means of documenting and tracking antibiotic usage and prescribing patterns. These experiments would promote understanding and
help to answer questions about the prevalence of antibacterial resistance, the amount of antibiotics used, and whether those quantities and reasons for prescribing are justified. In addition, this practice will aid to discover if those factors—usage patterns, prescribing patterns, and justified reasoning for the quantity of antibacterial dispensed—are associated with the prevalence antibiotic resistance.

Such a practice would not be unethical or by-pass Health Insurance Probability and Accountability Act (HIPAA) regulations because the staff collecting the data would be affiliates of the hospital. However, an IRB approval and informed consent forms from participants would be a prerequisite.

An alternate suggestion to explore other possible causes for the rise in antibiotic-resistant cases is to investigate the food industries. Chapter 2 indicated that the use of feed additives has some correlations between the use of those enhancers, such as antibiotic and growth hormones to improve, accelerate, and facilitate growth.\(^\text{116}\) The use of these enhancers is to create larger and faster productions. However, the use of these antibiotic and growth hormones does not seem to make a positive increase in the production but has demonstrated a detriment to human health over a longer period.\(^\text{117}\)

There has been a tremendous concern, progress, and awareness that led to the development of programs and practices suggesting to eliminate the threat of the rising pandemic, bacterial resistance. Thus far, clinicians, researchers, and patients have done their best to try and combat this issue. However, the fact is that the issue still exists. This existence can only mean

\(^{116}\) Soulsby, E.J., “Resistance to antimicrobials in humans and animals: Overusing antibiotics is not the only cause and reducing use is not the only solution,” British Medical Journal 331 (7527) (2005): 1219-20.

one thing, that some of the current practices in place to prevent the problem of antibiotic resistance are not effective. The next logical step is to seek other methods that would possibly address the problem. The truth is that different period of time employs different levels of effectiveness. That been said, our current time has a strong sense of technological advancement, such as Telehealth within the hospital systems, why not utilize these technological advances as our propelling forces to find new ways to combat antibiotic resistance. Some of these new and innovative ways mentioned above and throughout this thesis has set the stage for brainstorming new possibilities toward the war against the development of antibiotic resistance.
Chapter 5: Proposed Studies: Template for Future Experimental Studies

Introduction

The purpose of the proposed studies is to understand the choices people make when following antibiotic instructions. Chapter one illuminated the processes involved in formulating new antibiotics and the microbes involved to complete this process. Chapter two highlighted the current issues encountered and the rise in antibiotic-resistant cases. Chapter three narrows the focus of one possible cause that contributes to the problem of antibiotic resistance. That is, the behavior of physicians and patients when it comes to antibiotic prescribing patterns and usage patterns, respectively. In chapter four, many suggestions were made to study different causes to the development of antibiotic-resistant bacteria, but investigating patients’ and physicians’ behaviors toward antibiotic use seem especially pertinent. In this chapter, a proposal to study the effects of two variables, close monitoring of both physicians’ and patients’ behavior when using antibiotics versus the current practice, on the development of antibiotic-resistant bacteria. This experiment can yield promising findings and suggest ways to decrease the probability of the rise in antibiotic-resistant cases. By reviewing the following literature, the fact that antibiotic-resistant cases are increasing is well supported. In addition, the literature has also suggested patterns of use that might be a contribution to the development of resistant bacteria.

Literature review

Among the various kinds of literature within this thesis, the following have highlighted the existence of the resistant problem this thesis was purposefully written to illuminate. Bartoloni et al. discussed that the connection between antibiotic consumption and the emergence of bacterial resistance is well documented. Another point the author made was even in areas of

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low antibiotic use, there was still evidence of antibiotic resistance. This information further complicates the knowledge we have about the development of antibiotic-resistant bacteria. Initially, researchers and clinicians thought it was only the misuse and over-prescribing that led to the resistant strains. As a result of this revelation, it is more imperative now than ever to examine the solutions and propose innovative ones to get to the root of the problem.

Levy and Marshall reported that drug-resistant strains were apparent in hospitals because this was where the antibiotics were most commonly used. They reported evidence from the 1930s to the 1970s on the emergence of various bacteria and the development of resistance to antibiotic treatments. Those evidence further illuminated that antimicrobial resistance exists.

D’Costa et al. highlighted that there is a direct link between the development of drug-resistant infections and agricultural use of antibiotics.\textsuperscript{119} The authors suggested broadening the research boundaries by exploring the environment for other variables that could an effect on resistance. Findings from these exploratory researches can suggest other reasons for the development of resistant strains of bacteria.

Davies emphasized that the problem of antibiotic-resistant bacteria is nothing new despite the recurring times and places this type of news is being publicized.\textsuperscript{120} He provided evidence from the 1950s during the war in Japan. The evidence pointed to the development of resistance due to ineffective antibiotic treatments.

Finally, Ryan gave a historical sequence of the development of experiments and the

\begin{thebibliography}{99}
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The author discussed the prevalence of TB and pneumonia. He highlighted various experiments that were conducted to find a cure for each of those infections. He detailed the following experiments, which illuminated the scientific processes involved in formulating antibiotics: The Madras experiment, “The effects of salicylate on the oxygen uptake of the tubercle bacillus,” and the pneumococcal capsule experiment, to list a few. While doing this, he has demonstrated the difficulties involved in the formulation process, identified different bacteria, and highlighted new discoveries.

**Hypotheses**

**Study 1: Implementing a Monitoring Call Center and Follow-Up Procedures to Track its impact on Antibiotic Treatment Completion within the Veterans Administration Healthcare Facility**

H$_1$: I expect to find patients who are not closely monitored after being prescribed a course of antibiotic treatment will not complete the treatment if their symptoms subside.

H$_2$: When patients are monitored closely after being prescribed a course of antibiotic treatment, they are likely to continue and complete the treatment even if their symptoms subsided.

**Study 2: Presence of a Prop (Pocket-Sized Manuel vs. None) and Physician and Patient Usage Behavior**

H$_3$: When physicians are relying only on knowledge of commonly prescribed antibiotics, they are likely to prescribe inappropriate antibiotics.

H$_4$: Having a prop, such as a pocket-sized information book on antibiotics prescription, will encourage physicians to consult and prescribe effective antibiotic treatments.

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Data and Methods

Study 1: Implementing a Monitoring Call Center and Follow-Up Procedures to Track its impact on Antibiotic Treatment Completion within the Veterans Administration Healthcare Facility

Part 1: Table 1: Implement Intervention: Follow-up Monitoring versus No Follow-up Monitoring

<table>
<thead>
<tr>
<th>Physicians</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-Up Monitoring</td>
<td>No Follow-Up Monitoring</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
</tr>
</tbody>
</table>

*Even when the symptoms subsided.

Part 2: Table 2: Implement Intervention: Call Center versus No Call Center

<table>
<thead>
<tr>
<th>Physicians</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Call Center</td>
<td>No Call Center</td>
</tr>
<tr>
<td>Telephone Call**</td>
<td>No Telephone Call**</td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

*Even when the symptoms subsided.

**Presence or absence of telephone call.

Study 2: Presence of a Prop (Pocket-Sized Manuel vs. None) and Physician and Patient Usage Behavior

Table 3: Implement Intervention: Presence of Pocket-Sized Manuel versus Absence of Pocket-Sized Manuel

<table>
<thead>
<tr>
<th>Physicians Prescribing Patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of Pocket-Sized Manuel</td>
</tr>
</tbody>
</table>

Physicians reported that they were more likely to consult this additional resource | Physicians are more likely to prescribe appropriate treatment of antibiotics
Physicians are reported that they are less likely to consult this additional resource | Physicians are more likely to prescribe inappropriate treatment of antibiotics

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Analytical Strategy

Study 1: Implementing a Monitoring Call Center and Follow-Up Procedures to Track its impact on Antibiotic Treatment Completion within the Veterans Administration Healthcare Facility

Part 1: Implement Intervention: Follow-up Monitoring versus No Follow-up Monitoring

Follow-Up Manipulation:
Procedure:
1. Conduct survey by having patients and physicians answer questionnaires displayed in Figure two.
2. The patient will have an option on the survey to write in any self-reports on usage experience.
3. The physician will have an option on the survey to write in any self-reports about prescribing patterns.

Participants:
1. The study will consist of 28 physicians prescribing and 79 patients who are treated with antibiotics.

No Follow-Up Manipulation:
Procedure:
1. Conduct survey by having patients and physicians answer questionnaires displayed in Figure two.
2. The patient will have an option on the survey to write in any self-reports on usage experience.
3. The physician will have an option on the survey to write in any self-reports about prescribing patterns.

Participants:
1. The study will consist of 28 physicians prescribing and 79 patients who are treated with antibiotics.

Part 2: Implement Intervention: Call Center versus No Call Center

Call Center Manipulation:
Procedure:
1. Conduct survey by having patients and physicians answer questionnaires displayed in Figure two.
2. The patient will have an option on the survey to write in any self-reports on usage experience.
3. The physician will have an option on the survey to write in any self-reports about prescribing patterns.

Participants:
1. The study will consist of 11 physicians and 29 patients who are on antibiotics treatment.
No Call Center Manipulation:

Procedure:
1. Conduct survey by having patients and physicians answer questionnaires displayed in Figure two.
2. The patient will have an option on the survey to write in any self-reports on usage experience.
3. The physician will have an option on the survey to write in any self-reports about prescribing patterns.

Participants:
1. The study will consist of 11 physicians prescribing and 29 patients who are treated with antibiotics.

Study 2: Presence of a Prop (Pocket-Sized Manuel vs. None) and Physician and Patient Usage Behavior

Presence of Pocket-Sized Manuel Manipulation:

Procedure:
1. Conduct survey by having patients and physicians answer questionnaires displayed in Figure three.
2. The physician will have an option on the survey to write in any self-reports about prescribing patterns.

Participants:
1. The study will consist of 46 physicians prescribing treatments with antibiotics.

Absence of Pocket-Sized Manuel Manipulation:

Procedure:
1. Conduct survey by having patients and physicians answer questionnaires displayed in Figure three.
2. The physician will have an option on the survey to write in any self-reports about prescribing patterns.

Participants:
1. The study will consist of 46 physicians prescribing treatments with antibiotics.
Figure 2: Survey Sample One for Study 1

**Questionnaires for Physicians:**
1. When do you prescribe antibiotics? For example, indicate outpatient or inpatient visits.
2. How frequently do you prescribe antibiotics for an outpatient versus and inpatient client?
3. What instructions do you give each category of patients?
4. When do you monitor or follow-up with each category of patients upon prescribing the course of antibiotic treatment?
5. Write in any additional comments.

**Questionnaires for Patients:**
1. How often have you taken antibiotic treatments?
2. What kinds of medical diagnosis did you take antibiotics?
3. Have you taken it for a cold?
4. How many questions, if at all, do you ask your physicians about instructions for taking antibiotics?
5. How likely are you to finish the complete course of treatment?
6. If you get better before you finished your antibiotics treatment, how likely are you to continue taking the remaining medicine?
7. Write in any additional comments.

Figure 3: Survey Sample Two for Study 2

**Questionnaires for Physicians:**
1. How do you prescribe antibiotics?
2. How frequently do you prescribe antibiotics?
3. What instructions do you give each patient?
4. How often do you consult additional resources to supplement your knowledge to prescribe treatments for rare infections?
5. What additional resources do you have to aid you in researching antibiotics?
6. Write in any additional comments.

**Questionnaires for Administration:**
1. How do you monitor the physicians you’re supervising on the frequency of prescribing antibiotic treatments?
2. How do you access the physicians’ choice of antibiotics prescriptions as suitably or unsuitably prescribed?
3. How do you evaluate physicians’ performance?
4. How often do you conduct these evaluations?
5. Write in any additional comments.
Anticipated Findings

The findings of study one should be intuitive as reported in Tables 1-2. The fact is known that the full course of antibiotic treatments should be completed, and patients should not discontinue medication once they are symptomatically healthier. The findings from the proposed study should be that patients are likely to be compliant when monitored closely after a physician gives an antibiotic prescription. On the other hand, if patients are not monitored after an antibiotic prescription they are likely to revert to expected behaviors of truncating the treatment once the symptomology has subsided. As mentioned before, the Hawthorne effect supports this claim that monitored behaviors are those that indicate noticeable changes. If behaviors are monitored, people are more inclined to follow rules and regulation.

The findings in study two indicated that reminder cues are excellent resources for promoting effective decision-making. As a result, the expected findings would be that in the presence of a cue, such as the convenient pocket-sized manual with information on antibiotics prescription, physicians are more likely to consult that manual for appropriate antibiotic options than if it was not present. This projected finding is supported by the cues to action theory. This concept states that if a reminder to motivate a person’s behavior is present, then that behavior is likely to be continued.122

Discussion and Conclusions

Highlighted throughout this thesis are examples that illuminated the dangers of drug-resistant bacteria. On a global scale, the development of resistant bacteria could lead to a pandemic. The main reason for writing this thesis was to focus on solutions that have already

been established and to brainstorm other ways that might be employed to help remedy the problem of antibiotic-resistant bacteria. Exploring some of the social contributions that can also affect this problem of resistant bacteria can lead to advantageous future changes. For example, monitoring physicians’ prescribing patterns and patients’ drug usage can offer innovative ways to develop remedies for this problem the scientific community is facing.

The aforementioned proposed studies provide a template to develop future studies. The recommended solutions seem to be viable. The suggested findings of the proposed studies can be significant. For future research, the continuity and redevelopment of current programs to aid in retransforming and eliminating the disadvantages of drug-resistant bacteria are encouraged. This practice, in turn, enhances the information and knowledge related to the existing problem of antibiotic resistance.
Bibliography


“Biology online” Last modified June 3, 2015.
http://www.biology-online.org/dictionary/Binding_Site

“Hunting the Nightmare Bacteria.” pbs.org. Last modified October 22, 2013.

“National Antimicrobial Resistance Monitoring System for Enteric bacteria (NARMS).”
http://www.cdc.gov/narms/


Soulsby, E.J., “Resistance to antimicrobials in humans and animals: Overusing antibiotics is not the only cause and reducing use is not the only solution,” *British Medical Journal* 331 (7527) (2005): 1219-20.