Infections Not Fought: Antibiotic Resistance in Underserved Communities

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ABSTRACT

In 1928, the profound effects of penicillin were discovered and antibiotic treatments became extremely popular. Broad-spectrum antibiotics, like tetracyclines, have been since branded as cure-all prescriptions and used profusely in the Western World and abroad. Due to ignorance of specific biochemical mechanisms and the misuse of antibiotics these drugs inadvertently allowed the rise in prevalence of antibiotic resistant strains of certain bacteria as the century progressed. Now, the specific genetic causes and mechanisms of antibiotic resistance are being understood, but the fight against antimicrobial resistance is far from over. In the United States, thousands of fatalities are caused annually by infections of this variety. In impoverished nations, the reality is dimmer and antibiotic resistance demands research and funding so that lives can be saved.

Antibiotics, when used properly, have been one of the largest lifesavers humanity has ever had. But when used improperly, they can have a converse effect. In most developed countries, antibiotics have revolutionized the way conditions are treated. In just the first half of the last century, many people would lose their lives to tuberculosis, pneumonia and other common bacterial infections. Vaccines have worked to curb their incidence and antibiotics have been used to cure infected patients. However, increasing use of antibiotics has given way to bacteria that are resistant to many common forms of antibiotics. These antibiotic resistant strains now work to cause harm to thousands or hundreds of thousands of people.

ANTIBIOTICS AND THE CAUSE OF RESISTANCE

Even though antibiotics have successfully subdued many infectious agents, there are a few other infectious agents that continue to be problematic in countries like the United States and plague impoverished parts of the world. Before specific bacterial agents for disease are analyzed, however, it is proper to first discuss the contributing factors that produce resistant strains and allow curable infections to persist. Then, it should be determined how these problems are amplified in areas of the world that are remote, impoverished or subject to the high stresses from the environment, wars or other external factors. Then, solutions can be proposed.

Bacteria are single-celled organisms that live almost everywhere and provide a wide range of functions. They are diverse and normally not harmful. Many bacteria live in the human GI tract, contributing to normal digestion. Other bacteria may live

commensally on human skin. For example, certain kinds of bacteria living on skin consume the chemical compounds in perspiration. As a byproduct, body odor is produced by these bacteria, but they do not harm their host [17]. Bacteria that live non-parasitically on or in a person are said to be a part of that person's normal flora. Essentially, bacteria are widely diverse, inhabiting a variety of environments and able to adapt and survive in many different situations.

Some bacteria do inflict disease upon their host. Common infectious bacteria include various strains of *Escherichia coli*, *Staphylococcus aureus* and *Salmonella*. It should be noted that these microbes (and many others) may not cause symptoms of infection in a person unless they are present in significant amounts; a small amount of these bacteria may be a part of the normal flora. The common treatment for many bacterial infections is the use of a prescribed antibiotic. An antibiotic is a drug that acts to target bacteria with one or more specific features. There are four general classes of targets, called mechanisms of action, the antibiotic will utilize. These are targeting the cell bacterial wall, inhibiting protein biosynthesis, inhibiting DNA replication, and inhibiting folic acid synthesis [17]. So, a certain antibiotic may utilize one or more of these mechanisms of action to the detriment of bacteria at certain stages of growth and development.

For example, the antibiotics in the group oxazolidinones act to inhibit both the 50s and 70s subunits of the prokaryotic ribosome and therefore prevent protein biosynthesis. Quinilones, however, act to prevent DNA gyrase from producing and relieving supercoils during DNA replication [17]. The bacteria cannot replicate and die. The degree of

specificity for an antibiotic drug and its target bacteria varies widely. If the antibiotic can be used to treat both gram-positive and gram-negative bacteria it is called broad-spectum, as it is capable of effective treatment over a diverse group of infectious agents. Good examples of these are tetracycline, chloramphenicol and carbapenems. Narrow-spectrum antibiotics are those that are effective against a selective range of bacteria that is either gram-positive or gram-negative [25]. These are generally employed when the diagnosis is clear or antibiotic testing has been done to pinpoint the causative agent or when it is feared a more broad-spectrum treatment would harm normal flora. Additionally, physicians often prescribe antibiotics in tandem to amplify their effectiveness against a bacterial infection, a response called synergy. This way antibiotics with different mechanisms of action can work together to defeat an infection. This will generally shorten the illness and lessen damage to the patient.

Even with the largely beneficial properties of antibiotics, their overuse and misuse contributes to problems of destroying normal flora and the allowing of antibiotic resistance. Antibiotic resistance is simply the ability of certain strains of bacteria to be less affected by an antibiotic that would normally be effective against that kind of bacteria. It is important to clarify that there are degrees of resistance due to genetic variance and that the extent that a strain may be resistant may or may not be significant. Certain causative agents come into play in the development of this phenomena but the basis of resistance in bacteria is genetic. Bacteria, even within the same species, can have huge variations in their phenotypic expressions. Mutations as well as extra genes received in conjugation may allow the expression of these unique characteristics in a small portion

of a bacterial colony [17]. These mutations or genetic variations are generally not for avoiding antibiotics, but instead may harm the ability of the cell to grow and multiply and therefore be selected against under normal conditions. However, when the bacterial colony is being attacked by an antibiotic treatment, these useless or even harmful expressions may prove themselves to be useful mechanisms of resistance and be used to inactivate the antibiotic or reduce concentrations of it from the cell.

An example of one of these mechanisms is the employment of efflux pumps to force antibiotics out of the interior of the infectious prokaryote. In this way, certain strains may prevent treatment concentrations from rising to dangerous levels. Other resistant bacteria may alternate confirmations of the antibiotic's target molecule, essentially inactivating the treatment, such as modifying penicillin binding proteins on certain penicillin-resistant strains' cell walls [17]. There are many other mechanisms by which bacteria can accomplish these feats and persist through the course of a treatment. However, antibiotic resistant infections do not always arise because a person is colonized and subsequently infected by an already resistant strain. On the contrary, it is often that most of a target colony is sensitive to the treatment, but the strains allowed to persist may then grow and compose a larger percentage of the population that causes a second infection.

A theoretical example could be a person who is not feeling well and sees a physician for treatment. The person presents to the doctor with a sore throat and is diagnosed with strep throat, caused by *Streptococcus pyogenes*. As this is a common ailment, the doctor prescribes the normal treatment of a penicillin-derivative and sends

the patient home to recuperate. The 10-day antibiotic regimen is followed for the next six days, and the patient, feeling fully better decides to forgo the remaining days of treatment and save some left-over antibiotic in case of a future emergency or another bout with strep. However, the person soon is not feeling well again and, realizing the infection has returned starts to self-administer the remaining antibiotic to no avail.

In this scenario, the patient has taken the antibiotic long enough to become asymptomatic, but not long enough to be cured. Furthermore, while the original colony of bacteria was made up of nearly all penicillin-sensitive bacteria, as evidenced by the patient feeling better, the recurrence of infection may feature a colony that has had its population shifted so that the small number of penicillin-resistant bacteria could persist and make up a much larger portion of the next infectious colony. This ultimately rendered the second round of treatment ineffective and could have been prevented if the patient had completed all 10-days and adequately killed all the sensitive bacteria. This would leave the resistant bacteria at a level too low to cause infection.

Another hypothetical scenario for the rise of a resistant infection would be that of a mistaken identity. The goal of healthcare in any setting is two-fold; it is to provide quality services that sufficiently serve the quantity of patients. Therefore, if a patient presents to the hospital with symptoms of pneumonia, or strep throat or any number of common illnesses, it is normally the most efficient thing to do to prescribe the common antibiotic used for treating the diagnosis. This saves the patient money and the hospital a room and hours spent working to test each infection for positive identification. If each person who came into a hospital with a bacterial infection had to be swabbed, their

sample colonized, identified and sensitivity tested, hospitals would have a much larger workload. Also, the time it would take to test each sample would cause patients to have a persisting infection for two-three days until the diagnosis was confirmed. That is why antibiotics are generally prescribed based on presenting symptoms.

While the majority of cases will respond normally to the antibiotic, a small percentage of patients will maintain their symptoms. In these cases, the physician may prescribe other antibiotics as a sort of guesswork or test the bacteria in the patient for its sensitivity against these other antibiotics. Both are trial and error approaches and take time. It is not uncommon for a patient to endure weeks of hospital visits and leave with a large bill for an infection that at first seemed routine. In cases of patients with compromised immune systems, the weeks on end of infection may lead to permanent damage or even death.

It should be noted that no strain of bacteria is resistant to all treatments. Just as no antibiotic is truly a “cure-all” no “superbug”, as some are commonly called, is resistant to every mechanism of action. Infections may be hard to treat efficiently or find the antibiotic to best inactivate them, but this is no reason to declare a resistant colony incurable. The rest of this thesis will aim to summarize some of the biggest threats to people and how current research is attempting to quell these threats. With proper research and hospital techniques, the rate of hospital acquired and community acquired resistant bacterial infections can and will decrease, especially in underserved and impoverished communities.

TESTING: TIME AND COST

The most common way that resistant strains are tested for sensitivity to other antibiotics is via the Kirby-Bauer method. In this method, the suspect bacteria are plated on Mueller-Hinton agar and incubated for 24-28 hours. Disks containing certain antibiotics are put on the plates and the diameter of nongrowth around each disk, termed the “zone of inhibition”, is measured [27]. The zone of inhibition is roughly circular is produced when the bacteria around the antibiotic have been either killed or prevented from growing. The larger the diameter of the zone indicates that a low concentration of a certain antibiotic has diffused through the agar to inhibit a relatively large amount of bacteria. In this way, the disk diffusion test provides an easily observable and quantifiable test for antibiotic susceptibility. It is also relatively inexpensive to perform, making this the standard test for determining the most efficient antibiotic or antibiotics to use in treatment.

Another common procedure utilizes broth; well plates are inoculated with the bacteria causing the ailment and treated with serial dilutions of various antibiotics. This test is slightly more expensive, about $15, but allows for the testing of the antibiotics at differing concentrations [27]. Testing for effectiveness at varying concentrations is important because it helps healthcare professionals to prescribe the minimum concentration of antibiotic to treat with the maximum effectiveness and the smallest damage possible to normal flora in the vicinity of the infection. These factors cause broth microdilutions to be popular tests.

Other procedures include automated tests. The major advantage of automated instruments is the short time in which samples can be processed and results read. Siemens' MicroScan Walk Away, one of four FDA approved instruments of this class, can read and analyze numerous samples tested against different antibiotics in as little as 3.5 hours for gram-negative bacteria. For gram-positive or mixed samples, it can be accomplished in a minimum of 4.5 hours. The MicroScan Walk Away, like its counterparts, uses fluorescence reading to sense optical signals and detect reactions between an antibiotic and bacteria at much lower concentrations and much earlier stages than a manual culturing test [27]. This allows these machines to process every sample in under 24 hours, as opposed to about 72 hours for other testing methods. Yet, while the turnaround time is impressive, a quick online search will reveal price points for the MicroScan Walk Away falling between $12,000 and $15,000, making it effectively a non-option in many healthcare settings around the world. The challenge of healthcare, especially in areas with common antimicrobial resistant infections, is that finances must be used efficiently so that the best quality care can be given to the majority of patients.

SPECIFIC THREATS

Hospital-Acquired Infections

Hospital-acquired infections (HAI), also called nosocomial infections, are as the name indicates, infections that are contracted while a patient is at a healthcare facility. According to the Centers for Disease Control and Prevention (CDC), the United States has nearly 2 million infections of this variety causing 99,000 deaths annually. The two

major types are urinary tract infections (UTI) and surgical site infections (SSI) [12, 18]. If HAIs were considered their own category, they would rank sixth on a list of the top ten causes of death in the United States, just after strokes. Yet, since HAIs cover a broad variety of ailments, they often allude the public eye. Some HAIs cannot be prevented, regardless of how well the team of healthcare workers performs their duties. However, there are many instances where they are preventable. Sadly, patients still contract these infections, spend extra time in the hospital, and even pass away from them. This risk of fatality is amplified if the bacteria causing the infection presents itself with antimicrobial resistance. An understanding and a healthy fear of HAIs and antibacterial resistance in this context will undoubtedly save thousands of lives in the coming years.

While studying the nature of HAIs may not be quite as appealing as studying topics such as Alzheimer's disease, cancer or autism, the studies that have been done do show practices that can contribute to lowering of the risk of contracting infections. For example, studies found that MRSA infections in an American intensive care unit decreased by 25% when chlorhexidine was used for handwashing [11]. However, though preventative measures exist to stop the spread of HAIs caused by causative agents such as MRSA, HAI frequency will likely increase. This is due to the increasing intricacies of healthcare services [21]. Hospitals now have extensive therapies for patients with preexisting conditions such as diabetes, AIDs and other immunosuppressant diseases. These people already possess an increased risk of hosting bacterial infections and in the confines of a hospital the risk is often amplified. Therefore, despite proper hygiene, as medical care evolves to treat more immunodeficient patients, HAIs will continue to

plague patients unless proper prophylactic treatments are discovered. Antibiotic resistance will only exacerbate this issue.

Community-Acquired Infections

Community-acquired infections (CAI) are those infections that are transferred from the environment or other people. When it comes to acquiring infections that are resistant to antibiotics, the location plays a large role. Certain infections are more common in specific parts of the world. Tuberculosis and pneumonia are both diseases that are often CAIs and can be found in higher prevalence in places such as Russia and parts of Asia [15, 24]. *E. coli* infections are common in environments where the cleaning and preparation of food is less strictly regulated [10]. Generally, impoverished locales drive many CAIs.

But not all CAIs are infections like *E. coli,* which would cause American restaurants to shut down, or tuberculosis that would be a shocking diagnosis to a person who has not left the West. Methicillin-resistant *Staphylococcus aureus* (MRSA) is an example of a seriously threatening disease causative agent that can be spread as an HAI or via the community. Since it can be carried quietly and asymptomatically, MRSA can be spread person to person until an injury or otherwise immunocompromising procedure allows it to act and harm its host. Particular events are very conducive to the spread of MRSA and infectious agents like it. Wrestling, for example, has been shown to help MRSA spread from the skin of one person to another much more easily, as has been shown in American schools [3]. In many developing countries where the percentage of

the population that carries MRSA or similar bacteria is much higher similar circumstances will assuredly lead to higher transmission rates. The subsequent portion of this thesis will be dedicated to analyzing antibiotic resistant infections that pose a particularly serious threat to impoverished peoples.

Methicillin-Resistant *Staphylococcus Aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been kindly nicknamed a "super bug". This is because it is resistant to common antibiotics such as penicillin, oxacillin, methicillin and amoxicillin, and spread merely by contact. MRSA is the poster child for antibiotic resistance and, per the CDC, 2% of the population carries MRSA while 33% carry normal *S. aureus*. However, in developing countries, MRSA is overrepresented. One study has determined that around 50% of Egypt, Jordan and Cyprus' *Staph* carriers have MRSA [5]. The implications of this increase in prevalence are far-reaching. Hospitals that are often overwhelmed and underfunded, especially amid a refugee crisis, must battle to treat MRSA infections with unconventional antibiotics. Furthermore, because people from countries like Jordan, Egypt and the rest of the Middle East are emigrating all over the world, they are carrying a higher prevalence of MRSA with them. Going unchecked and unfought, the battle against MRSA could get much worse.

The current state of MRSA infections in the West is bettering. Multiple studies have indicated that cases and fatalities from invasive HA-MRSA infections in the United States have decreased by around 50% from the end of the 20th century to the beginning of

this decade [6, 36]. Yet, the threat is still very real and MRSA causes 80,000 infections and over 11,000 deaths annually in the United States [36]. Until there are no deaths from MRSA, the severity of MRSA infections in the West cannot be understated. Since the situation in the West, it is no surprise that in developing nations without the proper resources for adequate preventative methods the outlook would be even more concerning. Close quarters, poor sanitation, and lack of hygiene education and cleaning supplies all contribute to a worsening situation in these countries. In addition, generally impoverished countries like India, Algeria and countries in Central and South America have higher use of broad-spectrum antibiotics per the Center for Disease Dynamics Economics and Policy [37]. This same source indicates that many of these countries have high prevalence of MRSA. In India, where high amounts of broad-spectrum antibiotics are prescribed, 47% of the *Staph aureus* strains are considered to be MRSA. Venezuela has a 60% makeup of MRSA strains and a high prescription rate of broad-spectrum antibiotics [37]. There is a clear correlation between the prescription of broad-spectrum antimicrobial medications and the high incidence of MRSA and infectious agents like it.

Clostridium difficile

Clostridium difficile infections (CDIs) are caused gram-positive bacilli and are the number one hospital-acquired pathogen. They are also a serious threat in the realm of antibiotic resistance. In 94% of cases these infections are nosocomial, and patients undergoing antibiotic treatments possess an increased risk [1]. *C. difficile* is an opportunistic infection, meaning that it will not pose any serious threat to a person with a

healthy immune system and likely is already inhabiting their gut. However, if a person is immunocompromised they may be susceptible to infections by *C. difficile* causing diarrhea and bloating. Becoming immunocompromised may be the result of a preexisting condition (e.g. AIDS or a previous infection) or having significant portions of normal flora being wiped out by antibiotics. If the infection progresses and bacteria spills into the abdominal cavity, death can result.

The CDC reports that *C. difficile* is responsible for 250,000 infections and 14,000 deaths each year in the United States, which is four times higher than the rate ten years ago. Additionally, it is the cause of a financial burden of over 1 billion dollars annually in preventable costs [36]. Many *C. difficile* infections are unavoidable, because a person's immune system may be repressed out of necessity for treating a different infection with antibiotics that affect normal flora makeup. Then, provided the opportunity to grow, *C. difficile* will colonize the intestine and begin causing characteristic symptoms [4]. However, many infections can be prevented with proper healthcare techniques and antibiotic use. For example, treatments like colistin are used against specific gram-positive and almost all gram-negative infectious agents, making it a versatile broad-spectrum antibiotic. However, a byproduct of being so effective against such diverse harmful bacteria means that colistin also inhibits many species of microbiota that compose the normal flora. *C. difficile* is unaffected by colistin-like drugs and therefore is permitted to grow and become infectious [30]. The use of pathogen-specific narrow-spectrum antibiotics as determined by sensitivity testing could be helpful in preventing cases of *C. difficile* that arise by this pathway.

Once contracted, *C. difficile* is hard to treat because of inherent resistance to common broad and narrow-spectrum antibiotics such as cephalosporins, penicillins, carbapenems, aminoglycosides, and fluoroquinolones [13]. Additionally, effective treatments against gram-negative bacilli are sparse or may further damage the natural microbiota of a person. The need for an effective treatment is evident in the United States: there has not been a new antibiotic approved to treat CDIs in the last over twenty years [13]. Continuous treatment of *C. difficile* with broad-spectrum antibiotics, like vancomycin, is not a long-term solution as resistance to these may soon arise.

As is the case with many other antibiotic resistant pathogens, the havoc wreaked in low-income countries is hard to quantify because of a lack of studies and data. However, some studies have indicated that the reality is grim when it comes to CDIs contracted in the developing world. One study analyzed over 800 Swedes who were suffering from diarrhea. *C. difficile* was found to be the second largest pathogenic cause of the symptoms in the study and the majority of CDIs were found in participants who had recently traveled to low and middle-income countries [35]. While it is fallacious to assume that correlation is equivalent to causation, there are other indications that the part of the world that is less wealthy is subject to harsher effects of CDIs and antibiotic resistant strains.

Although generally not as precise as the studies conducted in the Western world, studies from Africa, Central America and developing Asia have shown that CDIs may be occurring at more alarming rates than in places like the United States [23]. Furthermore, these studies show that it is not only normal *C. difficile* causing the infections, but also

antibiotic resistant strains. One study in Peru identified and observed specific mutations in their replicating processes that conferred varying degrees of antibiotic resistance just like mutations that were observed in the bacteria that caused an outbreak in Quebec in 2004 that claimed the lives of over 1,000 people [23]. It makes sense though, that developing countries should show increased prevalence of *C. difficile* and exhibit resistant strains because of many factors. These factors generally boil down to two aspects; general hygiene and antibiotic use.

Whether it is because of a lack of supplies, inadequate health training or a myriad of other factors that change from nation to nation, low-income parts of the world generally do not exhibit the same standards of hygiene and sanitation as do the higher income parts of the world, especially in healthcare settings. Hospitals and health centers in war torn and poverty stricken areas are shown to less often use gowns and gloves while treating patients [23]. This makes it much easier for the passage of spores and infectious agents to occur. Increasingly unregulated use of broad-spectrum antibiotics, as opposed to regimented narrow-spectrum ones in certain situations, increases the probability of resistant strains to arise as well. Spore-killing cleaning supplies like bleach are not as readily available for household cleaning and, therefore, infections may spread quickly through whole villages. Statistics may not be available on the prevalence of antibiotic resistant strains or the numbers of deaths caused by them, but the developing world may very well be on the verge of an epidemic. Just as with other infectious agents, the key to preventing thousands of deaths each year by CDIs lies mainly in prevention. If the

number of cases of *C. difficile* can be reduced, so too then will the number of resultant deaths.

APPLICATION

Comparing MRSA prevalence and antibiotic usage around the world

Thus far this work has dealt with healthcare in rural and underserved settings in broad examples. Before closing it is appropriate to discuss a specific application of antibiotic usage and correlating issues of resistance. Three nations have been chosen to represent different demographics, and the rates of MRSA prevalence were compared with their general uses of antibiotics. The United States was chosen as a representative country of certain developed nations that have access to medical technologies that underdeveloped nations do not normally have, and prescribe large quantities of broad-spectrum antibiotics. Sweden has been chosen as a second representative country of the West as it has some of the lowest prescription rates of broad-spectrum antibiotics while simultaneously having some of the highest rates of narrow-spectrum antibiotic use.

In contrast to both countries, Syria has been studied as a country that has with a damage and overwhelmed healthcare system as a result of a civil war and political turmoil in recent years. The healthcare system in Syria is overwhelmed and undersupplied resulting in a higher proportion of treatments with broad-spectrum antibiotics. Syria has also been studied for two other important reasons, namely, that there is more data on Syria's healthcare than many other nations in similar circumstances and that the current political climate has caused a massive influx of refugees into

European countries, especially Sweden, providing a brand-new field of research. In studying these representative nations patterns should be evident between practices and prevalence of MRSA in the different populations. MRSA has been used as a representative pathogen because there is clearer data in regards to MRSA prevalence and sources than many other bacterial agents. Data on antibiotic use and prevalence has largely been obtained by the CDDEP, which synthesizes data from the CDC and equivalent organizations around the world.

The colonization rate of MRSA in the United States and Sweden is very similar, with most estimates placing it between 2-4% [37]. It is important to recognize that colonization rates are not the rate at which a population suffers from an infection, but rather what proportion of the population carries a specific agent, infectiously or non-infectiously. Syria's rate is much higher, 15-20%, and is descriptive of many countries with less access to proper sanitation and healthcare [26]. But the statistics become shocking when rates of infections are compared. There is no accurate data indicating rates of MRSA infections in Syria or its surrounding countries, but since there is a high rate of colonization, the incidence is assumed to be high. Sweden, conversely, has a very low prevalence for MRSA sitting at 0.3 infections per 10,000 people. Being that both the United States and Sweden are developed, well off countries with similar rates of colonization, one would expect the prevalence to be similar in the USA. But, the USA holds a rate of 2.6 cases per 10,000, roughly eight times the rate of Sweden [20]. Death rates are hard to determine due to simultaneous infections, but they tell a similar story.

How can two similar nations like Sweden and the USA present such drastically different rates of infection? It seems that the problem resides in the methods of treating bacterial infections that each nation employs. Per the CDDEP, Sweden prescribes 588 standard units of fluoroquinolones per 1,000 people in its population. The United States prescribes 1,430 standard units per 1,000, which puts the USA in the company of Egypt, Jordan, India and Brazil for similar rates; all of which are countries with overwhelmed healthcare systems [37]. The story is the same across the board for broad-spectrum prescriptions. The United States issues broad-spectrum penicillin derivatives (ampicillin, amoxicillin, carbenicillin and the like) at eight times the rate that Sweden does, adjusted for population [37]. Recall that MRSA, like *C. difficile* and many others, may colonize a person without causing any noticeable harm. It is when these infectious agents are permitted to grow beyond their normal capacities that a person becomes infected. Broad-spectrum antibiotics kill wide swaths of "good" and "bad" bacteria indiscriminately, and therefore, can be detrimental to normal flora. It should be expected then to see a correlation between high broad-spectrum prescription rates and high MRSA prevalence.

For a country like the United States, the key to defeating a pathogen like MRSA may be in taking cues from nations like Sweden. Not only does Sweden prescribe less broad-spectrums, they also issue higher rates of narrow-spectrum antibiotics. Sweden prescribes normal penicillin (effective against only gram-positive bacteria) and its narrow-spectrum derivatives at nearly ten times the rate that the USA does [37]. This implies that Swedes test for a pathogen's susceptibility to antibiotics more often than

their American counterparts. Perhaps imitating this practice can help reduce the burden, costs and harm caused by MRSA in the USA.

Sadly, the MRSA problem in Syria and many other countries is not easily solved. Infection and death rates may drop with more people willing to give of time and money to help Syrians and other impoverished and underserved peoples get the screening and treatment they require. However, if war, famine and poverty exist in a population, antibiotic resistance will surely be a plague to that group.

But the issue remains on what practices need to be employed so that countries like Sweden, who accept massive amounts of Syrians and other refugees, can keep rates of MRSA infections low. Sweden already has a shortage of doctors and cannot afford to have antibiotic resistant infections overrun the healthcare system. One possible solution may be the employment of a system for screening populations of people with higher risks of MRSA and prophylactically treating them. This system has been modeled by the Dutch, who have notoriously low rates of antibiotic resistant infections but also large refugee populations [26].

Per a recent study, the Dutch method, termed “Search and Destroy”, has greatly reduced costs associated with MRSA infections and prevented deaths. The method involves screening people who are members of groups with a high prevalence of MRSA (e.g. Syrian refugees) and preemptively isolating those who have tested positive. Those isolated receive prophylactic antibiotics and had their colonies repeatedly examined until they were considered uncontaminated [33]. The study concluded that the Search and Destroy method is cost and labor beneficial when used in populations with a prevalence

of 17% or greater [33]. Countries like Sweden may greatly benefit from employing a technique for screening, testing and prophylactically treating MRSA. Even the United States should be able to employ a similar strategy in its widely varied population to help cut down on healthcare costs, patient costs and death rates.

IMPORTANCE

So then, what is the reason for writing a thesis on the grim realities of antibiotic resistance and the tragedies they cause in developed and impoverished places? The first reason is to bring light to the issue. Antibiotic resistance, minus the misguided use of terms like "superbug", lacks the luster that other medical areas of interest has. Yet, the need for solutions is growing larger each day. A refugee crisis has driven large swaths of Middle Easterners and North Africans into Europe. Waves of immigrants have moved from Mexico to the US. The prevalence of certain bacterial infections and resistant strains will soon no longer be sequestered in the less developed parts of the world. MRSA, *C. difficile* and many others are being unnoticeably transferred over borders. To improve healthcare and end the suffering of these migrating peoples, the proper preventative measures and antibiotic resistance testing methods need to be commonplace in western hospitals.

However, just because the threat of antibiotic resistant infections is spreading does not mean that the threat in impoverished areas is going away. The other significant goal of this thesis is to awaken readers to the impressive need in these countries. Several services like Doctors Without Borders and Samaritan's Purse work to fight these

infections in developing countries. However, local hospitals and mission hospitals continually need supplies like gloves, gowns and cleaning supplies to curb the spread of infection. Donations to organizations like this can help to fight antibiotic resistance.

Additionally, organizations like Samaritan's Purse and Doctors Without Borders have a great need for committed workers that will work as healthcare professionals, office workers, administrators and scientists. To defeat the threat of infection more people will need to commit to the task. Furthermore, more time and money will need to be spent in labs working on viable testing methods for antibiotic resistance and infection diagnostics. Currently, rural and impoverished areas rely heavily on "dipstick" tests that can quickly test for the presence of an infection like *C. difficile* by using a patient's blood. While these tools can often be lifesaving by properly diagnosing a condition like a CDI before it causes sepsis and death, the tests are not always accurate. False positives or negatives can affect the course of treatment and lead to prolonged sickness or even fatalities. Even if the diagnosis is correct, these tests of the dipstick variety cannot replace lab tests in that they will be unable to determine if the bacteria present is a resistant strain or not. It will only be through diligence in the lab and on the field, that antibiotic resistance can be conquered in impoverished areas.

Finally, one purpose of this thesis has been to explain ways that exist already to prevent and treat antibiotic resistant infections. Hygiene and sanitation within healthcare settings is the major aspect of this. The good news about most antibiotic resistant infections being nosocomial is that the trend of increasing infections and fatalities can be reversed rather quickly with proper healthcare practices. Healthcare professionals need to

take the utmost care in their vocations by using gloves, proper handwashing techniques, effective sanitation and scrubs when needed to ensure that no infections will spread via the healthcare faculty. Just because a healthy doctor or nurse is not susceptible to a MRSA infection or CDI does not mean that the myriads of other immunocompromised and antibiotic treated patients are not.

For people who are developing symptoms associated with infections, it is important that proper sanitation measures are taken to prevent spreading the infection to others that the person may come in contact with. Per the CDC, bleach should be used to thoroughly clean bathrooms of infected persons if they have recently been treated at a hospital, been on antibiotics or visited a low-income area [36]. Bleach is often the only feasible way to kill endospores such as those produced by *C. difficile* that can remain on surfaces for days. Adequately cleaning and disinfecting can help to keep others healthy when one person is sick with a resistant infection.

At the core of this thesis is the notion that antibiotic resistance is not a thing that is unbeatable. There are no such things as “super bugs” that are completely resistant to every antibiotic in existence. The reality is that certain factors have driven antibiotic resistance to new heights. Broad-spectrum antibiotics like tetracyclines and ciproflaxin are not as effective in extinguishing certain ailments as their ancestor drugs were fifty years ago. Mutations have provided avenues for small pockets of bacteria to persist even through the harshest treatments with broad-spectrum antibiotics. This is not to say these antibiotics are useless; they are far from it and continue to save lives. But, it is time for medicine to adapt to the adaptations that bacterial infections have made. Pathogens are

adaptable and medical science must continue to be diligent to beat them. This has been the narrative since the dawn of the empirical age.

Vaccines have saved millions of lives since their inception. Yet, vaccines like the influenza immunization continually need to be made to adapt to the changing viral strains. Similarly, the advent of penicillin has saved millions of lives as well, but as bacteria that are affected less by the broad-spectrum penicillin-derivatives continue to multiply, broad-spectrum treatments such as carbopenems, ciproflaxin, doxycycline, and streptomycin should not be reverted to in a knee-jerk fashion. Testing methods must improve so that their costs will cheapen, and even hospitals in impoverished areas can one day afford to test the susceptibilities of bacterial strains against different antibiotics and receive the results within one day. Narrow-spectrum antibiotics need to be prescribed in synergy with broad-spectrum ones to completely inactivate infections. The only way to beat antimicrobial resistant infections, and to give developing countries a chance against them, is to make a concerted effort to increase the quality and lower the cost of prevention and care. It surely will take effort, but medical tasks just as hefty have been completed before.

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