The Threat of Antibiotic Resistance on Global Health

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A THESIS

Submitted to the Faculty of Graduate Studies

In Partial Fulfilment of the Requirements

For the Degree of

MASTER IN GLOBAL AFFAIRS

University of Prince Edward Island

(Charlottetown, Prince Edward Island, Canada)

Universidad Rey Juan Carlos

(Madrid, Spain)

August 6 2019

Submitted: June 15 2019

Accepted: July 12 2019

Published: August 6 2019

UNIVERSITY OF PRINCE EDWARD ISLAND
FACULTY OF GRADUATE STUDIES
UNIVERSIDAD REY JUAN CARLOS
FACULTY OF GRADUATE STUDIES

The undersigned certify that they have read and recommend to the Faculty of Graduate Studies at UPEI and URJC acceptance, a thesis entitled "THE THREAT OF ANTIBIOTIC RESISTANCE ON GLOBAL HEALTH" submitted by Emma McDermott in partial fulfillment of the requirements of the degree of MASTER IN GLOBAL AFFAIRS.

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Grade: [redacted]

Date: 06/08/2019

[redacted]

Abstract

One of the largest public health risks currently facing the world is antibiotic resistance. Antibiotic resistance is when bacteria develop a resistance against antibiotics that could previously have been used to treat them. The Organization for Economic Co-operation and Development (OECD) predicts that by 2050 an estimated 2.4 million deaths, in North America, Australia, and Europe alone, will be due to drug-resistant infections. Humans have become increasingly dependent on the success of antibiotics at treating bacterial infections, and therefore the looming threat of resistance is a critical global threat. This mini-thesis project is a part of UPEI's Master in Global Affairs program in partnership with the Universidad Rey Juan Carlos in Spain. It will use a multi-disciplinary approach to examine the threat antibiotic resistance poses on global health. Topics considered will include the causes of antibiotic resistance, the effects of widespread antibiotic resistance on social, economic, and political factors, and current global preventative actions/programs. Antibiotic resistance is a major emerging health risk, and the extent of its impact is underappreciated in the global community.

Acknowledgements

I would like to thank my supervisors, Dr. Christina Murray and Dr. James Moran, of the University of Prince Edward Island, for their time, expertise, and for teaching one of my favorite courses at UPEI. I would also like to thank Patti Taylor, Pharmacist at Murphy's Kensington Pharmacy, and the rest of the Murphy's Kensington Pharmacy team, for always being willing to discuss antibiotics, their role in the healthcare system, and suggest further resources. Further, I would like to thank the financial support of the W. Chester McLure Memorial Fellowship, the Roderick Stirling MacDonald Scholarship, the Florence Simmons Global Experience Scholarship, and the Canadian Federation of University Women Charlottetown Club Scholarship in Arts or Education for helping to fund my participation in this program. Finally, I would like to thank my family and friends for their support, with a special thank you to my classmates of the Master in Global Affairs program.

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1. Introduction

Since the commercialization of antibiotics in the mid 1900's, access to effective antibiotics has been taken for granted by people all over the world, but the increasing trend of antibiotic resistance threatens to take that all away. Antibiotic resistance is the term used to describe the phenomenon whereby pathogenic bacteria develop resistance to the antibiotics used to treat them. Due to widespread overuse and misuse of antibiotics, we are currently experiencing increasing rates of antibiotic resistance around the world (American Academy of Pediatrics, 2018; Aminov, 2010; Center for Disease Control and Prevention, 2018c; European Commission, n.d.-a; Government of Canada, 2018a; Klingeberg et al., 2018; World Health Organization, n.d.-d; World Health Organization, 2018a). Antibiotic resistance is "putting the achievements of modern medicine at risk" (World Health Organization, 2018a, para. 17), but the effects are expected to extend beyond global health, and impact the both the animal sector and global food security (World Health Organization, 2018a).

Increasing rates of resistance are rendering common antibiotics practically useless against infections they were once able to treat. Cases of 'super gonorrhea', a strain of extensively drug-resistant gonorrhea, have been reported in countries around the world, including France, Japan, Spain, Australia, and the UK (World Health Organization, n.d.-d). Bacteria have also begun to develop resistance towards colistin, a last-resort antibiotic, which has been referred to as "the only cannon left in the medical armoury to treat bacterial infections" (Agarwal et al., 2018, p. 78). Even worse, the World Health Organization reports that there is a there is a lack of new feasible antibiotics underdevelopment (World Health Organization, 2017b). If increasing rates of

resistance continue, in the United States alone, the death toll is expected to hit almost 30,000 antimicrobial-related deaths a year by 2050 (OECD, 2018). Further, based on the current trends, it has been projected that antimicrobial resistance will be responsible for 10 million deaths per year between 2015 and 2050, predominantly in Africa and Asia (European Commission, n.d.-a). The consequences of widespread global antibiotic resistance are so dire, some have gone as far as comparing our future to being transported back to a pre-antibiotic era (World Health Organization, 2018a).

Our time with effective antibiotics is slowly running out, and we need to take more urgent action to preserve this medical resource. To date, global responses have included international co-operation to create global task forces, mass education and awareness campaigns, worldwide surveillance systems, technology and research advancements, and the implementation of preventative measures, such as international guidelines for reserving last-resort antibiotics, but there is still opportunity for improvement. According to the World Health Organization, an effective solution to antibiotic resistance will require a cross-sectoral approach involving the co-operation of multiple sectors, like agriculture, fisheries, development, and economics, because each have their own role to play in decreasing rates of resistance (World Health Organization, 2013). Antibiotic resistance is proving to be a major emerging health risk, and the imminent danger needs to be more widely recognized in the global community.

2. A Brief History of Antibiotics

2.1 Pre-Antibiotic Era

Prior to the 20th century, a bacterial infection could make even a minor injury a death sentence. In 1900, at the turn of the century, the average life expectancy was a mere 47 years old (Adedeji, 2016; Centers for Disease Control and Prevention, 2017a). Before antibiotics, people attempted to cure infections through bloodletting, injecting bromine or mercury, and herbal remedies, none of which are as safe or proven as effective as antibiotics (Columbus, 2016). Luckily, in the early 1900's everything changed.

2.2 Discovery of Antibiotics

In the early 1900's, Paul Ehrlich came up with the idea of finding a 'magic bullet' that would selectively target pathogenic microorganisms and leave the host unharmed. For five years, Ehrlich and his team used a systematic screening program to synthesize hundreds of drugs in hopes of finding one to treat syphilis, an incurable and endemic sexually transmitted disease at the time. The 606th compound they tested, subsequently named Salvarsan, showed significant promise despite the side effects, like skin rashes and liver damage, and was prescribed the most frequently until it was replaced by penicillin (Aminov, 2010). Penicillin, discovered by Alexander Fleming in 1928, went on to become the first largely commercialized antibiotic in the 1940's, and started what has been named the 'antibiotic revolution' (Adedeji, 2016).

Since the discovery of antibiotics, the leading cause of death in the United States has switched from communicable diseases to non-communicable diseases, such as

cardiovascular diseases or cancer, and the average life expectancy has increased by slightly more than thirty years (Adedeji, 2016; Centers for Disease Control and Prevention, 2017a). The discovery of antibiotics was a world-altering moment in history, but increased rates of antibiotic resistance are threatening to send us back to a 'pre-antibiotic era', where what we currently consider to be minor infections could easily become life-threatening (World Health Organization, 2018a).

3. Antibiotic Resistance

3.1 What is Antibiotic Resistance?

Named one of the top 10 threats to global health in 2019 (World Health Organization, n.d.-c), antibiotic resistance is a natural process by which bacteria lose their susceptibility to antibiotics. This resistance enables bacteria to withstand the effects of antibiotics and allow them to continue to grow, and consequently continue to cause infection (Figure 1). Bacteria are gaining resistance fasters than humans are able to adapt, giving bacteria an upper hand in the evolutionary arms race. Bacteria, like most other living things, "will always look for ways to survive and resist new drugs. More and more, germs are sharing their resistance with one another, making it harder for us to keep up" (Centers for Disease Control and Prevention, 2018c, para. 8). Antibiotic resistance can be a natural trait in certain types of bacteria, can be acquired through genetic changes, or shared between bacteria, and gives mutated strains a competitive advantage for survival (Adedeji, 2016; Aminov, 2010; Government of Canada, 2018a). These antibiotic resistant bacteria can then spread throughout the global population like other communicable diseases through touching, coughing, sneezing, bodily fluids,

contaminated surfaces, animal contact, or contaminated food or water sources (Government of Canada, 2018a).

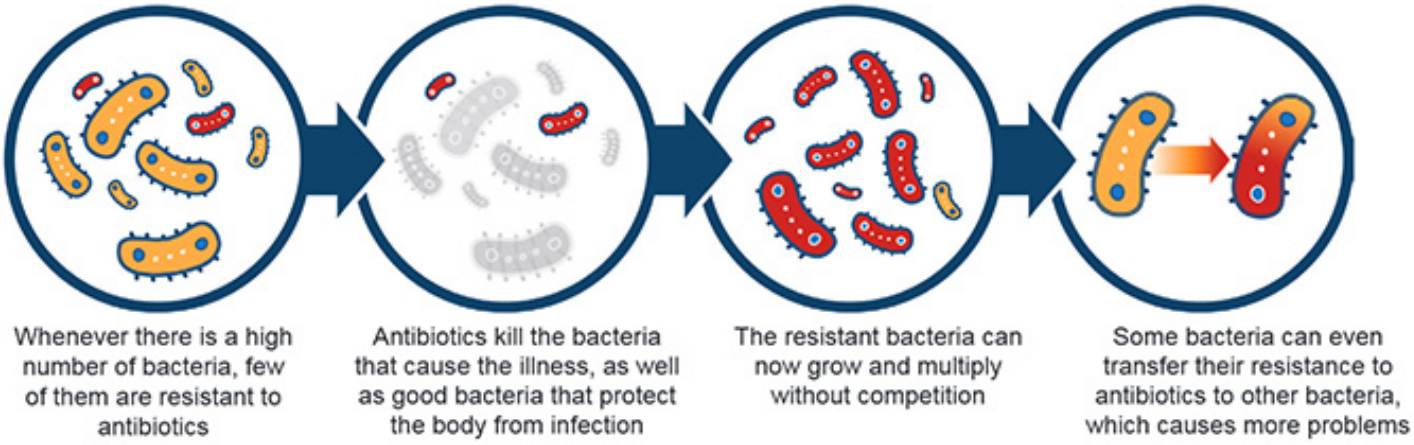

Figure 1. Visual representation of how antibiotic resistant bacterial infections can emerge and spread (Figure from Canadian Food Inspection Agency, 2017).

Bacteria are not the only pathogenic microorganisms that are developing resistance. Parasites, viruses, and fungi are also developing resistance to drugs that were once able to effectively treat them, which are more broadly referred to as 'antimicrobial resistance' (World Health Organization, n.d.-c). While this paper is primarily focusing on antibiotic resistance specifically, it is important to note that collectively, widespread antimicrobial resistance will put an even larger strain on global health, as antibiotic resistance alone has already been declared by the World Health Organization as "one of the biggest threats to global health, food security, and development today" (World Health Organization, 2018a, para. 1).

3.2 Causes of Increased Antibiotic Resistance

Antibiotic resistance may be a natural process, but our actions are drastically speeding up the process. Exposure to antibiotics increases the chance of those bacteria developing resistance (Goossens et al., 2005; Wistrand-Yuen et al., 2018). Klingeberg et al. found a significant association between patients with antibiotic resistant urinary tract infections (UTIs) and those who have previously taken antibiotics in the last two weeks. They also found resistance was significantly associated with previous occurrences of 2 or more UTIs in the past six months (Klingeberg et al., 2018), which since patients presumably received antibiotic treatment, further supports the fact that increased antibiotic use can lead to the development of antibiotic resistance. While this may be a natural process occurring over time, our current overuse and misuse of antibiotics is quickly accelerating the process, and creating this global health crisis. As said by Gerry Wright, Director of the Institute of Infectious Disease Research at McMaster University, “if we create a situation where we’re using antibiotics when we shouldn’t, then we create the selective pressures that increase the chances of the bacteria evolving into resistant organisms” (Ubelacker, 2018, para. 5). This relationship has been confirmed and reiterated by numerous organizations around the world (American Academy of Pediatrics, 2018; Canadian Food Inspection Agency, 2017; Center for Disease Control and Prevention, 2018c; Government of Canada, 2018a; European Commission, n.d.-a; World Health Organization, n.d.-d; World Health Organization, 2018a), showing the extent of the impact human actions have on antibiotic resistance.

Ever since the discovery of antibiotics, and even before, researchers have been aware of the existence of antibiotic resistance (Figure 2; Centers for Disease Control and Prevention, 2018c), but human actions are drastically accelerating the process and creating a global crisis. Antibiotics are only able to fight off bacterial infections, therefore, when antibiotics are taken unnecessarily, like in attempts to treat a viral cold or flu, it further contributes to the development of antibiotic resistance without providing an effective treatment. According to the Centers for Disease Control and Prevention, 269.4 million antibiotics were prescribed in the United States in 2015, which is equivalent to approximately 8.38 prescriptions for every 10 people (Centers for Disease Control and Prevention, 2015), and at least 1 in 3 antibiotic prescriptions in the United States are unnecessary, mostly because they were prescribed for viral infections (Centers for Disease Control and Prevention, 2016). Possible reasons for over prescribing could include time constraints, patient expectations, or fear of malpractice (Feller, 2019; Rodrigues et al., 2013), but none of these reasons make the risk of widespread antibiotic resistance worth it.

It isn’t just physicians who are responsible for increasing resistance by over prescribing antibiotics, but also those who misuse antibiotics. When antibiotics are prescribed, they typically include instructions indicating a specific number of doses per day and for a specific length of time. Unfortunately, people often start to feel better and stop taking their antibiotics before they finish the complete course. Even though you may feel better, some of the bacteria may not be completely killed off (Figure 1), resulting in a re-occurring infection, that due to previous antibiotic exposure, has an increased risk for being an antibiotic-resistant infection. This is why it is crucial to follow

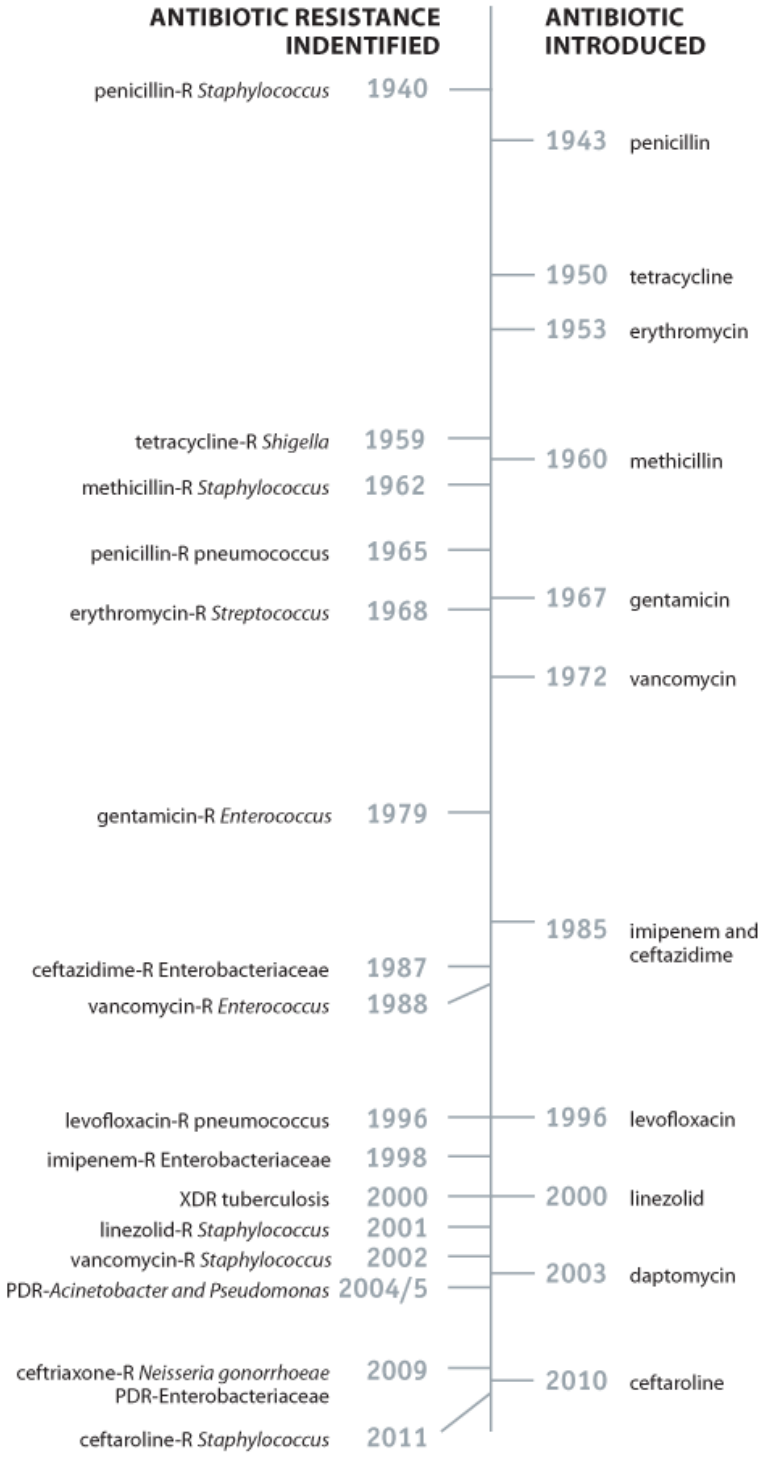

Figure 2. Timeline of the identification of antibiotic resistance compared to antibiotic development (Figure from Centers of Disease Control and Prevention, 2018c).

physicians' instructions and finish the entire course of antibiotics (Goldman, 2018; World Health Organization 2018a). Misuse doesn't just take place by people incorrectly following directions, but also when they take antibiotics without a prescription. For example, some pharmacies in Syria will sell patients antibiotics without a prescription from a physician (World Health Organization, 2017a), and in India, prescriptions are not commonly required in order to purchase antibiotics over the counter in open-air pharmaceutical markets (Kane & Sagan, 2018). This practice often results in people taking antibiotics when they aren't truly needed and further contributes to increasing rates of antibiotic resistance.

Even though some countries have regulations in place that require prescriptions to receive antibiotics, a similar trend is seen when patients save antibiotics from previous infections, to use for later self-diagnosed illnesses or to share with others. A new study shockingly found that in the United States alone, 48.2% of the surveyed parents said they would save leftover antibiotics instead of disposing of them. Further, of those that saved antibiotics, 73% admitted to giving those antibiotics to someone else without a prescription (American Academy of Pediatrics, 2018; Goldman, 2018). This practice, called prescription diversion, invokes concerns about incorrect dosages, medication interactions, and other issues surrounding taking medications not prescribed specifically for you, in addition to it's contributions to antibiotic resistance (American Academy of Pediatrics, 2018). For these reasons, antibiotics should only ever be taken when prescribed by a certified health professional, which in turn would also help prevent against antibiotic resistance developing further.

Overuse and misuse of antibiotics doesn't just take place within the healthcare system. The agriculture industry is a huge contributor to the spread of antibiotic resistance, as shown in Figure 3. While "antibiotics are an essential element of animal health … the increasing use of antibiotics in subtherapeutic concentrations for growth promotion and disease prevention (as a substitute for hygiene) is placing substantial selection pressure for resistance to evolve" (Laxminarayan et al., 2016, p. 168).

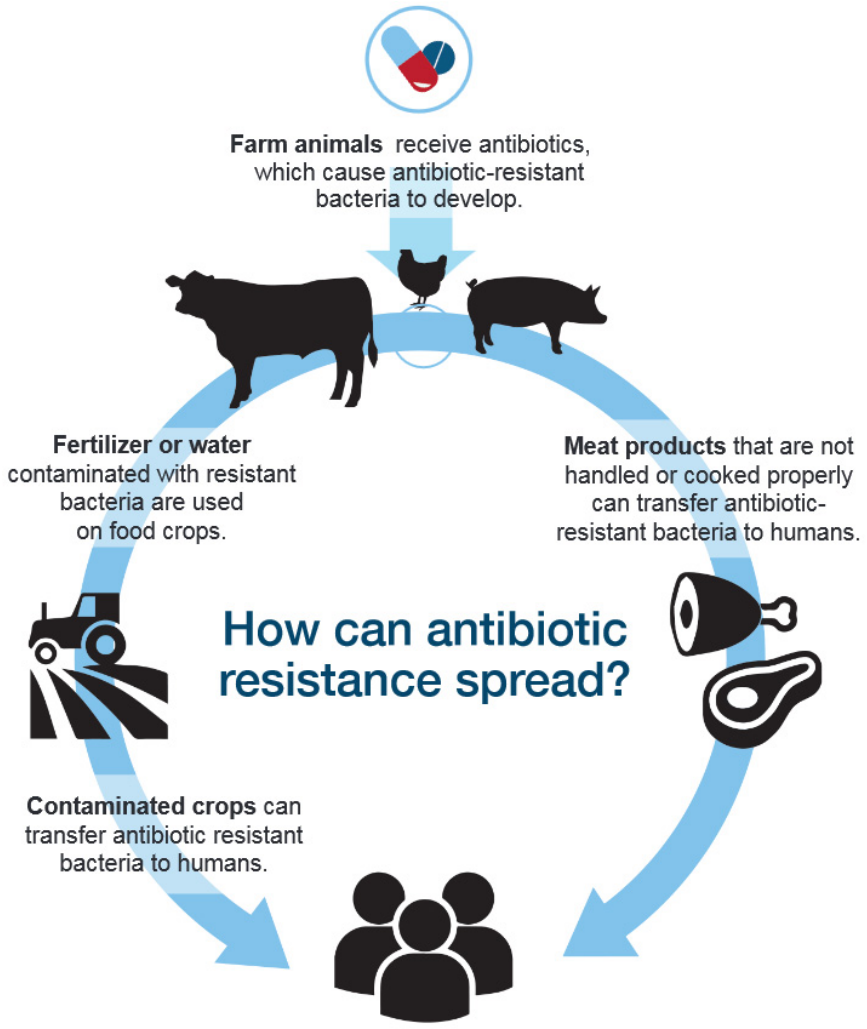

Figure 3. How antibiotic use in agriculture can contribute to the spread of antibiotic resistance (Figure from Canadian Food Inspection Agency, 2017).

In 2015, the total amount of antimicrobials distributed and sold in Canada for use in humans, animals, and crops totalled about 1.8 million kilograms, where 1.6 times more antimicrobials (82%) were used in animals compared to humans (17%), and the remaining were used for pets or crops (Canadian Food Inspection Agency, 2017). In the United States, up to 80% of the total annual consumption of antibiotics comes from livestock, and global consumption due to livestock is expected to increase by two-thirds by 2030 (European Commission, n.d.-a). During a global conference, entitled *Antibiotic resistance – a threat to global health security and the case for action,* Dr. Madeleine de Roasas Valera, the Undersecretary of the Department of Health in the Philippines, said "it is important to highlight that the misuse of antibiotics occurs not only in the treatment of humans but also in that of animals, and the need to improve the monitoring of the use of antibiotics in all relevant sectors" (World Health Organization, 2013, para. 11).

Additionally, another cause for the spread of antibiotic resistance is simply poor infection control strategies, such as lack of safe water, poor hygiene or poor sanitation services. These are all major risk factors for infectious diseases and antibiotic resistance bacterial infections are no exception. According to the World Health Organization, the uncontrolled release and disposal of wastes that have been exposed to antibiotics, like human or animal waste, can lead to traces and residues of antibiotic resistant bacteria being found in landfills, water, soil, or water-dependant food, such as seafood. These bacteria can continue to survive in these environments for extended periods of time, increasing the chances that they can re-infect (World Health Organization, 2015). Therefore, improving global infection control strategies will help to

reduce the spread of antibiotic resistance, along with the spread of countless other infectious diseases at the same time.

Antibiotics are an important tool in the healthcare setting to fight off bacterial infections, but their overuse and misuse is significantly accelerating the progression of antibiotic resistance and preventing antibiotics from protecting us when we need them most. The over-prescription and overuse of antibiotics are causing increasing the rates of antibiotic resistance around the world, specifically in countries without standard treatment guidelines (World Health Organization, 2018a). The rates of antibiotic resistance are being increasingly accelerated by human actions, which are proving to be a critical emerging health risk.

3.3 Emerging Health Risk

The risk of increasing global antibiotic resistance poses an imminent threat to global health. Antibiotics have widely been considered a “cornerstone of modern medicine” (World Health Organization, n.d.-b, para. 2), and the protection they offer has widely been taken for granted. The Organization for Economic Co-operation and Development (OECD) estimates that within the next 30 years, 2.4 million deaths in developed countries will be due to antibiotic resistance (OECD, 2018; Ubelacker, 2018) and the World Health Organization warns that we are heading for a post-antibiotic era (World Health Organization, 2018a). The emerging trend of increasing antibiotic resistance poses an imminent threat to global health.

The spread of antibiotic resistance is not limited by national borders. At the start of 2018, the World Health Organization issued a news release warning of high levels of

antibiotic resistant bacterial infections around the globe, in at least 500,000 people across 22 different countries (World Health Organization, 2018b). Additionally, they found that bacteria with resistance to at least one commonly used antibiotic varied from 0 to 82% between the different countries (World Health Organization, 2018b), showing that antibiotic resistance is currently more prevalent in some countries than others. These trends were reiterated by a recent OECD report that has forecasted that countries in Southern Europe, such as Italy, Greece, and Portugal, will be experiencing the highest mortality rates due to antimicrobial resistance. Additionally, it was found that countries such as Turkey, Korea, and Greece, currently experienced rates of antibiotic resistance seven times higher than that in Iceland, Netherlands, and Norway, and rates of resistance in Brazil, Indonesia, and Russia are already between 40-60% of all infections. Regardless of these regional differences, the OECD reports that collectively across all OECD countries there was an increase in resistance proportions of 3% between 2005-2015, (OECD, 2018) a trend that speaks to the increasingly imminent nature of this threat.

When routinely used antibiotics, often called first-line antibiotics, become less effective against their respective bacteria infections, healthcare providers are forced to use more potent second- and third-line options. As shown in Figure 4, the prescription of second-line antibiotics is already becoming more prominent, especially in the countries that have higher overall prescription rates. A recent study by Agarwal et al. (2018) examined antibiotic-resistant cases of ventilator associated pneumonia (VAP) in hopes to identify the different bacteria causing VAP and which were developing resistance to colistin. This research was important because carbapenems, the class of

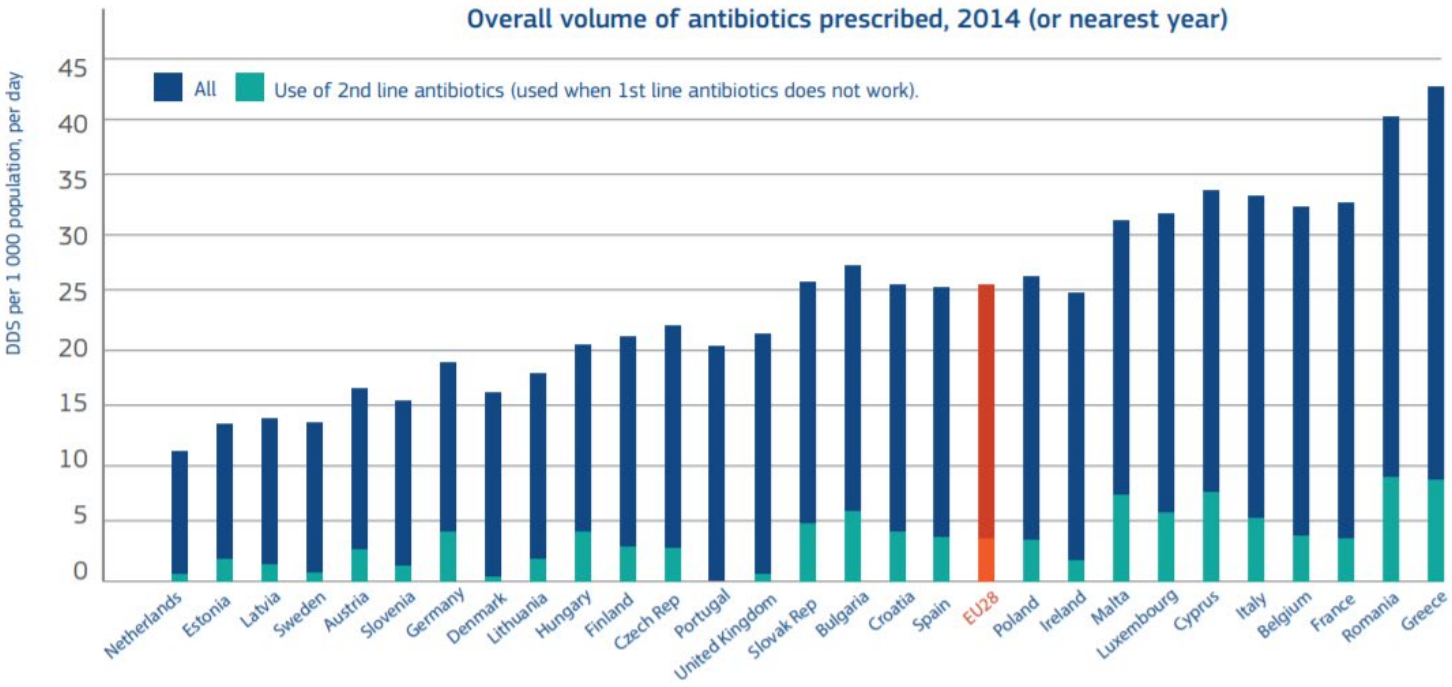

Figure 4. Overall volume of antibiotics prescribed in 2014 throughout the European Union, where the dark blue represents the total volume of antibiotics prescribed, and the green represents the portion of 2nd line antibiotics prescribed. The European Union average is shown in orange (Figure from European Commission, n.d.-a).

antibiotics that were traditionally used to treat VAP, are no longer effective due to increased resistance. In turn, healthcare providers have had to turn to colistin, which is one of the last-resort antibiotics that are effective against carbapenem-resistant gram-negative bacteria, in order to treat these infections. Unfortunately, Argarwal et al. were able to identify that 19 of the VAP-causing organisms had already begun to develop resistance to colistin to some degree (Agarwal et al., 2018), which brings the concern that we are already beginning to lose our last line of defense against bacterial infections. Additionally, last-resort antibiotics can often come with a hefty price tag and numerous side effects (Centers of Disease Control and Prevention, 2018c), which is

most likely why they were used as the last line of defense in the first place. For example, aminoglycosides, which are potent last-resort antibiotic against gram-negative bacteria, are considered for use in only the most serious cases due to the high risk of hearing loss and kidney damage (Gonzalez & Spencer, 1998; O'Sullivan et al., 2017; Prayle et al., 2010; Selimoglu, 2007). The OECD has reported the resistance to second- and third-line antibiotics is expected to rise across OECD countries by 70% in the next 10 years in comparison to the rates in 2005, and specifically within the European Union, resistance to last-resort, or third-line antibiotics is expected to double (OECD, 2018).

Unfortunately, since the end of the golden era of antibiotic discovery in the 1970s, no new classes of antibiotics have been discovered (Aminov, 2010). In 2017, the World Health Organization released a report confirming that there was a lack of new antibiotics in development, and of the few that were, most were simply modification of current antibiotics, which would only be a short-term solution to the mounting threat of antibiotic resistance (World Health Organization 2017b; 2017c). Therefore, it is critically important to preserve the last effective antibiotics we have left.

The clock is slowly ticking away towards a future without antibiotics. Data has shown that between 2010-2014, Europe has almost doubled their use of antibiotics used to treat multidrug-resistant bacterial infections (European Commission, n.d.-a), and it has been estimated that, around the world, only about half of antibiotics are used properly (European Commission, n.d.-a), which results in increasing rates of antibiotic resistance. Due to increase rates of travel, antibiotic resistance has the potential to easily travel across the global, and will require an international response in order to prevent the loss of a lifesaving resource (World Health Organization, 2018a)

4. Social, Economic, and Political Implications

The effects of antibiotic resistance will greatly affect the healthcare industry. Antibiotics are required to decrease the risk of infections during chemotherapy, caesarean sections, joint replacements, and organ transplants. Antibiotics are also critical for the treatment of premature newborns in intensive care or for those with chronic diseases, such as diabetes, asthma, or rheumatoid arthritis (Centers for Disease Control and Prevention, 2018-c; Canadian Food Inspection Agency, 2017; Prestinaci et al., 2015; World Health Organization, 2018a). Without antibiotics, it will be impossible to preform these routine procedures and treatments, or at least make them extremely risky (Ubelacker, 2018). Antibiotic resistant infections are already one of the main morbidity and mortality factors for patients receiving these procedures and treatments (Prestinaci et al., 2015), and increased rates are going to further extend the duration of illnesses and increase mortality rates and increase the risk of death (Canadian Food Inspection Agency, 2017; World Health Organization, 2018a).

Antibiotic resistance is going to put increased pressure on our already strained healthcare system. When infections are harder to prevent and treat, the length of hospital stays will increase. This will not only increase medical costs, but also increase the risk of further complications and even death. “A growing list of infections – such as pneumonia, tuberculosis, blood poisoning, gonorrhoea, and foodborne diseases – are becoming harder, and sometimes impossible, to treat as antibiotics become less effective” (World Health Organization, 2018a, para. 6). For example, in Thailand, Pumart et al. estimated that antibiotic resistance was responsible for an additional 3.2 million days in hospital per year (Pumart et al., 2012; Centers for Disease Control and

Prevention, 2017b), which not only incurs extras costs and depletes resources, but also takes a hospital bed away from another patient who may need it. Additionally, widespread antibiotic resistance is also going to increase the total volume of appointments required with healthcare providers, a commodity which is already scarce. Further, people with chronic illnesses, along with children and the elderly, will be at a higher risk for developing antibiotic resistant infections (Centers for Disease Control and Prevention, 2018c; OECD, 2018), putting these already vulnerable populations at an even further risk. More persistent bacterial infections are also going to require more resources in addition to the economic burden on families and societies.

Antibiotic resistance, with an expected death toll of 10 million worldwide (Ubelacker, 2018), currently costs about 3.5 billion US dollars a year (OECD, 2018) and has been predicted to cost the global economy upward of $100 trillion US by 2050 (Ubelacker, 2018). The European Union estimates that antimicrobial resistance is responsible for 33,000 deaths in the EU each year, and annually costs the EU approximately 1.5 billion euros due to the additional healthcare costs and loss of productivity (European Commission, n.d.-b). If there is still an option for an effective last-resort antibiotic, they are typically more expensive than their first-line counterparts, less accessible especially to those in rural or developing areas, and come with increasingly risky side effects (Centers for Disease Control and Prevention, 2013; World Health Organization, 2018a). The medical costs to treat someone with an antibiotic resistance infection are estimated to range from $18,588 to $29,069 in the United States, which in addition to loss of wages and emotional stress for their loved one, will take a toll on families and communities (Ventola, 2015), Antibiotic resistance is already

a social and economic burden for families and local and global societies, which will only continue to increase as antibiotic resistance increases.

Highly resistant infections are already starting to take their toll. For example, tuberculosis, caused by a bacterium called *Mycobacterium tuberculosis*, currently has mortality rates of about 1.6 million people a year. Yet in 2017, it was found that approximately 600,000 cases of tuberculosis were already exhibiting resistance to rifampicin, the most effective first-line antibiotic, worldwide. Additionally, 82% of those cases were multi-drug resistant cases, meaning the bacterium was resistant to multiple other antibiotics in addition to rifampicin (World Health Organization, n.d.-c). Similarly, strains of drug-resistant *Neisseria gonorrhoeae*, the bacteria responsible for the sexually transmitted infection (STI) gonorrhea, are already exhibiting a high level of resistance to many current recommended treatments, including ceftriaxone, azithromycin, penicillin, sulphonamides, tetracycline, fluoroquinolones, and macrolides, leaving very few, if any, options for antibiotic treatment. As the second most common bacterial STI, gonorrhea already has a high morbidity rate and large global economic consequences (World Health Organization, n.d.-d). STIs can lead to further complications such a infertility, and research suggests there may also be an increased risk of contracting HIV in individuals with HIV (Ward & Rönn, 2010). Therefore, the consequences of increasing rates of resistance in gonorrhea alone could in turn cause a five-fold increase of HIV transmission, increased infertility rates, and increased maternal death, which all come with additional health and financial burdens, in addition to the risk of a worldwide epidemic (World Health Organization, n.d.-d). The effects of antibiotic

resistance will take a tremendous toll on our healthcare system, but the effects will not be isolated to just this sector.

Antibiotic resistance also poses a threat to global food security. The World Health Organization estimates, that in some countries, the animal sector consumes about 80% of the total consumption of antibiotics (World Health Organization, 2017d), including the United States (European Commission, n.d.-a). Most are not used to cure infection, but simply to promote growth (World Health Organization, 2017d). According to Dr. Kazuaki Miyagishima, Director of the Department of Food Safety and Zoonoses at the World Health Organization, “the volume of antibiotics used in animals is continuing to increase worldwide, driven by a growing demand for foods of animal origin, often produced through intensive animal husbandry” (World Health Organization, 2017d, para. 8). While the use of antibiotics in agriculture is contributing to increasing rates of resistance, the complete loss of antibiotics would severely harm today’s agriculture industry, and in turn threatening global food security. Without any effective antibiotics, which would be the case with widespread antibiotic resistance, farmers would have no resources available to treat infectious diseases in their animals, which could easily spread to infect their entire herd. This could result in shortages of food, or on the contrary, cause humans to eat infected meat, and allow for the spread of these infectious diseases throughout the food chain.

Political affairs will be greatly impacted as rates of antibiotic resistance increase around the world. Mass disease outbreaks threaten international trade, national security, and public peace of mind. Take the early 2000’s outbreak of SARS (Severe Acute Respiratory Syndrome), for example. SARS was first spotted in southern China

and spread to 37 countries within a matter of weeks. People were scared. There was a rapidly increasing number of cases and experts did not yet have the answers to make the public feel secure. Very little was known about the emerging disease and how it was transmitted, and there was no vaccine available. Experts were predicting that SARS would have a similar death toll to the 1918 influenza pandemic, which was responsible for the deaths of about 40 million people, and the widescale conflicting and uncertain media coverage created a global state of panic. People were scared of going into public for the risk of infection, and the outbreak negatively impacted numerous sectors including the travel industry, global trade, and food security. Fear of the unknown disease that was rapidly spreading across the globe created public anxiety, international tension, reduced confidence in public health, and cost the global macro economy anywhere between $30-100 billion US. Luckily, SARS did not leave the devastating health impact it was initially expected to (Smith, 2006), but that may not be the case with the next health outbreak.

Antibiotic resistance has already been spotted at high levels in at least 500,000 people across 22 different countries (World Health Organization, 2018b), and with increased global travel, medical tourism, international food production, and global trade (Canadian Food Inspection Agency, 2017), national borders will not be able to contain the threat of antibiotic resistance. When there is a widespread public sense of uncertainty and loss of faith in government's ability to protect, like as in the case of SARS, political instability can soon follow. Epidemics are unpredictable and their management is a highly political event, in order to reassure the public and efficiently contain the threat (World Health Organization, 2018c). Without any effective antibiotics,

one multi-drug resistant bacteria could change everything. Director-General of the World Health Organization Dr. Tedros Adhanom Ghebreyesus agrees, saying “a lack of effective antibiotics is as serious a security threat as a sudden and deadly disease outbreak” (World Health Organization, 2017d, para. 4). Antibiotic resistance will continue to spread, putting the entire global population at risk, and introduces the possibility of international political instability and a state of global panic.

5. Current Actions, Limitations, and Areas for Improvement

5.1 Global Response

Dr. Tedros Adhanom Ghebreyesus identified that “strong, sustained action across all sectors is vital if we are to turn back the tide of antimicrobial resistance and keep the world safe" (World Health Organization, 2017d, para. 4), and the looming threat of antimicrobial resistance is slowly starting to be recognized by the global community. In December 2014, 30 countries attended a high-level meeting to address concerns of increasing global antimicrobial resistance (World Health Organization, 2014), and in 2016 antimicrobial resistance became the fourth ever health topic to be discussed in the history of the United Nations General Assembly (World Health Organization, 2016).

At the World Health Assembly in 2015, a global action plan on antimicrobial resistance was created to “ensure the prevention and treatment of infectious diseases with safe and effective medicines” (World Health Organization, 2018a, para. 19). The five main goals described in this plan included; increasing awareness and understanding, strengthening surveillance and supporting research, optimizing use,

reducing the overall incidence of infections, and promising sustainable investment in the fight against antimicrobial resistance (World Health Organization, 2018a). The World Health Organization has also created a Global Task Force to help coordinate, collaborate, and assist countries with developing their own individual action programs aimed at reducing rate of antibiotic resistance (World Health Organization, 2013).

The World Health Organization is taking a primary role in the fight against antibiotic resistance, but they are not alone. Antibiotic resistance is starting to be recognized by the international community. The United Nations Secretary-General has created an Interagency Coordination Group on Antimicrobial Resistance, co-chaired with the World Health Organization Director General, which brings together different UN agencies, international organizations, and experts, in order to improve coordination and take more effective action against this increasing threat (World Health Organization, 2018a). Regional agreements are also emerging, as in 2009, an agreement between Canada, the European Union, Norway, and the United States created the Transatlantic Taskforce on Antimicrobial Resistance (Centers for Disease Control and Prevention, 2018b).

The European Union has also begun taking actions. In 2006, the European Union banned antibiotics in agriculture for growth promotion, and in June 2017 created the One Health Action Plan against Antimicrobial Resistance, with the three key objectives of “making the EU a best practice region, boosting research, development and innovation, and shaping the global agenda” (European Commission, n.d-b, para. 3). In addition, the Organization for Economic Co-operation and Development, the G7, and G20 have all joined in in the fight against antibiotic resistance (OECD, n.d.), and other

countries are following suit. From creating national policies to antimicrobial stewardship programs (Bordier, 2018; Canadian Food Inspection Agency, 2017; Centers for Disease Control and Prevention, 2018a; Government of Canada, 2018b; National Collaborating Centre for Infectious Diseases, 2017; Public Health Ontario, 2018) the global community is finally starting to help aid in the urgent fight against increasing rates of antimicrobial resistance.

Unfortunately, this still isn't enough. Programs to prevent and control antimicrobial resistance are present in less than 40% of the world's countries, and only a quarter have adopted national policies regarding resistance (European Commission, n.d.-a). At the start of 2019, the United States released a Worldwide Threat Assessment, describing threats to national security, which only mentions drug resistance when specifically talking about the threat of Malaria, and fails to mention antibiotic resistance in its entirety (Coats, 2019). It would have been easy to create a drug resistance section to address malaria and all other drug-resistant infections, but instead the United States chose to underestimate the threat antibiotic resistance poses to society by failing to include it in the assessment. According to the World Health Organization, "increased global cooperation and partnership is needed to identify and promote incentives needed to develop effective business models for development of new therapeutics, diagnostics and antibiotics, including ways to control the distribution, use and misuse of antibiotics" (World Health Organization, 2013, para. 6). A multi-sectoral international response is the only way to help prevent the rates of antibiotic resistance rising any further, or at least to buy us time to find other alternatives.

5.2 Increasing Awareness Through Educational Campaigns

One way to help reduce the increasing risk of antibiotic resistance is to educate health professionals and the general public about the causes and consequences. World Antibiotic Awareness Week, is one of the 8 official global health campaigns, and the only week-long campaign, organized by the World Health Organization (World Health Organization, n.d.-a). Every November since 2015, World Antibiotic Awareness Week "aims to increase global awareness of antibiotic resistance and to encourage best practices among the general public, health workers and policy makers to avoid the further emergence and spread of antibiotic resistance. (World Health Organization, n.d.-b, para. 1).

Similar local and national campaigns have emerged, like the Canadian community education program *Do Bugs Need Drugs?* (Alberta Health Services and the British Columbia Centre for Disease Control, 2013), but individuals are also taking action. For example, three Syrian pharmacists, who had recently learned about the dangers of antibiotic resistance, were concerned with how pharmaceutical practices in Syria may be contributing to the problem. In Syria, many pharmacies will sell antibiotics to patients without needing a prescription from a physician, resulting in the misuse and overuse of these valuable medications. Hanaya Raad, Sarah Safadi, and Nour Allahham worked with the Syrian Pharmacists' Association to address their concerns and develop "an awareness campaign targeting antibiotic-prescribing habits among pharmacists and antibiotic misuse in the population" (World Health Organization, 2017a, para. 5). Through this educational campaign, the trio were able to reach over 400 pharmacies within the capital city of Damascus, in addition to members of the general

public and pharmacy students. They hope to expand their campaign into more regions across the country (World Health Organization, 2017a). With the help of these campaigns more people are learning about the dangers of antibiotic resistance, and what they can do to help stop it.

Despite the best efforts of these campaigns, a large majority of the global population is still not aware of the imminent danger of antibiotic resistance. One survey found that out of 1,500 Canadian adults, 44% thought antibiotic resistance was “more concern for developing countries” than their own (Ubelacker, 2018, para. 12). Another found that while 92% of the Americans surveyed recognized that the unnecessary use of antibiotics contributed to increasing antibiotics resistance, over 40% of respondents still believed that antibiotics were an appropriate treatment for classic viral infections, like a runny nose or sore throat (Carter et al., 2016). Even more worrisome, only 30% agreed that antibiotic resistance was a problem (Carter et al., 2016). Similarly alarming results were found in another study in Japan. Kamata et al. found that 80% of the 3,390 participants were not aware that antibiotics would not work against viral colds or flus, and 23.6% admitted to having pre-maturely stopped or adjusted the dose by themselves (2018). Likewise in London, a study by Mason et al. (2018) found that educational campaigns did not increase public knowledge about antibiotic resistance, and “exposure to an antibiotic campaign made no significant impact on knowledge about concordance/adherence” (Mason et al., 2018, para. 3). These results show that more education is needed to adequately inform the global public of the dangers of antibiotic resistance, and more importantly, how they can help prevent it.

5.3 Implementation of Surveillance Systems

The World Health Organization has created The Global Antimicrobial Resistance Surveillance System, commonly referred to as GLASS, to help monitor rates of antimicrobial resistance, and control interventions, around the globe. According to Dr. Marc Sprenger, the director of the World Health Organization's Antimicrobial Resistance Secretariat, "some of the world's most common – and potentially most dangerous – infections are proving drug-resistant. And most worrying of all, pathogens don't respect national borders. That's why WHO is encouraging all countries to set up good surveillance systems for detecting drug resistance that can provide data to this global system" (World Health Organization, 2018b, para. 6). The GLASS system collects, analyses, and shares their data to inform decision makers and support action at the local, national, and international level (World Health Organization, 2018a), and based on the design of previous systems is expected to help "estimate disease burden, plan diagnostic and treatment services, monitor the effectiveness of control interventions, and design effective treatment regimens to address and prevent future resistance" (World Health Organization, 2018b, para. 11).

One of the major limitations of our current surveillance systems for antibiotic resistance is that they are still emerging, and it will take years before they are established. As of January 2018, 52 countries were enrolled in the GLASS program, and the World Health organization was actively helping additional countries create their own surveillance systems so they can further contribute to GLASS (World Health Organization 2018b). This is an impressive start, but considering almost half of the participating countries are considered high-income, and only seven are considered low-

income countries, this creates concerns surrounding the validity of their data. The average rates and values reported by GLASS will be majorly based on only one income class, and therefore may not truly represent the universal global values (World Health Organization, 2018b). Further, the World Health Organization recognizes that surveillance of antibiotic resistance is still developing and that the first GLASS report varies “widely in quality and completeness” (World Health Organization, 2018b, para. 9), since the program relies on each countries individual surveillance systems, which are all developing at different rates, if they exist at all. However, they do stress the importance of further developing to surveillance allow us to “anticipate and tackle one of the biggest threats to global public health (World Health Organization, 2018b, para. 8). While the World Health Organization already has established surveillance systems in place for drug-resistance in tuberculosis, with contributions from 188 countries in 24 years, HIV, with over 50 contributing countries in 12 years, and malaria, which all produce reliable and meaningful data (World Health Organization, 2018b), they all took personnel, funds, infrastructure, and most importantly, time to establish. The threat of antibiotic resistance is not going to wait.

Another possible limitation to surveillance systems is that they may be overestimating the current levels of antibiotic resistance, and therefore underestimating the effectiveness of the few antibiotics we have left. For example, a study by Klingeberg et al. found that the actual rates of antibiotic resistance in community-acquired uncomplicated urinary tract infections (UTIs) were significantly lower than the rates reflected in the Antimicrobial Resistance Surveillance System (ARS) data. This was most likely due to the fact that urine culture testing is typically only completed, and

therefore recorded in ARS, in complicated or recurrent cases. Overestimation of the rates of antibiotic resistance in surveillance data may lead to healthcare providers resorting to prescribing reserved antibiotics more frequently, because the data makes it look like there are less feasible options, instead of reserving them for when we need them most (Klingeberg et al. 2018).

5.4 Technology and Antibiotic Resistance

Improvements in technology are aiding the fight against antibiotic resistance. A local example is the addition of a new MALDI-TOF machine at the Queen Elizabeth Hospital (QEH) in Charlottetown, Prince Edward Island. The MALDI-TOF machine, standing for ‘matrix-assisted laser desorption ionization time-of-flight’ mass spectrometry, allows for physicians to complete rapid on-site testing to identify infections, including heart, blood, lung, urinary tract, and other severe organ infections. Results are now available within seconds, whereas previously patients had to wait 24 hours for these results. Health practitioners can then use the new BD Phoenix antimicrobial susceptibility machine to determine the best antibiotic to treat the specific infection. The QEH Provincial Laboratory typically runs 1.7 million tests per year, so these machines will also help reduce the operation costs. While costly upfront, a test that once cost more than $5 each is now costing less than 50 cents, due to the reduction in time and labour required to run them. Dr. Greg German, the QEH medical microbiologist and infectious disease consultants, also talks about how this machine is improving patient care, because the reduced wait time for tests means that patients will receive treatment sooner and therefore start to recover faster (QEH Foundation, 2019; Russell, 2019). Investing in the development of other rapid point-of-care tests and

technology will help reliably confirm doctors diagnoses and inform them of whether or not antibiotics are a proper treatment (Llor and Bjerrum, 2014). Technological advances are making it easier to identify infections, determine the best plan of treatment and whether antibiotics are actually required to treat this infection, and conserve the effectiveness of antibiotics.

While technology may be providing solutions to antibiotic resistance, it may also be contributing to its development. Telemedicine is a new technology service that allows patients to audio-video conference with physicians through their electronic devices. A recent study examining telemedicine found that children were much more likely to receive antibiotics during telemedicine visits, compared to urgent care clinics or doctor's offices. Over half of the telemedicine appointments received prescriptions for antibiotics, compared to only 32% in doctors' offices and "a higher proportion of those prescriptions disregarded medical guidelines" (The Associated Press, 2019, para. 2), with only 59% of appointments following the clinical guidelines for antibiotic prescriptions. Researchers concluded that telemedicine visits may result in over prescription since physicians are unable to physically examine patients or preforms tests through the platform, resulting in greater difficulty in differentiating between bacterial and viral infections (National Institutes of Health, 2019; Ray et al., 2019). Telemedicine in healthcare may be increasing the convenience and the accessibility of seeing a doctor, but in turn, could be threatening the future effectiveness of antibiotics.

5.5 Balancing Preservation and Research

With increasing rates of antibiotic resistance, it is important that we preserve the effectiveness of the antibiotics we have left. It is for this reason that the World Health

Organization has created an antibiotic section on the Essential Medicines Lists, created in 1977 to help address public health needs, and it now includes a section advising " which antibiotics to use for common infections and which to preserve for the most serious circumstances" (World Health Organization, 2017e, para. 1). Based on when different antibiotics should be used, the World Health Organization split them into three categories: ACCESS, which they recommend should be commonly available to treat typical infections, WATCH, which are antibiotics that can be used as first or second line treatments but should be reserved for particular infections, and finally RESERVE, which consists of the last-resort options that should only be used in life threatening circumstances when no other options remain. "The overall objective is to encourage prudent use to slow down antimicrobial resistance and preserve the effectiveness of the most critical antibiotics for medicine. The guidelines issued today incorporate this objective in its recommendations for antibiotic use in agriculture" (World Health Organization, 2017d, para. 13). This list provides hope for the preservation of the most critically important antibiotics for human health.

Preservation is important, but we need to be careful to not restrict the use of antibiotics too strictly. Currently, more children die annually from lack of access to antibiotics in lower-and middle-income countries than they do from drug resistant infections (Laxminarayan et al., 2016). So while resistance will threaten the long-term viability of antibiotics' effectiveness, short-term improvements must include improving their accessibility in these countries (Laxminarayan et al., 2016; Nadimpalli et al., 2018). Increased restrictions on the use of antibiotics will reduce their accessibility. Therefore it

makes sense that the World Health Organization created different categories to find a balance between accessibility and preservation.

Unfortunately, the hope of developing new antibiotics may not be realistic. Gerry Wright, director of the Institute for Infectious Disease Research at McMaster University, says that “the difficulty is that the pharmaceutical industry is no longer investing time or money looking for new antibiotics” (Ubelacker, 2018, para. 7) because not only is it a difficult task, but it is also very expensive. Gerry Wright and Dr. Andrew Morris, director of the antimicrobial stewardship program at the Sinai Health System and University Health Network in Toronto, both agreed that “drug manufacturers aren't prepared to commit the average $1-billion outlay to develop an antibiotic that can cure an infection in five to 10 days, when they can put their resources into medications for conditions like high cholesterol or blood pressure, which typically are taken for life. Add that to the fact that a new antibiotic may have a limited shelf life because the bugs it's meant to treat may develop resistance and there's little incentive” (Ubelacker, 2018, para. 9). Further, even though some researchers are working on developing new antibiotics, the World Health Organization reports that they are not expected to be significantly effective against antibiotic-resistant bacteria (World Heath Organization, 2018a). It is not without reason that one of the major slogans for the most recent World Antibiotic Awareness Week was “Change Can’t Wait. Our Time with Antibiotics is Running Out” (World Health Organization, n.d.-b), and we cannot rely on the hope of simply developing new antibiotics to replace the ones that have already lost their effectiveness.

Focusing on new research and development, such as extending the lifespan of our current antibiotics, may be a solution. The World Health Organization and the Drugs

for Neglected Diseases initiative have joined forces to create the Global Antibiotic Research and Development Partnership. Through public-private partnerships, this program encourages research and development and aims to “develop and deliver up to four new treatments, through improvement of existing antibiotics and acceleration of the entry of new antibiotic drugs” by 2023 (World Health Organization, 2018a, para. 25). In the past many new antibiotic treatments have simply been new developments based on previous antibiotics. For example, amoxicillin is a β-lactam antibiotic that bacteria eventually developed resistance toward. These resistant bacteria have the ability to create β-lactamase, an enzyme that can break down amoxicillin and render it ineffective. This ability allowed the bacteria to survive despite treatment with amoxicillin. In order to restore the effectiveness of amoxicillin, researchers created a drug that was a combination of amoxicillin and clavulanic acid. Clavulanic acid is a powerful β-lactamase inhibitor, meaning it has the ability to deactivate the bacteria’s β-lactamase enzymes. This allows the amoxicillin to continue to target the bacteria undisturbed and extended the lifespan of amoxicillin’s effectiveness (Todd and Benfield, 1990). New developments do not always need to include waiting for a chance discovery of a novel antibiotic, but could also include the restoration of current antibiotic’s effectiveness.

5.6 Sustainable Development Goals as a Solution

Achieving the United Nation’s Sustainable Development Goals may also help reduce increasing levels of antibiotic resistance. Set in 2015, the United Nation’s Sustainable Development Goals, also known as SDGs, aim to “provide a shared blueprint for peace and prosperity for people and the planet, now and into the future” (United Nations, n.d., para. 1). The 17 SDGs aim to comprehensively address the many

global challenges we face, from climate change to poverty and inequality, and many of the specific goals outlined in these SDGs focus on improving global health, such as increasing the availability of vaccines, improving access to healthy food and clean water sources, and reducing rates of communicable diseases. A multilateral multisectoral approach is needed to effectively fight antibiotic resistance, and many of the goals outlined in the SDGs target the causes of antibiotic resistance. Therefore, achieving these goals would also contribute to reducing the spread of antibiotic resistance.

The most obvious goal that would contribute to reducing the spread of antibiotic resistance would be Number 3: Good Health and Well-being. Achieving accessible universal healthcare for all would also reduce the risk of antibiotic resistance. According to the study that looked at prescription diversion, “one of the common reasons parents gave for diverting antibiotics was that they wanted to avoid the costs involved with a second trip to the doctor” (American Academy of Pediatrics, 2018, para. 10). Vaccinations are another way to reduce antibiotic resistance. If you are protected against vaccine-preventable diseases, then you won’t need to use antibiotics to treat them, and therefore don’t further contribute to antibiotic resistance.

Similarly, progress on SDG Number 6: Clean Water and Sanitation would improve infection control and prevention, in turn reducing the spread of all diseases, including those caused by antibiotic resistant bacteria. Nadimpalli et al. (2018) detail a One Health approach focusing on ensuring that the treatment of contaminated waste and improving access to clean water and sanitation would improve the currently predicted outlook, in addition to improving food supply chains, and managing antibiotic use in both humans and agriculture (Nadimpalli et al., 2018). The World Health

organization agrees that both the better use of vaccinations, and improved hygiene would be able to help limit the increasing rates of antibiotic resistance (World Health Organization, 2017d). While pursuing the SDGs can also help stop antibiotic resistance, widespread antibiotic resistance could prevent the achievement of the SDGs.

In terms of antibiotic resistance, the biggest limitation of SDGs is the fact that they fail to even mention antibiotic resistance, unless you count the umbrella goal to combat all communicable diseases. This oversight is just another example of how we are severely underestimating the threat of widespread antibiotic resistance. Others have recognized this gap and some have even gone on to explain how antibiotic resistance severely impacts our ability to reach the SDGs, including more apparent targets like universal health coverage or communicable diseases, and less foreseeable goals like no poverty or sustainable economic growth (Jasovský et al., 2016; Cars and Jasovský, 2015). "The world urgently needs to change the way it prescribes and uses antibiotics. Even if new medicines are developed, without behaviour change, antibiotic resistance will remain a major threat. Behaviour changes must also include actions to reduce the spread of infections through vaccination, hand washing, practising safer sex, and good food hygiene" (World Health Organization, 2018a, para. 5). While the later may be addressed by achieving the SDGs, none of the goals explicitly speak to the prescription and use of antibiotics, which may mean this threat may lose the global attention it deserves to other causes. We continue to underappreciate how vast the implications of widespread antibiotic resistance will be, and our remaining time with effective antibiotics is running out.

6. Conclusion

Antibiotic resistance poses an imminent threat to global health that has not yet been adequately recognized by the global community. Despite the current actions taken at local, national, and international levels, many people are still unaware of the risk and more action is needed in order to ensure the preservation of antibiotics for years to come. Human actions are directly responsible for increasing rates of antibiotic resistance and “although the discovery of antibiotics has revolutionized medicine, it is imperative that clinicians emphasize the importance of use and dispose of these medications properly to make sure they remain an effective tool against infectious diseases” (American Academy of Pediatrics, 2018, para. 8). As dire as it may be, our time with antibiotics is running out. We need urgent action from all sectors and from all levels of society to protect ourselves against the imminent threat posed by increasing rates of antibiotic resistance. For as Dr. Andrew Morris said, “barring global war or some catastrophic runaway virus emerging, ‘I think the greatest health-care threat moving forward around the world is absolutely antimicrobial resistance’”(Ubelacker, 2018, para. 24).

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