

Appropriate Use of Antibiotics is Essential to Slow the Emergence of Resistance and Extend the Useful Lifetime of Effective Antibiotics

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ABSTRACT

When pathogens become resistant to antibiotics, they find ways to stop other antibiotics from working that they used to be sensitive to. Pathogens of different types can improve defenses or tactics in more than one way, such as through natural or learned means. When a virus can protect itself from any drugs, this is called innate resistance. This may have happened because the capsules don't let pathogens through easily. There may be other reasons, such as differences in the chemical makeup of the drug and the viruses' membrane structures. Acquired resistance is the development of antibiotic resistance that can happen for a number of different reasons. For example, the pathogen may have been sensitive to the pills at first, but through the process they build up resistance mechanisms. Transformation, transduction, conjugation, and transfer of plasmids are the most common ways for bacteria or pathogens to make the resistance stronger.

KEYWORDS: Capital, intellectual, formation, diffuse, model

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1. INTRODUCTION

It was Abraham and Chain (1940) who first talked about bacteria called *Bacillus coli*, which is now known as *Escherichia coli*, being resistant to antibiotics. This was before penicillin was used to treat different pathogens in humans by Chain et al. (1940). A lot of antimicrobials used in medicine are made with the help of soil pathogens and microbes. These pathogens are where the unique resistance genes found in most clinical bacteria were found more than 40 years ago by Benveniste and Davies. Antimicrobial resistance is a natural biological process that has been going on since antibacterials were first discovered. When the 20th century began, ABR was a rare and easily manageable issue that could be fixed by making new drugs. At the moment, though, the overuse of antibiotics has sped up the growth and spread of ABR, leading to the appearance of "superbugs" that can't be handled with current medicine. Antibiotics resistance (ABR) has hit scary levels in most parts of the world, both in human and animal medicine. It is now seen as a major threat to global food security and public health. Because of a 2014 report from the World Health Organization that showed how serious the problem was, countries all over the world have been forced to admit how big it is. A statement on AMR was passed by the Food and Agriculture Organization of the United Nations (FAO) at its governing Conference in June

2015. These included the World Organization for Animal Health (OIE) and the World Health Organization (WHO) passing decisions on AMR at the same time in May 2015. This was the start of a global effort by all three groups to fight AMR. Considering everything that has been said, the goal of this senior class paper is: To look into antibiotic resistance

2. LITERATURE REVIEW

2.1. The History Antibiotics Resistance

Abraham and Chain (1940) were the first to report antimicrobial resistance in *Bacillus coli*, which is now known as *Escherichia coli*. This was just a few months before penicillin started being used to treat infectious diseases in people that same year. There are also many ways to change the effect of an antibiotic by getting genes that code for proteins that stop or weaken antibiotics' strong binding to their biological targets. In the same way, enzymes control the antibiotic goal to stop drugs from sticking. Getting these kinds of factors either from scratch or from an outside source means that the host mobile gains the ability to apply good factors. Different microbes have different ways of lowering the antibiotic's effectiveness. There are substances that can change the structure of an antibiotic so that it is no longer active. These can be enzymes that break down the antibiotic or molecules that add energy to the antibiotic. It is also

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possible for efflux pumps to lower the amount of drugs that get into cells. Efflux pumps usually have broad substrate specificities and can move a lot of different molecules across the host cell membrane, which is in line with their main cleaning roles (Nicholas Wagglechner and Gerard D Wright, 2017). The problem of antibiotic resistance (ABR) is complex all over the world. Misusing medicines in medicine, veterinary care, and agriculture can cause antibiotic resistance to spread. Some examples of this are giving antibiotics to the wrong people, using them too much on animals, and not keeping hospitals clean enough. Changes in the world and travel are also speeding up the spread. At the same time, the process of making new antibiotics has slowed down, mostly because there aren't enough incentives. This has let microorganisms grow faster than new capsules (Merrett GLB, 2013). When medicines that used to kill microorganisms don't work on them anymore, we call them "antibiotics-resistant" or "drug-resistant." This type of resistance is known as "acquired resistance," and it is controlled by genes in the microbe's DNA. Mutations that happen on their own in the DNA of microbes can lead to resistance genes. These genes can make microbes resistant to antibiotics and also change them from being immune to drugs to being sensitive to them. In a therapeutic setting, the first drug-resistant bacterium was found in the late 1940s, just four years after penicillin became widely used for treatment. Since then, the number of microbes that are immune to drugs has continued to rise and spread. A lot of hospital-acquired diseases are caused by bacteria that are very resistant to antibiotics, like methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (Holmes AH et al., 2016).

2.2. The Occurrence of Antibiotics

Resistance and Taking It into Account Some microorganisms become less sensitive to antimicrobial drugs or become completely resistant to them. This is called antimicrobial resistance. Some microorganisms that cause infections become resistant to the medicine that was used to kill them. This is called ABR. So the microorganism can live and spread, creating illnesses called "superbugs" that are hard to treat. Resistance happens when a microbe's biology changes, either because its genes change or because it gets resistance genes from outside sources. When treatment doesn't kill all bacteria, strains that are resistant are more likely to grow and spread, eventually replacing strains that are weak. Because of this, a fix that used to work really well at getting rid of infections no longer does. For each type of microbe, a different antimicrobial agent is used. Antimicrobial use (AMU) explains how the drugs are used, including the dose, route of administration, frequency of administration, and length of treatment period. In places where AMU is common and diseases are frequent, like hospitals, veterinary clinics, and intensive cattle production facilities (PHAC 2015), resistant microbes are likely to be present. Over the past ten

years, however, the rise of ABR has made resistance more usual in the wider neighborhood putting (O'Neill 2016). The situation in Canada is the same (Fishman 2006). More and more people agree that too much and unsuitable AMU is the main thing that is making antibiotic resistance worse and faster (Bronzwaer, 2002; Holmes et al., 2015). There is, however, competition and debate when we try to figure out where most of this wrong use comes from—that is, whether AMU in human or animal fitness makes a bigger addition to AMR. About 1.4 million kilograms of antimicrobials that are medically important were given out and/or sold in Canada in 2013. 78% of the whole mass was used to feed animals for food. Only 21% was used on people, 1% on pets, and much less than 1% on crops (PHAC, 2015). When population and weight were taken into account, about 1.4 times more antimicrobials were given out for use on animals than on people (PHAC, 2015). People and animals often use the same antibiotics for medical reasons, so it's clear that both industries add to ABR and the effects that will soon happen to human health (PHAC, 2015). To stop AMR and definitely stop the speeding up and spreading that is putting the world at risk, it is important to know what each quarter brings to the table. Policymakers and scientists who have different goals and points of view (for example, human fitness vs. animal health) need to agree on what AMU is and what its risks and benefits are (Bell, 2001). To make this happen, all areas need to have access to correct, up-to-date information on AMU through increased oversight, surveillance, and sharing of data around the world. In turn, this more complete information will lead to more study skills on how to deal with ABR in a safe and long-lasting way. Some people think that fighting ABR at an international level will cost forty billion USD over ten years. However, the price of not doing anything is even higher. At this point, it is thought that 700,000 people die every year from causes related to ABR. On the basis of the current level of tolerance for six pathogens, this number should reach 10 million a year by 2050 if nothing is done, which would have a global cost of 100 trillion USD to the economy. This is also a conservative estimate of the costs, because doing nothing will also increase the risk of death linked to medical treatments that leave patients open to infection, like cancer treatment, organ transplants, and invasive surgery. The continued growth of AMR will make many clinical approaches less likely to work, which will negatively impact health care (O'Neill 2016).

2.3. Antibiotics Resistance Consequence

There are different reasons why people keep dogs, cats, and horses. In wealthy areas, most people keep these animals as pets for social reasons and for fun. About 25% of homes in the European Union have a pet (FEDIAF, 2012). People often think of their dogs and cats as family members or friends (O'Haire, 2010), and some people feel very close to their horses. It's no surprise that people are willing to spend a lot of money on their pets, and there is a need for high-tech

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medical care. When it comes to puppies, antibiotics are often used for skin problems (including wounds) and urinary tract infections. When it comes to horses, antibiotics are used for skin and reproductive system problems (Thomson, 2010). For veterinary care, puppies and cats are often seen at animal hospitals or offices of different sizes. Both routine care and hospitals take care of horses. In modern animal hospitals, there are usually high-tech diagnostic tools available, and there are chances for both intensive care and advanced treatment. There may be a lot of animals in these places, and medicines are often used, which can lead to nosocomial infections. There have been more and more reviews in the last ten years about MRSA and other multi-resistant Gram-negative bacteria that are not killed by third-generation cephalosporins or even carbapenems in horses and puppies (Catry et al., 2010; Ewes et al., 2012; Stolle et al., 2013). There have also been reviews about methicillin-resistant *Staphylococcus pseudo intermedius* (MRSP) infections in puppies (Van Duijkeren et al., 2011). Not much is known about how common these microorganisms are for causing major infections, so the effects on everyone are not well known. One way to talk about some of the bad effects of drug resistance could be to use the rise and spread of MRSP as an example. The main cause of skin, ear, and wound infections in dogs is *Staphylococcus pseudo intermedius*, an opportunistic bacteria (Van Duijkeren et al., 2011). Since 2006, MRSP has quickly spread around the world. Studies of isolates from Europe and North America have shown that two main clonal lines are present. Both of these are usually not affected by the main types of antibiotics used in veterinary medicine (Perreten et al., 2010; Ruscher et al., 2010). A study looked at what happened when dogs with pyoderma caused by MRSP or methicillin-susceptible *Staphylococcus pseudo intermedius* were treated. Most of the cases got better, even when the bacteria were resistant to methicillin. But it took longer to treat some cases of MRSP pyoderma, and systemic treatment, especially chloramphenicol (Bryan et al., 2012), had more bad effects than good ones. In the MRSP group, topical treatment with antibacterial shampoos or mupirocin by itself was used more often, either before or after systemic medicine was stopped because it was harmful. Topical antibiotic shampoo takes a long time to work, but it was shown to get rid of or greatly improve almost half of all cases of pyoderma when used twice or three times a week for three weeks (Loeffler et al., 2011). In the study by Bryan et al. (2012), it's possible that because the owners didn't have any other choices, they were willing to put up with this painful topical treatment. Even though pyoderma in puppies with MRSP might still be treatable without systemic antibiotics, deeper infections and some surgical site infections can be life-threatening or even cause the animal to have to be put down for animal care reasons if they are not treated. This is also true for illnesses in dogs, cats, and horses caused by MRSA and other multiresistant Gram-negative bacteria. Some different

antibiotics, like carbapenems, oxazolidinones, and glycopeptides, are now called choices in case reports and medical reviews (Corley et al., 2007; Foster., 2014; Papich, 2013). There isn't much known about the pharmacokinetics, safety, and effectiveness of these capsules for specific animal species and warning signs. They are no longer allowed for use in animals. But more importantly, the vet has to decide if the pills that are needed to treat infections in people with multi-resistant bacteria should even be given to dogs. This is because there is a chance that pathogenic or commensal bacteria could become resistant and spread to humans. Most writers who talk about these picks stress how they should only be used on animals when no other treatment options are available. In Finland and Sweden, regulators have limited the number of times that veterinarians can give these drugs. This means that there will be times when suicide is the only option. Many people who own dogs or cats think of their pet as a part of the family, as was already said. A Canadian study looked at how pet owners react to the death of a pet and found that 30% of those people were in serious grief, with euthanasia being one of the main causes (Adams et al., 2000). This means that when dogs get infections with multiresistant microbes, which are also likely to happen with horses, the owners and their families will likely have bad mental and social effects. More severe social consequences may also happen to people who lose support dogs for disabled people, since the animal may also be necessary for them to do daily tasks.

2.4 Economic impact of Antibiotic resistance

In addition to being bad for the animal, antibiotic resistance can also cost the owner money. If "cure at any cost" is picked, this effect can be big. For instance, Foster et al. (2014) talk about how linezolid helped a dog with MRSP bacteremia and disco scoliosis get better. The dog was cared for for 23 weeks, and the antibiotic cost 176,000 Swedish crowns, which is about US\$25,600. This is based on the amount used in the case record and the prices at Swedish pharmacies. Clearly, most owners would not be able to pay this fee. Animal fitness costs of antibiotic resistance can be seen in records from Pharmacy checker online, prices in the US are a lot cheaper, but the drug would still cost between US\$1,500 and US\$4,800. It was likely also more expensive for follow-up visits, lab work, and other tests than in similar cases with bacteria that are usually killed by first-choice medicines. When partner animals and horses get surgery site infections, there is also a chance that the original problem doesn't go away. There is a fee for the animal's death if the pollution directly causes it or if euthanasia is chosen. This is especially important for animals that have been trained with a lot of money, like provider dogs, animals that are cherished for breeding, and some animals that are used for sports. When breeding animals, you should also think about the bigger effects of losing genetic material that could be useful. There are a number of ways that cases of multi-resistant

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microorganisms can hurt hospitals and clinics' bottom lines. A case of MRSA spreading to an equine clinic in Sweden and affecting eight horses was once thought to have cost 1.2 million Swedish crowns, or about \$170,000 (Bergstrum et al., 2012). A long-lasting outbreak of Salmonella Newport that is multi-resistant at a large animal hospital was predicted to cost US\$4.12 million in lost revenue (Dallap et al., 2010). Costs that were included in the estimate were lost income because the clinic had to close, fewer cases, cleaning up, building back up, and paying for patients' bills. One hundred and sixty-one animals, mostly horses, got sick in this outbreak, and 36% of those animals died. Therefore, there was also a big loss for the people who owned the animals. After the outbreak, an infection control program that was changed and made stronger was put in place. There are costs that were not included in the figures we talked about above, but they apply to all locations. These costs include investments in continuously increased infection control and prevention and continuously increased laboratory diagnostics. Lastly, it's hard to put a number on the possible loss of buyer confidence in places where outbreaks are happening, but it's probably a big deal. If an animal health center-like infection is added to a breeding farm or a racetrack and spreads, fees similar to those of an animal health center may also be charged. Veterinary bills are likely to go up, and there will be a cost for things like losing babies or horses that don't race as planned. Also, germs like MRSA can be passed from animals to people, and people who work with animals are more likely to be infected with MRSA than people who don't work with animals (Catry et al., 2010).

2.5 Causes of Antibiotic Resistance

These days, there are many things that can cause drug resistance. Some of these are bad antibiotic policies and use, not enough knowledge, and not enough attention on the use of antibiotics. Antibiotic resistance is mostly caused by using too many of them. Sir Alexander Fleming warned that "the public will demand [the drug] and then will begin a generation of abuses." While antibiotics kill sensitive microbes, they don't kill pathogens that are immune. These pathogens then reproduce and grow through natural selection. It is strongly advised that antibiotics not be used in excess, but this still happens around the world. Antibiotics are used to make animals grow quickly all over the world. A rough guess is that about 80% of the antibiotics sold in the US are only used as growth supplements or to control infection in animals (Aslam et al., 2018).

2.5.1 Overuse

Antibiotic resistance can happen when they are used too much. Epidemiological study shows that the excessive use of antibiotics can cause the development and spread of microorganisms that are resistant to antibiotics. In bacteria, genes can be passed down from mate and children or from nonrelatives on plasmids and other mobile genetic factors. This horizontal gene switch can make it possible for different

types of bacteria to share drug resistance. Resistance can also appear on its own through change. Antibiotics are given too often around the world, even though there are warnings about this (C. Lee Ventola, 2015).

2.5.2. In splendid prescription

Incorrect prescribing can happen when doctors don't know how to tell the difference between different types of infectious diseases or how antibiotics work best for different types of illnesses. Even in developed countries, medical school curriculums don't cover much about the biology of antibiotics, including how they work, the range of antibiotics they can be used for, and problems that can arise due to resistance. This means that prescribers aren't well-informed. This is why working together to stop antibiotic resistance on a global level will need countries from all over the world to work together and teach people about drug resistance and the effects of using antibiotics incorrectly. It was also said that diagnostic confusion and the desire for a quick fix played a role in the misuse and prescription of antibiotics (Teixeira Rodrigues et al., 2013). It is clear that over-prescriptions will make the chances of AMR higher, but it is not yet clear whether less prescribing actually lowers AMR (Priest et al., 2001). But some studies have shown that changes in how doctors prescribe have been linked to lower levels of AMR, even if the effects were small (Simpson, 2007, Seppala et al., 1997, Wise, 2004, and Holmes et al., 2015). In short, the link between less use and less resistance is complicated, with some searches showing great results and others not. According to some, this is because AMR is usually dealt with with more than one action at the same time, making it hard to say for sure what caused the decrease in resistance (Fishman, 2006).

2.5.3 Change in prescription

AMR is mostly caused by changes in prescriptions (Wise, 2004), but some argue that the best way to fight ABR is to stop the development of new resistant strains, since there isn't a clear link between decreasing resistance and decreasing AMU. While most people would agree that all of these tactics are likely useful and necessary in the fight against ABR, we need a better understanding of the link between less resistance and less use in order to make better interventions (Holmes et al., 2015).

2.5.4 Non-prescription purchase

It is not possible for everyone to have controlled access to antibiotics or antimicrobials. In many countries, there are few or no rules about how antimicrobials are made or sold. This leads to the production of therapeutic drugs of very different quality that can be bought by anyone for a low price and in large quantities. When the Internet first came along, people in first-world countries could only get antimicrobial materials from returning tourists (Al-Faham et al., 2011). As reported by Al-Faham et al. (2011), 78% of pharmacies in Saudi Arabia and 87% to 97% of pharmacies in Syria sold medicines without a prescription. Besides what doctors

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prescribe, there are also AMU behaviors in people and sufferers that many people think are adding to AMR. Individual/patient AMU behavior is just as hard to measure as prescribing behavior. It includes patients not following through with their antibiotic prescriptions, not stopping the full course of treatment, and saving extra antibiotics for later self-medication (Simpson et al., 2007, Hart et al., 2006, Hansen et al., 2015, Muras et al., 2013). It is also thought that patient education and appreciation of antibiotics can help lower AMR. For example, study shows that up to one-third of patients think antibiotics are very good at fighting the common cold and flu (Hansen et al., 2015). If you asked Canadians in 2006, 53% of them said they thought antibiotics could help treat viral infections, and almost half said they thought they could help fight a flu outbreak. It's interesting that 63% of those polled think they can avoid ABR infections by using antimicrobials wisely. They don't realize that ABR is caused by bacteria, not the person taking the drugs. These results show that more teaching and attention should be paid to AMU/AMR, and the role of advertising in increasing patient demand should be studied (Ardal et al., 2015; Holmes et al., 2015). AMU in health care is complicated. It happens in a lot of places, is linked to many different kinds of personal and environmental behaviors, and is a difficult part of public health to both measure and manage. Also, it's important to note that AMU in Canadian hospitals and communities has gone down since 2001 (PHAC, 2015). Even so, it is suggested that any action taken to treat AMR in humans will need a mindset shift involving doctors, patients, and society as a whole in order to fully understand AMU/AMR. There is also the unfortunate fact that doctors often think writing a prescription is faster than describing why an antibiotic prescription is not needed (Freidman 2008). This needs to change. It's also important to note that many experts who study AMR in human health warn that while fighting resistance in human health and healthcare settings is important, these efforts and any progress made could be seriously undermined by the continued widespread use of AMR in animal health and agriculture (Ardal et al. 2015). However, Canada has made some steps that have been shown to have some positive, if not huge, effects on AMU/AMR. These include giving antimicrobial tool kits to all doctors and veterinarians, creating a website to keep track of ongoing ABR activities, and starting programs to encourage responsible prescribing (Conly and Johnston 2000).

2.6. Status of Antibiotics Resistance

The percentage of *E. coli*, *K. pneumoniae*, and *S. aureus* that were not killed by commonly used antibacterial pills was higher than 50% in many places, according to national records. Some common community-acquired infections don't have many good treatment options in many countries, and there aren't many, if any, treatment options for some common extreme and healthcare-associated infections in many places. This is based on suggested and published facts. In all WHO

regions, *K. pneumoniae* is said to be resistant to carbapenems, which are generally the last treatment option. In both gonorrhea and tuberculosis, treatment can fail because of drug resistance. But because of doubts about who is being represented and big gaps in coverage, it's not clear how big the problem is on a world scale and needs to be made clear. It's also not clear how much differences in reported data for some bacteria-antibacterial drug mixtures are due to real differences in resistance trends or to differences in how patients were sampled, how well the lab performed, or how the methods used were different. WHO says that international cooperation and surveillance rules have been put in place for two types of bacterial contamination: tuberculosis and gonorrhea. However, these rules have not yet been put in place for other common bacteria. To make data better and easier to compare, people around the world need to work together using a standard way (WHO, 2014).

2.7. Mechanisms of Antibiotics Resistance

Microorganisms build resistance in a number of ways, including adding resistant genes to the organism and passing on resistance through genetics (Kumar and Varela, 2012). When resistant microbes cause an infection, it doesn't react to treatment, and resistant lines are chosen (Walsh, 2000). Some types of bacteria are generally not affected by certain antibiotics, while others are. This is because of how they build up resistance. Resistance can also be natural or learned. Natural means that microorganisms naturally don't have target sites for the capsules, so the drug doesn't affect them; or they naturally have low permeability to those sellers because of differences in the chemical nature of the drug and the structures of the microbial membranes, especially for those that need to get into the microbial cell in order to change their movement (Fluit, 2001). Acquired resistance is when a microorganism that is usually weak to the drug learns how to not be affected by it. In many places, bacteria can easily trade genes that make them resistant to antibiotics with bacteria that are nearby. This can show up as spontaneous mutations, which happen when microbes copy their DNA and make mistakes as they grow. Mutations that help microorganisms live in places where others can't are good, and they are passed on from one generation to the next. Antibiotic resistance genes are often found on cell genetic elements, like plasmids, transposons, and integrons. These can easily move between bacteria of the same species or different species, and they make it easier for resistance to a few capsules to spread through more than one type of bacteria (Marshall and Levy, 2011). Plasmids are round pieces of bacterial DNA that are found naturally inside many bacterial cells. They may also contain genes that make bacteria resistant to antibiotics. Different methods, like transformation, transduction, conjugation, and transfer, are used to get the plasmids into other bacterial cells. When a bacterium dies, it breaks apart and releases its DNA into the world. This changes the genetic material. Microorganisms nearby can pick up pieces of this

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floating DNA and add them to their own genomes. This creates an easy way for drug resistance to spread. A piece of DNA with an insertion sequence thing repeated at each end can move from one plasmid to another within the same cell, to a bacterial chromosome, or to a bacteriophage. This is called transposition. The transposition process doesn't seem to depend on the host's usual recombination process. If two microorganisms are close to each other, they can pass genetic material between cells at the same time, or a hollow shape called a pilus, also called a hole, can form between the two cells. This pilus can be used as a bridge by plasmids to send copies of themselves to other cells (SGM, 2015). There is a part of DNA called an insertion sequence that can move from one plasmid to another within the same cell, to a bacterial chromosome, or to a bacteriophage. This is called transposition. The transposition process doesn't seem to depend on the host's usual recombination process. If a disease-causing microbe is transmitted to animals, it can lead to infections, and resistant bacteria that aren't pathogenic might also store plasmids for harmful microbes (Walsh, 2000). These resistance mechanisms are controlled by plasmids and include efflux pumps, which remove antibiotics from the cell; modifying enzymes, which change the shape of the antibiotic; and degrading enzymes, which break down the antibiotic completely (Kumar and Varela, 2012). In general, drug resistance can be broken down into several main groups. These include active efflux pumps, drug inactivation or alteration, changes to drug binding sites or targets, and changes in cell permeability that lead to less drug accumulation inside cells (Shimels Tikuye Yalew, 2020). Antimicrobials are broken down by bacteria in a number of ways, including the enzymatic breakdown of antibiotics, the group switch process, and the redox process. Antibiotics can be stopped by enzymes found in bacteria. One example is β -lactamase, which harms the active part (the β -lactam ring) of penicillins, which are very important medicines for treating infections in people. After some time, ESBL-producing bacteria (bacteria that make extended-spectrum β -lactamases) have grown into a major issue. They can break down a wide range of β -lactam antibiotics, which are sometimes the last pills that can kill bacteria illnesses. The second way that antibiotics are rendered inactive is by enzymes changing the structure of the drug. There are times when bacteria can make enzymes that can add certain chemicals to medicines. This, in turn, stops the antibiotic from binding to its target in the bacterial cell and makes it unable to bind to the target because of the change in structure. This reaction can't be undone. Redox response is the third way that antibiotics are turned off (Shimels Tikuye Yalew, 2020).

2.7.2. Target Modification

Changes that happen in the drug-related receptor and the antibiotics' target areas are one-of-a-kind. These areas can include complex enzymes and ribosomes. The macrolide

antibiotics are the ones that are most often found to be resistant to changes in the ribosome goal. Some examples of this are how penicillin resistance has grown because of changes in penicillin-binding proteins beta-lactamase enzymes in strains of *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Enterococcus faecium*. In the case of *Staphylococcus aureus*, these proteins are needed for making bacterial cell walls, which is what β -lactam antibiotics are trying to stop. Because it doesn't react well to β -lactam antibiotics, the new penicillin binding protein is not affected by them. This means that the bacteria can live with treatment. This kind of tolerance is what makes MRSA (methicillin-resistant *Staphylococcus aureus*) possible. Hayder Hasan et al. al., 2020).

2.7.3. Enzymatic inactivation

Antibiotics that are broken down by enzymes Most microorganisms make enzymes that break down antibiotics. One of the most important ways that antibiotics are resistant is through enzymatic breakdown (Pérez-Llarena et al., 2016).

2.7.4. Reduction of the inner and outer membrane permeability

This type of process is caused by changes in the permeability of the cell's inner and outer membranes, which makes it harder for drugs to get into the cell. Some changes to the bacterial barrier make it harder for things to get through. This keeps a lot of the drug from getting into the bacteria. Because of changes in porins, membrane permeability decreases. These changes can also happen in proteins of resistant strains. For example, a change in porins called OprD can make a *Pseudomonas aeruginosa* strain immune to carbapenem. Lowering the porosity of the outer membrane can be a key part of quinolone and aminoglycoside resistance (Thualfakar Hayder Hasan et al., 2020).

2.7.5. Mutation

Some changes happen naturally in the DNA sequence inside the gene. These changes can cause the target in the bacterium to change its makeup or shape. If this happens, the antibiotic won't be able to connect with the target. Other than that, the microorganism can change the structure of the target in a way that protects it from the drug. Many mutations happen in bacterial genomes because of base changes caused by outside agents, DNA polymerase mistakes, deletions, insertions, and duplications (Shimels Tikuye Yalew, 2020). When animals are kept for food production, the development of tolerance has shown us that we need to change how we care for them and use good biosecurity practices instead of using antibiotics to stop diseases. Dogs and cats that are healthy no longer need medicines. To lower the need for medicines and the number of infectious diseases in companion animals and animals raised for food, the main goal of future efforts must be to lower the number of infectious diseases. It's even more important to remember this because it's not likely that new drug lessons will be safe

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enough for animals to use. If there are any new types of antibiotics on the market in the future, they will almost certainly only be used in human health care. It is clear, though, that making new antibiotics better can't be the only important way to stop AMR. Costs for clinical studies are very high, and sales of new capsules are low at first because regular capsules still work sometimes (Fishman 2006). Others have said that pushing for new antibiotics and ways to make sure they are used well is like "squeezing the balloon" (Bell 2001). This comparison shows that the resolution pressure would definitely shift to the newly developed antibiotics, but it doesn't answer the problem of using them in the wrong way.

CONCLUSION

Antibiotics resistance (ABR), the process by which bacteria become resistant to the antibiotics that are usually used to treat infections, is what makes infections resistant to drugs. Common infectious illnesses are harder to treat and people stay sick longer when there aren't any good antibiotics available. It costs more to stay in the hospital and get care, and there is a greater chance of getting the disease and dying. The problem of AMR is made worse by the fact that drug resistance is developing and spreading much faster than new drugs that can stop illnesses are being made. One of the main reasons why antibacterial drugs are becoming less effective is that they are being misused and used too much, both in health and in farming. There are several types of drug resistance mechanisms, such as active efflux pumps, drug deactivation or alteration, changes in drug binding sites or targets, and changes in cell permeability that make it harder for drugs to build up inside cells. In general It's hard, and sometimes impossible, to treat infections that are caused by germs that are resistant to antibiotics. To stop the development of resistance and make sure that effective antibiotics last longer, it is important that they are used correctly in healthcare, animal health, and farming.

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