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The Impact of the COVID-19 Pandemic on Antimicrobial Stewardship Practices and Their Effect on Veterinary Medicine

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THE IMPACT OF THE COVID-19 PANDEMIC ON ANTIMICROBIAL
STEWARDSHIP PRACTICES AND THEIR EFFECT ON VETERINARY MEDICINE

by

Erin N. Bradstreet

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of the Requirements for a Degree with Honors
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Advisory Committee:

James Weber, Associate Professor of Animal and Veterinary Sciences, Advisor

Robert Causey, Associate Professor of Animal and Veterinary Sciences

Suzanne Ishaq, Assistant Professor of Animal and Veterinary Sciences

Melissa Ladenheim, Associate Dean of the Honors College

Anne Lichtenwalner, Extension Veterinarian, Associate Professor, and Director of
Veterinary Diagnostic Lab

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ABSTRACT

Antimicrobials are essential in the treatment of diseases in both humans and animals, but antimicrobial resistance threatens their efficacy. As more microorganisms become resistant to an ever-growing list of antimicrobials, diseases that used to be simple to treat are becoming increasingly difficult to manage. The major factors contributing to antimicrobial resistance are overuse and misuse of antimicrobials. In order to combat the problem of resistance, antimicrobial stewardship programs that aim to improve antimicrobial prescribing and use practices are becoming increasingly widespread. These programs are quite common in human medicine, but the COVID-19 pandemic disrupted many aspects of life, including antimicrobial stewardship. In this study, three classes of antibacterials, beta-lactams, macrolides, and fluoroquinolones, will be reviewed as well as two antiparasitic classes, quinolines and avermectins, before investigating the effect the COVID-19 pandemic has had on antimicrobial stewardship in human medicine. The aim of this study is to assess the impact the pandemic had on these programs, and whether this decreased their effectiveness in reducing the behaviors and practices associated with the development of antimicrobial resistance. This information will then be applied to veterinary medicine using a One Health perspective, which recognizes that human, animal, and environmental health are intimately connected.

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TABLE OF CONTENTS

LIST OF FIGURES, TABLES, AND DEFINITIONS.....	vi
INTRODUCTION	1
METHODOLOGY	3
WHAT ARE ANTIMICROBIALS?.....	4
WHAT IS ANTIMICROBIAL RESISTANCE?	7
Factors Contributing to Antimicrobial Resistance	7
Mechanisms of Antimicrobial Resistance Sharing	9
Problems Associated with Antimicrobial Resistance.....	10
WHAT IS ANTIMICROBIAL STEWARDSHIP?	12
THE ONE HEALTH PERSPECTIVE.....	15
ANTIBACTERIALS	18
Beta-lactams	18
Mechanism of Action.....	19
Resistance	19
Macrolides	20
Mechanism of Action.....	21
Resistance	21
Fluoroquinolones.....	22
Mechanism of Action.....	23
Resistance	23
ANTIPARASITICS	25
Quinolines.....	25
Mechanism of Action.....	25
Resistance	26
Avermectins.....	26
Mechanism of Action.....	27
Resistance	28
ANTIMICROBIAL USE DURING THE COVID-19 PANDEMIC.....	29
Changes in Antibacterial Use	29
Changes in Antiparasitic Use	31
IMPLICATIONS FOR VETERINARY MEDICINE	34
CONCLUSIONS	36
REFERENCES	39
AUTHOR’S BIOGRAPHY	47

LIST OF FIGURES, TABLES, AND DEFINITIONS

Figures

Figure 1. Visual representation of the relationship between key terms regarding antimicrobials.....	5
Figure 2. Selection of resistant microorganisms when antimicrobials are used.....	8
Figure 3. Percentage of hospitals that met all seven CDC core elements of antimicrobial stewardship in 2019 (CDC, 2021a).....	13
Figure 4. Antimicrobial resistance can spread between humans, animals, and the environment (Walsh, 2018).	17
Figure 5. Antibacterial use during the COVID-19 pandemic compared to 2019 (CDC, 2021a)	30
Figure 6. Ivermectin prescriptions from retail pharmacies (Lind et al, 2021).....	33

Definitions

Anthroponotic Disease – diseases that can be spread from humans to animals

Antibacterial – An antimicrobial that is effective against bacteria

Antibiotic – An antimicrobial that is naturally produced by another organism

Antifungal – An antimicrobial that is effective against fungi

Anthelmintic – An antimicrobial that is effective against helminth worms

Antiparasitic – An antiparasitic that is effective against parasites

Antiprotozoal – An antiparasitic that is effective against protozoa

Antimicrobial – A substance that kills or inhibits the growth of certain microorganisms

Antimicrobial Resistance (AMR) – A microorganism is not affected by an antimicrobial

Antimicrobial Stewardship Programs – Programs that aim to measure and improve how antimicrobials are used

Antiviral – An antimicrobial that is effective against viruses

Bacterial Co-infection – A bacterial infection that is present in conjunction with another

infection

Bacterial Secondary Infection – A bacterial infection that occurs after another infection, often as a result of the primary infection

Horizontal Gene Transfer – the transfer of genetic material between individuals that may or may not be the same species

One Health – a collaborative cross-disciplinary approach to obtain the optimal health for humans, domestic animals, wildlife, plants, and the environment

Vertical Gene Transfer – the transfer of genetic information from the parent or parents to their offspring

Zoonotic Disease – diseases that can be spread from animals to humans

INTRODUCTION

The COVID-19 pandemic has had substantial effects on the healthcare system. These effects also have the potential to impact veterinary medicine because human and animal health are closely interrelated. One key aspect of human and animal health is antimicrobial use. The COVID-19 pandemic affected the use of these medicines by disrupting clinical service delivery, changing the antimicrobial supply chain, contributing to misinformation, and leading to the overtreatment of COVID-19 patients with antibacterials (Lynch et al., 2020). The effects brought about by the pandemic have the potential to affect antimicrobial use in veterinary medicine by changing the availability of certain drugs and increasing antimicrobial resistance in both humans and animals.

Humans and animals are often treated with the same medicines and a decrease in the availability of certain antimicrobials can lead to animals being more at risk of disease complications and inadequate treatment. The development of antimicrobial resistance is also a threat to both human and animal health. Antimicrobial resistance is correlated with increased economic costs and more severe infections in humans and animals (Bengtsson & Greko, 2014; CDC, 2019). Some of the major strains of resistant bacteria that infect both humans and animals are methicillin-resistant *Staphylococcus aureus* (MRSA), other methicillin-resistant staphylococci, vancomycin-resistant enterococci, carbapenemase-producing enterobacteria, and extended-spectrum beta-lactamase (ESBL) Gram-negative bacteria (Palma et al., 2020). Human infections associated with these strains can lead to worse health outcomes, increased medical costs, and increased risk of death (CDC, 2019).

The changes in antimicrobial use brought about by the COVID-19 pandemic can have serious effects on veterinary medicine by contributing to the development of resistance in microorganisms. A decrease in the availability of certain antimicrobials for animal use can lead to the incorrect drug being used to treat infections. This can lead to the development of resistance since inappropriate antimicrobial use can allow some microorganisms to survive. The increase in antimicrobial use in humans can also increase antimicrobial resistance. As many microorganisms are capable of sharing their resistance with other strains through mechanisms of horizontal gene transfer, antimicrobial resistance can be spread to a wide variety of microorganisms. This can also lead to microorganisms that infect animals to also develop resistance. As animals rely on humans for their healthcare, increases in antimicrobial resistance in human pathogens can also lead to increases in animal diseases and decreases in animal welfare. Increases in human healthcare costs, longer hospital stays, and more serious infections can lead to people not having the resources available to care for their animals.

This review aims to assess how the COVID-19 pandemic has affected antimicrobial use in human medicine. This information will then be used to assess the possible impacts that changes in human medicine could have on veterinary medicine. The results will then be used to understand how the COVID-19 pandemic affected the development of antimicrobial resistance and highlight the importance of considering the interdependence of human and veterinary medicine.

METHODOLOGY

The information gathered in this literature review was obtained by utilizing the University of Maine's Raymond H. Fogler Library using the One Search database function and the United States Center for Disease Control website. The CDC's website was used exclusively for investigating the recommendations for COVID-19 treatments, and the One Search databases were used for all other searches. The search terms used include "antimicrobials", "antibiotics", "antibacterials", "antiparasitics", "COVID-19", "pandemic", "resistance", "One Health", "veterinary", "stewardship", "beta-lactams", "macrolides", "fluoroquinolones", "quinolines", "ivermectins", "ivermectin", and "hydroxychloroquine."

WHAT ARE ANTIMICROBIALS?

Antimicrobials are substances that are used to treat a variety of diseases by killing or inhibiting the growth of certain microorganisms (WHO, 2020). Antimicrobials are often divided into antibacterials, antivirals, antifungals, and antiparasitics, each of which is further divided into subcategories. It should be noted that one substance can have several properties, such as being antibacterial and antiparasitic. While the term antibiotic is often used interchangeably with antibacterial, not all antibacterials are antibiotics. The term antibiotic refers to an antimicrobial that is produced naturally by microorganisms to inhibit the growth of another microorganism. Antibiotics can have antibacterial, antiviral, antifungal, or antiparasitic activity. An example of an antibiotic that is also an antibacterial is penicillin, which is produced by the fungus *Penicillium* to inhibit the growth of bacteria, though today penicillin is also produced synthetically (Lowe, 2020). For the purposes of this review, the term antibiotic will not be used to refer to antibacterials, but it should be noted that this is a common practice (WHO, 2019). Figure one displays a diagram that highlights the relationship between the key terms regarding antimicrobials.

Antimicrobial

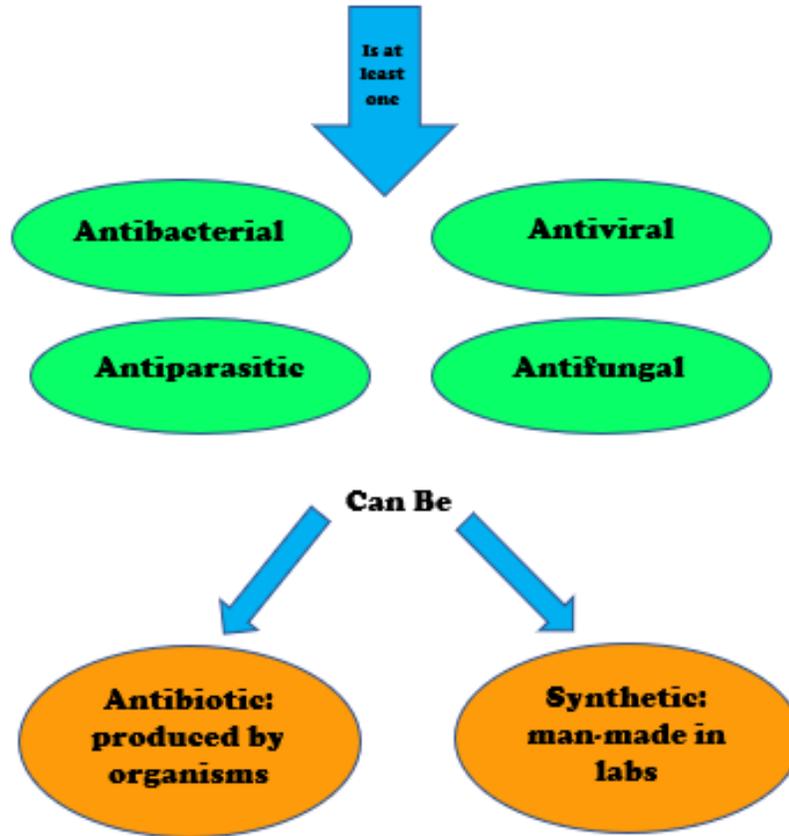


Figure 1. Visual representation of the relationship between key terms regarding antimicrobials

Antimicrobials are critically important for the treatment of infectious diseases, and their discovery led to a large global decline in mortality. From 1938 to 1952, the infectious disease mortality rate in the United States declined by 8.2% each year as a result of antimicrobial use (Aminov, 2017). As of 2019, antibacterials were the most commonly prescribed drugs in hospitals worldwide (Yimenu et al., 2019). These drugs have contributed to safer childbirth, surgical procedures, and organ transplants (Marston et al., 2016). In addition to their applications in human health, antimicrobials are used in

the maintenance of animal welfare by treating and preventing diseases (Landers et al., 2012). As the use of antibacterials and antiparasitics was most affected by the COVID-19 pandemic, they will be the focus of this paper. The effects of the COVID-19 pandemic on antibacterial use are largely related to the fact that antibacterials were commonly prescribed to individuals suffering from COVID-19 to combat possible secondary- or co-bacterial infections (Langford et al., 2020). Antiparasitic use was also affected as there was research into the antiviral properties of several antiparasitics. These studies have focused on the possible uses of hydroxychloroquine and ivermectin in treating COVID-19, however, the CDC has stated that there is not enough evidence to support their use (“Chloroquine or hydroxychloroquine”, 2021; “Ivermectin”, 2021). Despite this, some people still used these drugs to treat COVID-19. The three antibacterial classes covered are beta-lactams, macrolides, and fluoroquinolones. Two antiparasitic classes, quinolines and avermectins, will be discussed.

WHAT IS ANTIMICROBIAL RESISTANCE?

Antimicrobials are invaluable in protecting human and animal health, but the effectiveness of these drugs is becoming increasingly threatened. Microorganisms have adapted, and some have developed antimicrobial resistance (AMR) and are no longer affected by the antimicrobials we rely on to save lives. The situation is so dire that the WHO named AMR as one of the top ten global public health threats to humanity (“Antimicrobial Resistance”, 2020). Antimicrobial resistance is a global threat that crosses country and species lines as the vast majority of antimicrobial classes are used in human, animal, and plant applications (McEwen & Collignon, 2018).

Factors Contributing to Antimicrobial Resistance

Antimicrobial resistance develops through the process of natural selection. Some microorganisms have genes that allow them to be unaffected by the antimicrobial, and these microorganisms survive while those who are affected by the antimicrobial die when antimicrobials are used. Figure two demonstrates how the use of antimicrobials can lead to resistant organisms being the dominant strain. It should be noted that for simplicity figure two does not take into account the effects of the host’s immune system. The immune system also acts against pathogenic microorganisms, which reduces the chances of antimicrobial use contributing to the development of antimicrobial resistance by eliminating resistant organisms.

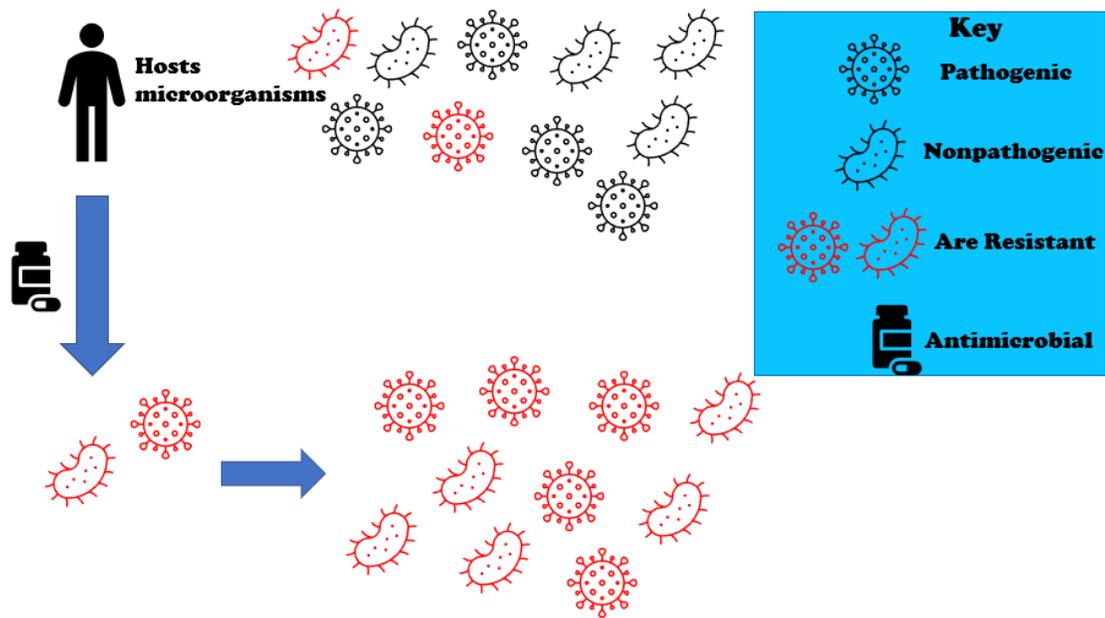


Figure 2. Selection of resistant microorganisms when antimicrobials are used

There are many factors that contribute to the development of AMR. The first is that many microorganisms reproduce quickly. For example, the bacterium *Staphylococcus aureus* can replicate and reproduce roughly every half hour. This means that in less than twelve hours, their numbers can increase by over one million-fold (Marston et al., 2016). Each replication provides the chance for new mutations to develop in the microorganism's genome, and their rapid generation time allows them to quickly evolve to overcome the effects of antimicrobials.

When antimicrobials are used, the organisms present undergo selection pressure, and only those that are resistant survive. The resistant organisms are then able to reproduce and quickly grow in numbers while the non-resistant organisms die, as seen in figure two. This selection process forms the basis for the development of AMR.

Human behavior arguably has the greatest effect on the development of AMR. While the genetics of the microorganisms is what confers resistance, antimicrobial use

selects for the organisms that are resistant. Some factors that contribute to the development of AMR include over-use of antimicrobials, misuse of antimicrobials, poor disease prevention, and inadequate access to vaccines and medicine. (WHO, 2020). Over-using antimicrobials provides more chances that a microorganism will be exposed to the antimicrobial and lead to the selection of resistant individuals. Similarly, misuse of antimicrobials can lead to the development of resistance since the antimicrobial may not be used in a way that will ensure the elimination of the microorganism. This can lead to more microorganisms surviving the exposure and developing resistance. Also, if the incorrect antimicrobial is used, it can select for resistant microorganisms that are not the ones causing the disease. These species can then transfer their resistance to other species, as discussed in the next section. Poor disease prevention can lead to the development of AMR because if a disease is prevented, there would be less use of antimicrobials to which the microorganism could be exposed. Preventing the disease limits the use of antimicrobials and therefore the chances of selecting for resistant organisms.

Mechanisms of Antimicrobial Resistance Sharing

All organisms are capable of vertical gene transfer, which refers to the transfer of genetic information from the parent or parents to their offspring. This allows for resistance genes to be passed on to the next generation. In addition to vertical gene transfer, microorganisms, particularly bacteria, have mechanisms that allow them to share their resistance with other individuals through horizontal gene transfer. In horizontal gene transfer, genetic information is shared with other individuals that may or may not be of the same species. In bacteria, antimicrobial resistance genes are often found on plasmids,

and bacteria can share DNA on these structures with each other. As plasmids are found in a variety of bacterial species, this allows for resistance to be shared between different species (Marston et al., 2016). In conjugation, a bacterium will replicate its plasmid and transfer one copy to another bacterial cell. If this plasmid contained a gene that confers resistance, both bacteria are now resistant (Graf et al., 2018).

Bacteria can also acquire resistance genes through phage-mediated transduction, where a virus called a bacteriophage transfers bacterial DNA into a bacterium. The bacterial DNA that was transferred by the virus may contain genes for resistance, which leads to the spread of AMR. Transformation is a process where bacteria can take up DNA in their environment, which also has the potential to lead to the development of resistance (Graf et al., 2018). Some bacteria also possess mobile genetic elements, like transposons that are capable of moving within and between bacterial cells (Johansson et al., 2020). As these genetic sequences can move between the chromosomes and plasmids of different bacteria, they can confer resistance on more bacteria (Babakhani & Oloomi, 2018).

Problems Associated with Antimicrobial Resistance

Antimicrobial resistance is harmful in regard to human and animal health as well as in relation to economic costs. According to the CDC's 2019 AR threat report, more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die from these infections (CDC, 2019). Antimicrobial resistance makes diseases more difficult to treat and correlates to worse health outcomes.

Antimicrobials are also important for other medical procedures. Chemotherapy, organ transplants, surgeries, and intensive care treatment all depend on the availability of

effective antimicrobials. The effects on animal health are also considerable as antimicrobial resistance can lead to more complicated treatment and higher rates of euthanasia and death (Bengtsson & Greko, 2014).

In addition to its effects on health, antimicrobial resistance also has a large economic impact. In 2013, the CDC estimated that AMR cost the U.S. \$55 billion in excess health care costs and lost productivity (Prestinaci et al., 2015). Similar increases in costs are associated with antimicrobial resistance in animals. There are also other costs associated with AMR in animals. Money spent training and raising the animals, particularly in horses, service animals, and production animals, is lost upon the animal's death (Bengtsson & Greko, 2014).

WHAT IS ANTIMICROBIAL STEWARDSHIP?

The goal of antimicrobial stewardship programs, also called antibiotic stewardship programs, is to measure and improve the use of antimicrobials in order to effectively treat infections, prevent harm caused by unnecessary antimicrobial use, and combat antimicrobial resistance (CDC, 2021b). In order to treat infections, an antimicrobial that is appropriate and effective needs to be selected. Similarly, many antimicrobials have adverse side effects, so they should only be used when necessary. Ensuring the appropriate use of antimicrobials helps to maximize positive patient outcomes while limiting possible negative side effects. As overuse and misuse of antimicrobials contribute to antimicrobial resistance, these steps also help to prevent the development of resistance.

The responsible use of antimicrobials involves ensuring that the right antimicrobial is prescribed and taken for the correct amount of time. This is done through a combination of providing guidelines and education to medical professionals, patients, and the community (Doron & Davidson, 2011). Prescribers should ensure that they are making accurate diagnoses and following antimicrobial guidelines (Dyar et al., 2017). Antimicrobial stewardship programs can be found in hospitals, communities, veterinary practices, and the WHO global stewardship framework (Dyar et al., 2017). The CDC identifies seven core elements of antimicrobial stewardship, which are Leadership, Accountability, Pharmacy expertise, Action, Tracking, Reporting, and Education (CDC, 2021c). Figure three shows the percentage of hospitals by state that met all seven of these elements in 2019 (CDC, 2021a).

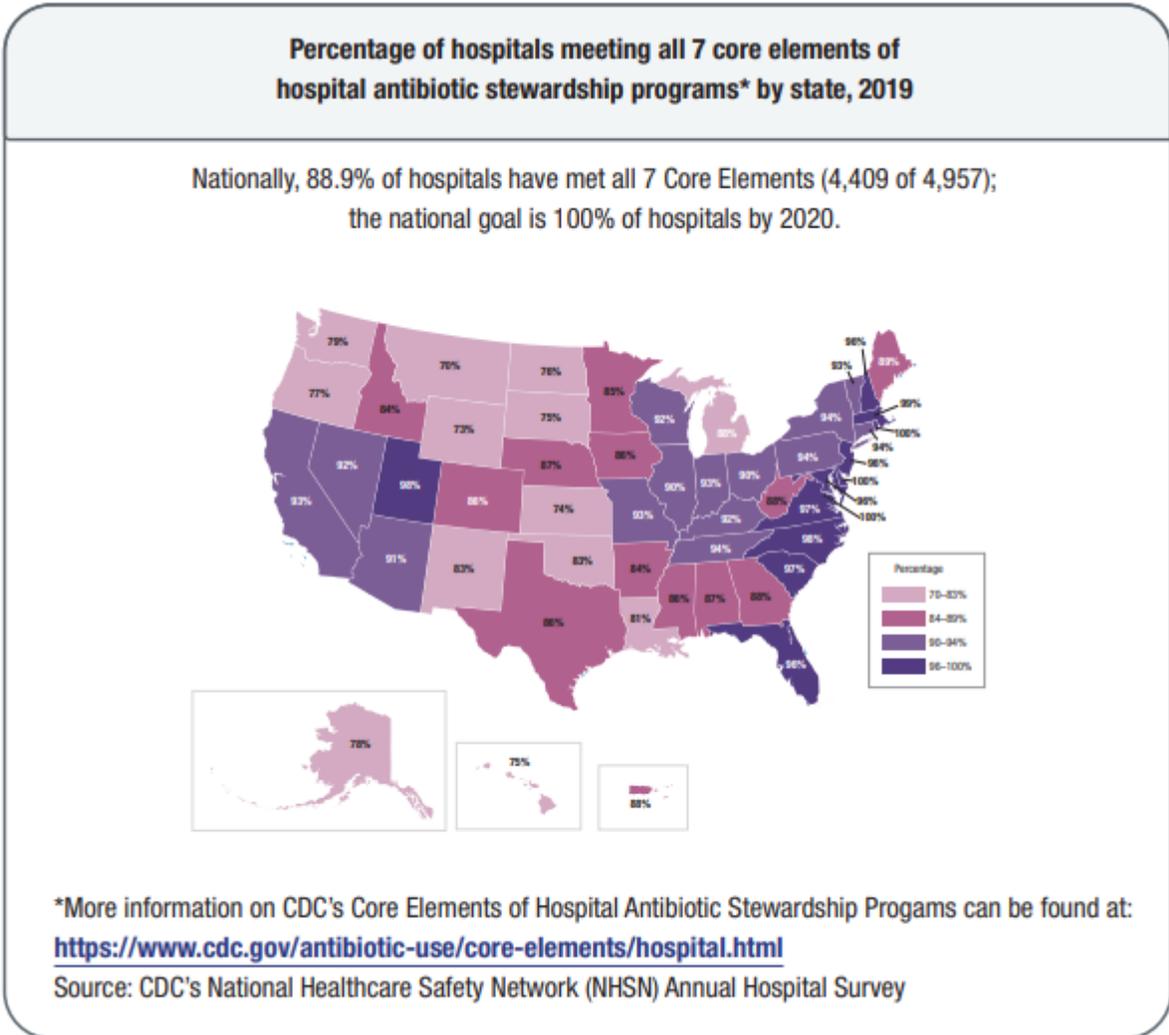


Figure 3. Percentage of hospitals that met all seven CDC core elements of antimicrobial stewardship in 2019 (CDC, 2021a)

While the CDC does not require the presence of clinical microbiologists on antimicrobial stewardship teams, the inclusion of these individuals can greatly increase the success of these programs. This increase in success is related to providing patient-specific culture and susceptibility data that can be used to identify the pathogen and which antimicrobials it is susceptible to. A survey of hospitals in Quebec found that 89% of hospitals included a clinical microbiologist in their stewardship programs while other

surveys have found that only 26% of hospitals in California and 42% of hospitals in Florida included microbiologists in their stewardship programs, indicating that stewardship programs can still be improved (Morency-Potvin et al., 2017). The use of antimicrobial sensitivity tests, which are more common in veterinary medicine than in human medicine, would improve the use and effectiveness of antimicrobials which would help to limit the development of antimicrobial resistance. It would also improve the health outcomes of patients by providing more effective treatment (Khan et al., 2019).

THE ONE HEALTH PERSPECTIVE

The universal use of antimicrobials and the interconnectedness of human, animal, and environmental health has led to the development of a One Health approach to address many health-related problems, including antimicrobial resistance. One Health refers to a collaborative cross-disciplinary approach to obtain optimal health for humans, domestic animals, wildlife, plants, and the environment (McEwen & Collignon, 2018). The One Health perspective takes into account that antimicrobial resistance in one sector can impact all of the others. This is true of both human and veterinary medicine.

Humans and animals are infected with many of the same species of microorganisms. Zoonotic diseases, or zoonoses, are diseases that are caused by organisms that can spread between animals and humans. It is estimated that every six out of ten known diseases are zoonotic and three out of every four new or emerging infections in humans originate from animals. Some examples of zoonoses are influenza, salmonellosis, West Nile virus, rabies, Lyme disease, and COVID-19 (CDC, 2021d).

One example of how the environment influences human and veterinary medicine is the presence of natural resistance in organisms in the environment. Mechanisms of resistance to penicillins were discovered in soil bacteria years before penicillins were clinically used in humans. Bacterial modes of horizontal gene transfer allow for these soil organisms to transmit their resistance genes to other bacterial species that can cause disease. The rapid increase in AMR to penicillins likely had its foundations in the presence of these genes in soil organisms that were exposed to these compounds by the fungi with which they shared an environment (Fernandes et al., 2013).

Antimicrobial use in human and veterinary medicine can also affect the environment. Fluoroquinolones are widely used in both animal and human medicine, which can lead to their introduction into the environment. Unused medications can be improperly disposed of and end up in wastewater, and a certain amount of these antibacterials end up in the feces of those treated with them. Spreading manure and sewage sludge to agricultural fields is a common practice that can introduce these drugs into the environment. Resistant pathogenic bacteria have been detected in wastewater and sewage-treatment plants (Picó & Andreu, 2006). These bacteria can then infect animals and confer their resistance genes to other bacteria. Plants can also take up these chemicals from the soil and their presence has been detected in carrots and lettuce (Boxall et al., 2006). In the United States and Spain where fluoroquinolones are commonly used in animals, high rates of resistance, sometimes over 80%, have been detected in food-borne pathogens. In Australia, where fluoroquinolones are not approved for animal use, fluoroquinolone resistance rates in these pathogens were significantly lower, indicating that human and animal health are closely related (Pham et al., 2019).

Animals share the same environment as humans and often the same infections (McEwen & Collignon, 2018). The same antimicrobials are used in almost all applications and microorganisms have developed ways to share resistance both among and between species. In order to ensure that antimicrobials stay effective, antimicrobial use must be monitored in human, animal, and environmental health sectors. Figure four shows how antimicrobial resistance organisms and genes can spread (Walsh, 2018).

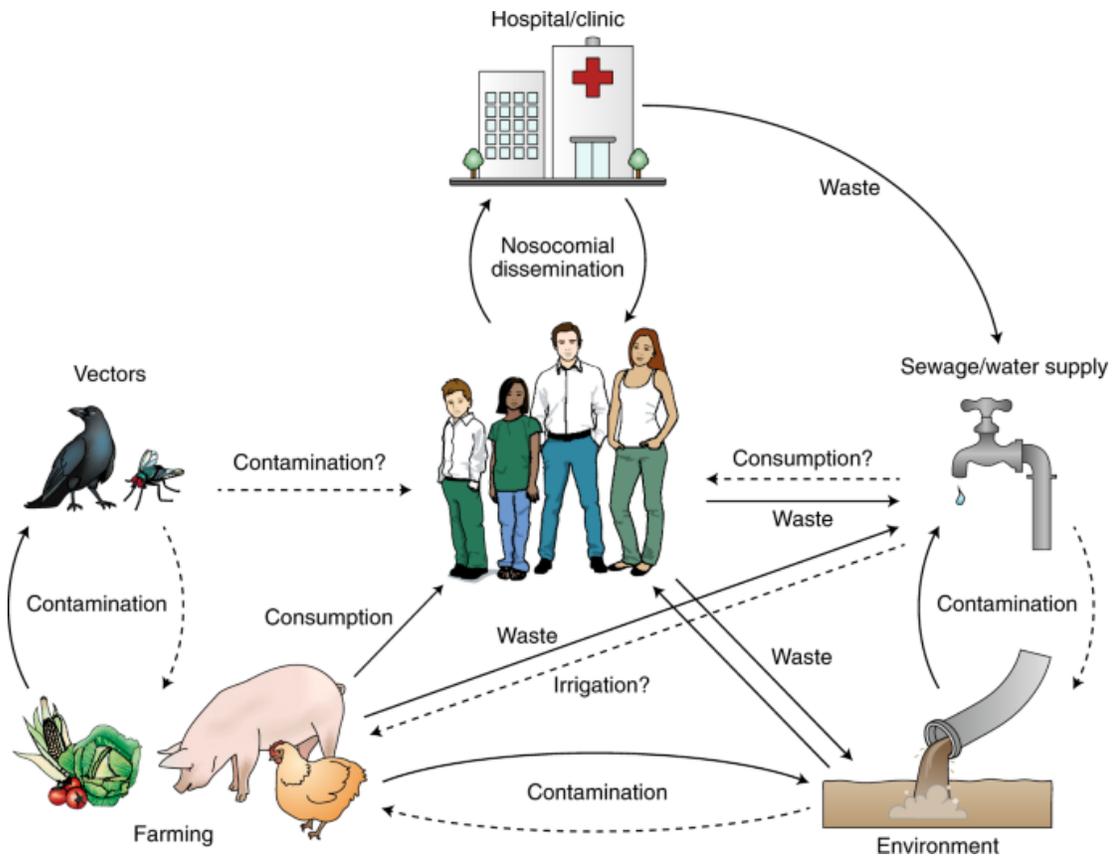


Figure 4. Antimicrobial resistance can spread between humans, animals, and the environment (Walsh, 2018).

ANTIBACTERIALS

Antibacterials are a class of antimicrobials that kill or inhibit the growth of bacteria. As of 2019, antibacterials were the most commonly prescribed drugs in hospitals worldwide (Yimenu et al., 2019). The three antibacterial classes that will be reviewed in this paper are beta-lactams, macrolides, and fluoroquinolones. All three classes are used in both human and veterinary medicine. These three classes were chosen because they are all important in the treatment of both humans and animals and are widely used.

Beta-lactams

Beta-lactams are the most widely used class of antibacterials, accounting for 65% of all prescriptions of injectable antibacterials in the U.S. (Bush & Bradford, 2016). Beta-lactams are characterized as having a beta-lactam ring, which is a four-cornered ring containing a nitrogen atom (Fernandes et al., 2013). Some beta-lactams have sidechains connected to the ring, and a small percentage of patients have an allergic reaction to beta-lactams due to these side-chain determinants. Penicillin G was the first beta-lactam to be used clinically. Some examples of beta-lactams are penicillins, cephalosporins, monobactams, and carbapenems (Bush & Bradford, 2016).

Beta-lactams are broad-spectrum antibacterials that are widely used in both human and veterinary medicine to treat and prevent infections caused by bacteria. They are effective against many bacteria, including *Streptococcus* and *Staphylococcus* species, Gram-positive, Gram-negative, enteric, and anaerobic bacteria (Bush & Bradford, 2016).

They have also been used to improve growth rate and feed efficiency in food animals (Li et al., 2007). The basis for their growth-promoting effect is not known, but some hypotheses include that the antibacterial works against microorganisms present in the animal feed that consume some nutrients, inhibit the absorption of nutrients, or negatively impact the animal's health (Chattopadhyay, 2014). Beta-lactams are listed on the World Health Organization's (WHO) list of critically important antimicrobials for human medicine and the World Organization for Animal Health's (OIE) list of antimicrobials of veterinary importance (OIE, 2021; WHO, 2019).

Mechanism of Action

Almost all bacteria cells have a cell wall that functions to maintain the shape of the cell and withstand intracellular pressure. These cell walls are made of peptidoglycan, which is found only in bacterial cells (Scheffers & Pinho, 2005). Beta-lactams interfere with the formation of the cell wall by binding to penicillin-binding proteins, which are enzymes essential for peptidoglycan cross-linking (Bush & Bradford, 2016). The enzymes become non-functional, and the bacteria cannot build their cell wall. As bacteria cannot survive without their cell wall, this results in their death.

Resistance

As beta-lactams have been widely used for many years, bacteria have developed resistance to them. Resistance to beta-lactams developed rapidly. Six years after its introduction to the market, resistance to benzylpenicillin in staphylococci went from less than 10% to 60%, and resistance is found in over 90% of staphylococci today (Fernandes

et al., 2013). The most common form of resistance is the presence of beta-lactamases in bacteria. These enzymes alter the beta-lactam ring of the antibacterial, which renders them ineffective. Many of the genes associated with beta-lactamases are found on plasmids and transposons, which facilitates the spread of resistance to other bacterial species (Fernandes et al., 2013). In order to combat this resistance problem, beta-lactamase inhibitors were developed that prevent the beta-lactamase enzyme from altering the beta-lactam ring (Bush & Bradford, 2016).

Another form of resistance involves the alteration of the structure of the penicillin-binding proteins so that they are not affected by the binding of a beta-lactam. These altered penicillin-binding proteins are still functional even in the presence of beta-lactams. Some bacterial cells have developed resistance by developing efflux pumps that actively remove the antibacterial from the cytoplasm or alterations in the cell membrane that limit beta-lactams from entering in the first place (Fernandes et al., 2013).

Macrolides

Macrolides are a group of compounds that are made up of a 12-, 14-, 16-, or 17-membered macrocyclic lactone ring with various attachments that have antibacterial activity. They were first isolated from a *Streptomyces* bacterial strain (Dinos, 2017). Macrolides are the second most prescribed antibacterial class in the United States, and azithromycin was the most prescribed antibacterial agent (Hicks et al., 2015). Other macrolides are erythromycin, clarithromycin, and fidaxomicin. Macrolides have a slightly broader spectrum of activity than beta-lactams, and they are often used in those with penicillin allergies (Aminov, 2017).

Macrolides are broad-spectrum antibacterials that are widely used in both human and veterinary medicine. Their uses in human medicine include infections caused by *Mycoplasma* species, *Chlamydia* species, and some Gram-negative bacteria. Veterinary applications include preventing and treating bovine respiratory disease complex and mastitis in cattle as well as a variety of other bacterial infections in companion animals, swine, and sheep (Anadón & Reeve-Johnson, 1999; Trott et al., 2021). Macrolides are listed as critically important antimicrobials on both the WHO's list of critically important antimicrobials for human medicine and the OIE's list of antimicrobials of veterinary importance (OIE, 2021; WHO, 2019).

Mechanism of Action

All cells need to be able to create proteins in order to perform the functions necessary for life. Macrolides interfere with this process and disrupt protein synthesis. The macrocyclic lactone ring of the macrolide binds to the 50S ribosomal subunit and blocks where newly synthesized proteins are released. The macrolide disrupts protein synthesis by either disrupting peptide bond formation in the protein or inhibiting elongation of the peptide through steric hindrance (Lenz et al., 2021). As the bacteria can no longer synthesize the proteins it requires, it will be unable to divide and will die.

Resistance

Bacteria have developed resistance to macrolides through two main mechanisms. The first is through modification of the ribosomes to prevent the macrolide from binding. Some bacteria add methyl groups to the binding site of the macrolide, which prevents the

macrolide from binding there and preventing protein synthesis. Nearly forty genes associated with this type of resistance have been identified and many are found on plasmids and transposons. Other bacteria have mutations in the genes that code for the part of the ribosome that macrolides bind to. This mutation alters the structure enough so that the macrolide cannot attach. Genes for this type of resistance are generally spread through transformation. The other form of resistance is through the use of efflux pumps that actively pump out the macrolide molecules. These pumps remove the macrolide from the cytoplasm before it has a chance to disrupt protein synthesis. The genes for this type of resistance are found on plasmids as well as large transposons (Leclercq, 2002).

Fluoroquinolones

Fluoroquinolones, also known as quinolones, have a bicyclic structure that contains a fluorine atom. Examples of fluoroquinolones include ciprofloxacin, ofloxacin, levofloxacin, enrofloxacin, danofloxacin, and orbifloxacin (Picó & Andreu, 2006). They are active against Gram-positive and Gram-negative bacteria as well as mycobacteria. Fluoroquinolones are broad-spectrum antibacterials that are used in both human and veterinary medicine to treat a wide variety of bacterial diseases. In humans, fluoroquinolones are used to treat urinary tract infections, digestive tract infections, and respiratory infections. Some specific diseases that are targeted are typhoid caused by *Salmonella* and pneumonia (Pham et al., 2019). Fluoroquinolones are important in veterinary medicine, especially in the treatment of septicemias, respiratory, and enteric diseases (OIE, 2021). Fluoroquinolones are listed on the WHO's list of antimicrobials

important for human medicine and the OIE's list of antimicrobials as critically important (OIE, 2021; WHO, 2019).

Mechanism of Action

All cells need to be able to synthesize DNA in order to divide, and bacteria are no exception. The mechanism of fluoroquinolones involves interfering with bacterial DNA synthesis by inhibiting two topoisomerase enzymes, DNA gyrase and topoisomerase IV. These two enzymes are involved in the unwinding of DNA so that the replication machinery can access the DNA molecule (Blondeau, 2004). If these enzymes cannot function, the bacterial cell cannot separate its DNA, which prevents DNA replication. Without DNA replication, the bacterial cell cannot divide to make more cells, which limits its growth and leads to its death.

Resistance

Bacteria can develop resistance to fluoroquinolones through two main mechanisms. The first is through alteration of the structure of DNA gyrase and topoisomerase IV. A mutation in even one single amino acid sequence of these enzymes leads to decreased ability of the fluoroquinolone to bind and inhibit the enzyme. If the fluoroquinolone cannot bind to the enzyme, then it cannot inhibit DNA synthesis (Pham et al., 2019). Another form of resistance relies on decreasing the concentration of fluoroquinolones in the cytoplasm. This can be done by reducing the ability of fluoroquinolones from entering the cell through decreased porin structures. Efflux pumps can also be used to remove the fluoroquinolone once it has already entered the cytoplasm.

Several genes related to both types of resistance can be found on plasmids, allowing for horizontal gene transfer between bacteria (Pham et al., 2019).

ANTIPARASITICS

Antiparasitics are a class of antimicrobials that kill or inhibit the growth of parasitic organisms, which includes endoparasites like helminths and protozoa, as well as ectoparasites, such as arthropods. The two antiparasitic classes reviewed in this paper are the quinolines and avermectins, which are used in both human and veterinary medicine.

Quinolines

Quinolines are antiparasitics that are derived from the quinoline molecule. Examples of quinolines include chloroquine, hydroxychloroquine, quinine, and mefloquine. In human medicine, they are primarily used to treat and prevent malaria, which is caused by a protozoan. They are also used to treat several autoimmune disorders including rheumatoid arthritis and systemic lupus erythematosus (Schrezenmeier & Dörner, 2020). Quinolines can also be used in veterinary medicine for the treatment of some autoimmune diseases in dogs (Oberkirchner et al., 2011). Chloroquine is also used in fish to treat and prevent some protozoal diseases (Hemdal, 2020).

Mechanism of Action

For part of its lifecycle, the protozoan that causes malaria, *Plasmodium*, breaks down the hemoglobin of host red blood cells in order to acquire nutrients. This occurs in the protozoal food vacuole. One of the by-products, heme, is toxic to the organism and is normally detoxified by being converted into a crystalline structure called hemozoin. Quinolines prevent the detoxification of heme by binding to the heme and preventing the

protozoan's enzymes from acting on it. The free heme can then destabilize the food vacuole's membrane and enter the cytoplasm. From there, several effects can cause the organism's death. Heme is capable of inhibiting protein function, disrupting membranes, and creating reactive oxygen molecules that can damage DNA, proteins, and lipids (Sigala & Goldberg, 2014).

Resistance

One of the most studied quinolines is chloroquine. Resistance to chloroquine relies on the organism's ability to decrease the amount of chloroquine that accumulates in the food vacuole, though the exact mechanism of this ability is not known. One proposed mechanism is the use of efflux pumps that actively remove the quinoline molecules. Another possible mechanism is that less quinoline accumulates in the first place. This could be due to changes in pH difference between the vacuole and the cytoplasm which would reduce the amount of chloroquine that enters the food vacuole. Finally, decreased chloroquine concentrations could be due to changes in the proteins involved in the transport of the quinoline into the cell that decrease the amount of chloroquine that enters (Foley, 1998).

Avermectins

Avermectins have a 16-membered macrocyclic lactone structure and have antiparasitic activity. They were first isolated from the bacteria *Streptomyces avermitilis* (Shoop et al., 1995). Ivermectin, abamectin, doramectin, eprinomectin, moxidectin, and selamectin are all avermectins. These compounds have anthelmintic and insecticidal

properties (El-Saber Batiha et al., 2020). In human medicine, avermectins are used to treat river blindness, various roundworm infections, whipworm, lice, and mites. In veterinary medicine, avermectins are used to treat and prevent infections caused by roundworms, lungworms, heartworms, mites, lice, and ticks (Crump & Omura, 2011).

Mechanism of Action

Avermectins target the nervous system of parasites in order to paralyze them. The nervous and muscular systems rely on the movement of ions through voltage-gated ion channels to create electrical impulses. Avermectins bind to glutamate-gated chloride channels, which are found only in invertebrates (Wolstenholme, 2012). By binding to these channels, avermectins prevent the channel from closing and let more chloride into the cell. This keeps the cell's cytoplasm more negative and prevents the formation of an electrical signal. As the organism can no longer move, it eventually dies (Lenz et al., 2021). Avermectins also have the potential to bind to other channels, such as GABA-gated chloride channels, which are present in both invertebrates and vertebrates. This can lead to potential adverse side effects in the patient, particularly at high doses (Chen & Kubo, 2017). Early uses of ivermectin were associated with extreme neurotoxicity in some collie dogs due to their genetics. Some dog breeds, such as collies, have a deletion mutation of the *mdr1* gene, which allows the ivermectin molecules to cross the blood-brain barrier. As this mutation also leads to increased sensitivity to other drugs, genetic testing before treatment in these breeds, as well as other species, is becoming increasingly common (Mealey et al., 2001).

Resistance

There are two main mechanisms of resistance to avermectins. The first is through mutations in the genes coding for glutamate-gated chloride channels, which would result in a different structure for these channels. This different structure makes it less likely that avermectins can bind to the receptors and affect the organism (Chen et al., 2016). The other mode of resistance is through the metabolism of avermectins into a less toxic chemical. If the avermectin is metabolized quickly enough, this prevents the molecule from exerting its effect (Riga et al., 2014). The organisms that survive can then pass the genes that confer resistance to their offspring.

ANTIMICROBIAL USE DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has had a profound effect on the healthcare system, and antimicrobial stewardship programs were no exception. These programs were disrupted by changes in clinical service delivery, antimicrobial supply chain changes, and overtreatment of COVID-19 patients with antibacterials (Lynch et al., 2020). While COVID-19 is caused by a virus, there has been an increase in the use of antibacterials and antiparasitics in the treatment of COVID-19 patients. Antibacterials are commonly prescribed to those with a viral infection either because they were misdiagnosed or to treat or prevent a bacterial infection. A bacterial co-infection is a bacterial infection that is present in conjunction with another infection, such as a viral infection. A bacterial secondary infection is an infection that occurs after the first infection. Bacterial secondary infections occur with viral infections because these infections can weaken the immune system and disrupt mechanisms to prevent infection (Langford et al., 2020). The lack of treatment options for COVID-19 has also led to increased use of certain antiparasitics including ivermectin and hydroxychloroquine because of their possibly antiviral properties.

Changes in Antibacterial Use

The COVID-19 pandemic coincided with an increase in antibacterial use since antibacterials were commonly prescribed to individuals suffering from COVID-19. Recent studies have found that 72% of COVID-19 patients were treated with antibacterials, but only 7% had a bacterial co-infection (Lansbury et al., 2020; Rawson et

al., 2020). A study in the United Kingdom found that out of 49,000 patients, 37% were prescribed antibacterials before they were even admitted to a hospital and 85% received at least one antibacterial while in the hospital (Kuehn, 2021). Figure five demonstrates the increase in antibacterial prescriptions in hospitals at the beginning of the COVID-19 pandemic (CDC, 2021a).

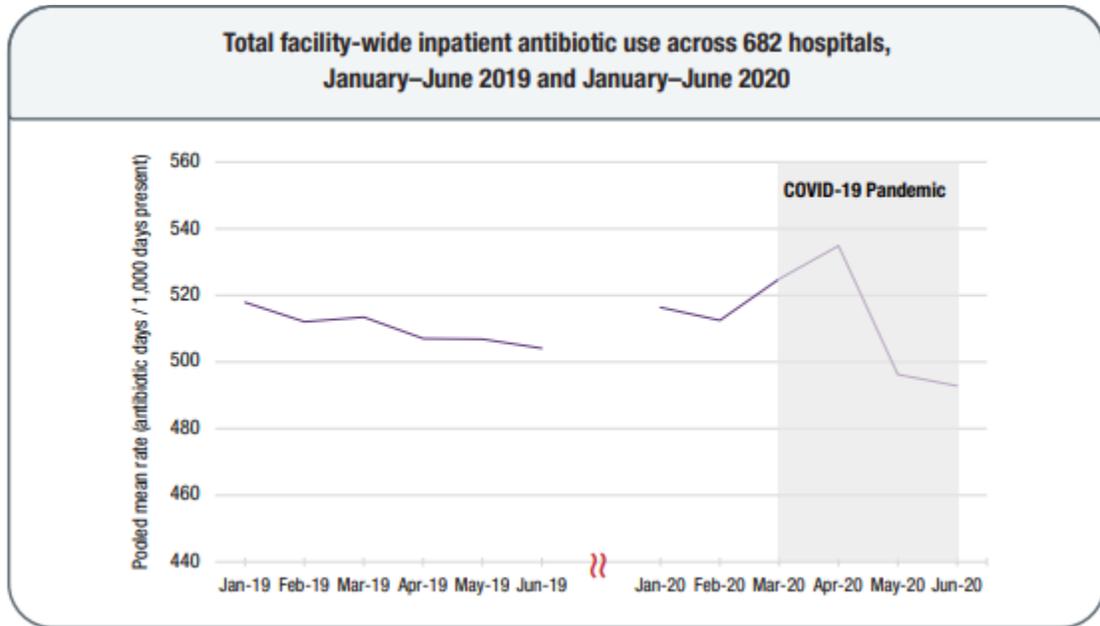


Figure 5. Antibacterial use during the COVID-19 pandemic compared to 2019 (CDC, 2021a)

The increase in antibacterial use is likely due to a variety of factors. The main symptoms of COVID-19 are nonspecific and can be attributed to a number of respiratory diseases, some of which are caused by bacteria. This combined with a lack of a diagnostic test for COVID-19 at the beginning of the pandemic made it difficult for healthcare providers to rule out the possibility of a bacterial infection and led to increased use of antibacterials (Pulia et al., 2020). A study that surveyed 166 participants from twenty-three countries found that the decision to prescribe antibacterials to COVID-19

patients was made mainly on the presentation of clinical symptoms rather than lab tests (Beović et al., 2020). There were also concerns regarding bacterial co-infections and secondary infections with COVID-19 because these infections are relatively common with other viral respiratory diseases. For example, bacterial co-infections can occur in as many as 20-30% of severe influenza cases (Langford et al., 2020). In contrast, a review of 3,338 patients with COVID-19 found that only 3.5% had a bacterial co-infection and only 14.3% developed a bacterial secondary infection (Langford et al., 2020). The reasons behind this discrepancy have not been well studied. Since COVID-19 was a novel infection, healthcare providers had to make prescribing judgments without research on the prevalence of bacterial co-infections in COVID-19 patients, which contributed to the overuse of antibacterial use. Other factors that likely impacted antibacterial use were the increased workload on prescribers and the severity of COVID-19. A lack of specific guidelines for the treatment of COVID-19 combined with a dangerous and highly contagious disease hindered the effective use of antibacterials.

Changes in Antiparasitic Use

There has been a significant amount of research into possible treatments for COVID-19. While antiparasitics are generally used to treat parasitic infections, some antiparasitics also have antiviral properties. Studies have been done, and are still being conducted, on the possible uses of hydroxychloroquine and ivermectin in treating COVID-19, however, there is not enough evidence to support their use. Claims that hydroxychloroquine can be used to treat COVID-19 rely on research that shows that hydroxychloroquine can inhibit the binding of the SARS-CoV-2 virus to the host cell

membrane *in vitro* (“Chloroquine or hydroxychloroquine”, 2021). While early uncontrolled and non-peer-reviewed studies stated that hydroxychloroquine was effective in treating COVID-19, subsequent randomized controlled studies have demonstrated that hydroxychloroquine has no effect and can even be harmful (Udupa et al., 2021).

Similarly, the claims supporting the use of ivermectin are also not verified, and its use can lead to serious medical complications (Zaheer et al., 2021). While ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell cultures, doses of up to 100-times higher than recommended for human use would be needed, negating any potential positive effect (“Ivermectin, 2021). The use of ivermectin or hydroxychloroquine to treat or prevent COVID-19 is not recommended by the FDA or the WHO.

Despite a lack of research, hydroxychloroquine was promoted as a COVID-19 treatment by prominent members of society, including President Trump. The CDC reported that there was an eighty-fold increase in new hydroxychloroquine and chloroquine prescriptions from March of 2019 to March of 2020 (Bull-Otterson et al., 2020). Ivermectin prescriptions and sales have also significantly increased during the pandemic. A 24-fold increase in outpatient retail pharmacy prescriptions of ivermectin was seen. Figure six shows the estimated number of outpatient ivermectin prescriptions from retail pharmacies This does not include the ivermectin sold over-the-counter for veterinary applications, mail-orders, or non-oral formulations. There has also been a five-fold increase in ivermectin-related calls to the poison control center (Lind et al., 2021).

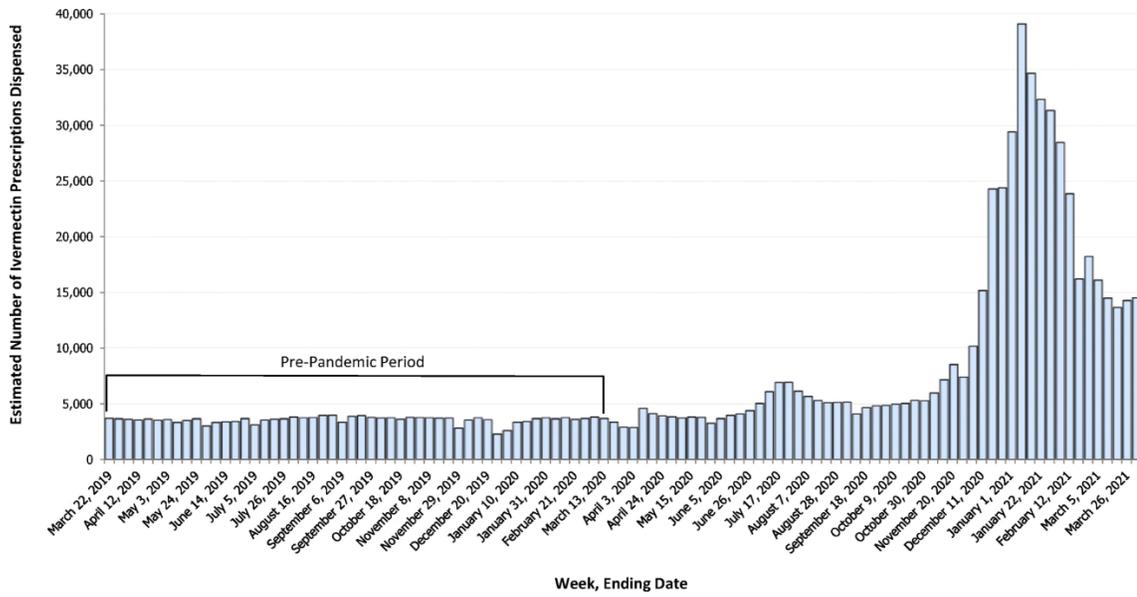


Figure 6. Ivermectin prescriptions from retail pharmacies (Lind et al, 2021)

IMPLICATIONS FOR VETERINARY MEDICINE

The COVID-19 pandemic had a major impact on antimicrobial use in human medicine, and these changes have serious implications for antimicrobial use in veterinary medicine. One of the implications is that changes in human medical use affect the availability of these antimicrobials for veterinary applications. Increases in hydroxychloroquine prescriptions for those with COVID-19 made it difficult for those who needed it for malaria or autoimmune diseases to acquire it. As hydroxychloroquine is also used to treat some autoimmune diseases in animals, owners of these animals likely faced similar barriers. Also, many pharmacists started to decline prescriptions, including those made out for dogs in fear that these prescriptions were questionable (Sullivan, 2020). Demand for hydroxychloroquine also caused prices to drastically increase for chloroquine phosphate, which is used to treat and prevent protozoal infections in fish. In some cases, prices went from ten dollars a bottle to five-hundred dollars (Rahhal, 2020). An increase in ivermectin sales also made it difficult for people to acquire the drug to treat their animals (Sinclair, 2021). The limited supply and increased prices of these drugs may have had a negative impact on animal health as they were not available to treat infections in animals.

Perhaps the most pressing issue related to antimicrobial use during the COVID-19 pandemic is the development of antimicrobial resistance. An increase in AMR infections in humans can negatively impact animal health since production and companion animals depend on humans for their healthcare. With increases in human healthcare costs, longer hospital stays, and more serious infections, people may not have the resources available

to care for their animals. Mechanisms of resistance may also be shared with the animal's microorganisms, or the pathogen itself may infect the animals. These factors could lead to increases in disease and decreases in animal welfare.

As mentioned earlier, human, animal, and environmental health are closely related, so antimicrobial resistance anywhere is a threat to antimicrobial effectiveness everywhere. The increase in antibacterials in the treatment of individuals with COVID-19 may lead to an increase in antimicrobial resistance in bacteria. This increase in AMR is a problem for veterinary medicine as well since humans and animals share many of the same pathogens. Bacteria have also evolved mechanisms of sharing resistance between each other. Even if resistance develops in non-pathogenic bacteria, these species can act as a reservoir for antimicrobial resistance and transmit their genes to other more problematic species. Antimicrobials are critical for human and animal health, and they need to be used appropriately. Changes in antimicrobial use are expected in pandemics, but adequate antimicrobial stewardship practices are still important. If we do not conserve the effectiveness of antimicrobials, we will once again find ourselves in the middle of a pandemic with no effective treatments. In order to reduce the development of antimicrobial resistance, the use of antimicrobials should be reduced. More emphasis should be put on using treatments that do not rely on antimicrobials and conducting culture sensitivity tests when antimicrobials must be used to ensure that the antimicrobial will be effective.

CONCLUSIONS

The COVID-19 pandemic had a dramatic effect on antimicrobial stewardship practices in human health. There were increases in the use of antibacterials and antiparasitics in particular. These increases in the use of antimicrobials in human medicine have impacted veterinary medicine as well. The availability of these antimicrobials for veterinary use was decreased through a lack of supply and increased prices. The increased use of antimicrobials also has the potential to accelerate the development of resistant organisms. Antimicrobial resistance is a serious concern for human, veterinary, and environmental health. Antimicrobials need to be used in a responsible way that preserves their effectiveness and maintains human, animal, and environmental health.

One of the factors that may impact the effective use of antimicrobials, specifically antibacterials, is medical professionals' fear that they will be sued for malpractice for not prescribing an antibacterial. Estimates place the risk of a physician being sued during their lifetime between 75% and 99% (Jena et al. 2011). In addition to the financial costs associated with legal defense, the physician can also suffer damage to their reputation. In order to prevent possible lawsuits, some medical professionals use defensive medicine where they administer tests, treatments, or medications that may not be effective. An example is when a physician prescribes an antibacterial against their own clinical judgement. One study found that medical professionals respond to liability pressure by prescribing more antibacterials and introducing a cap on noneconomic damages led to them being 6% less likely to prescribe antibacterials (Panthöfer, 2016). For

antimicrobials to be effectively used, the malpractice system needs to be revised to adequately protect patients while ensuring that medical professionals can make the decisions that they think are correct without outside pressure.

While antibacterials are incredibly important in treating bacterial diseases, there are other options for the treatment of bacterial infections that should be emphasized and used when possible. This helps to preserve the effectiveness of antibacterials for when they are truly necessary. The first step should always be preventing the disease through vaccinations and reducing the risk of contracting the disease. If the patient has already contracted the disease, there are options besides the use of antibacterials. One is the use of lytic bacteriophages, which are viruses that specifically target bacteria. They can be highly specific and target certain bacterial species (Opal, 2016). There are also drugs that were developed to block toxin formation by Gram-positive species, such as *Staphylococcus aureus*, which allows for the immune system to clear out the now harmless bacteria. Also, since toxin production is not necessary for the bacteria to survive, there is less selective pressure to lead to the development of resistance to the drug (Greenberg et al., 2018). Other options include drugs that stimulate the immune system and decrease the immune response as well as neutralizing antibody therapies.

The world is more connected through the internet and other media than at any other time in history, which allowed for more communication at a faster rate during the COVID-19 pandemic than during previous pandemics. The increase in communication also has the possibility to affect antimicrobial use, which was seen during the COVID-19 pandemic. The increased access to information has allowed for people to access more information regarding treatments for COVID-19 that were not yet adequately studied,

including the use of ivermectin and hydroxychloroquine to treat COVID-19. In order to prevent harm caused by the use of non-approved drugs, there needs to be an increase in education and regulation of drugs. Medical professionals should be educated on the risks of prescribing non-approved drugs and the general public should also be educated about the importance of the correct use of drugs. It would also be helpful if the public was educated on how to evaluate research and new articles to determine their validity. Finally, media outlets should ensure that they are reporting accurate information and including the risks associated with what they are talking about.

While technological advances in communication have led to some issues regarding antimicrobial use, they have also helped to accelerate research. Research could be shared more quickly which allowed for new research to be utilized more effectively by a larger group of people. During the COVID-19 pandemic, the drug discovery and approval process was prominently covered in the news as companies worked to develop vaccines and treatments for this new disease. The FDA worked to update and streamline its drug approval processes and created the Coronavirus Treatment Acceleration Program to increase the speed of drug approval for the treatment of COVID-19 (FDA, 2022).

This review has highlighted ways in which the COVID-19 pandemic affected antimicrobial stewardship in human medicine and how these changes have and could impact veterinary medicine. Further studies should investigate how the pandemic directly affected stewardship in veterinary medicine, whether the pandemic led to an increase in antimicrobial resistance, developing new guidelines for antimicrobial use in regard to COVID-19, and improving stewardship programs to reduce the possible impact future pandemics have on stewardship practices.

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AUTHOR'S BIOGRAPHY

Erin N. Bradstreet was born in Brunswick, Maine on July 8, 2000. In 2018, she graduated from Brunswick High School and attended the University of Maine to major in Animal and Veterinary Science with a concentration in Pre-Veterinary Science. After graduating from the University of Maine, she plans on studying Pharmacology at the University of New England. She has a specific interest in working in veterinary pharmacy.