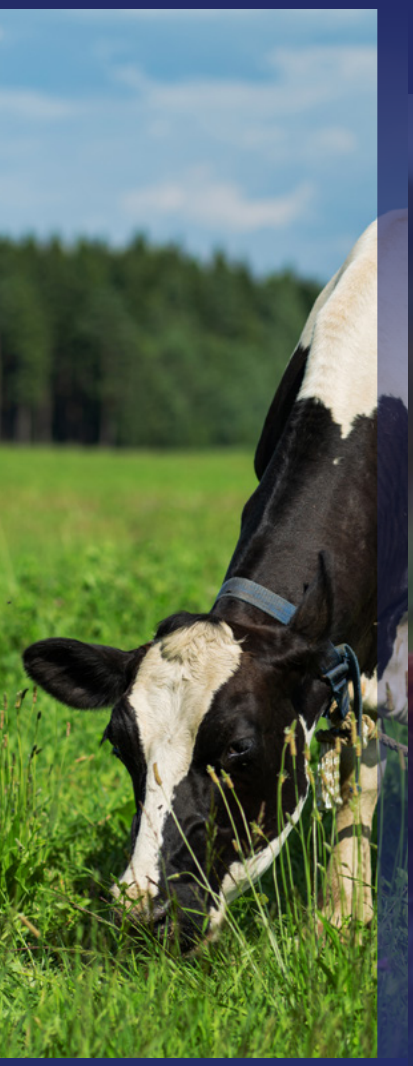
Antimicrobial Use and Resistance in ANIMAL AGRICULTURE in the United States

2016-2019




SUMMARY REPORT

Center for Veterinary Medicine

JUNE 2022

FDA U.S. FOOD & DRUG ADMINISTRATION

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Table of Acronyms

ADAA: Animal Drug Availability Act

ADUFA: Animal Drug User Fee Act

AMDUCA: Animal Medicinal Drug Use Clarification Act

AST: Antimicrobial Susceptibility Testing

AVMA: American Veterinary Medical Association

CDC: Centers for Disease Control and Prevention

CLSI: Clinical Laboratory Standards Institute

CVM: Center for Veterinary Medicine

DNA: Deoxyribonucleic acid

DSA: Decreased Susceptibility to Azithromycin

DSC: Decreased Susceptibility to Ciprofloxacin

ECOFF/ECV: Epidemiologic Cutoff Value

ELU: Extralabel Use

EPA: Environmental Protection Agency

ESBL: Extended Spectrum Beta Lactam

FAO: Food and Agriculture Organization

FDA: Food and Drug Administration

FFDCA: Federal Food, Drug, and Cosmetic Act

GATS: Global Agricultural Trade System

GFI: Guidance for Industry

MDR: Multidrug Resistance

MIC: Minimum Inhibitory Concentration

NARMS: National Antimicrobial Resistance System

NIR: Not Independently Reported

OIE: Office International des Epizooties (World Organisation for Animal Health)

OTC: Over-the-Counter

Rx: Prescription

TAB: Target Animal Biomass

USDA: United States Department of Agriculture

USDA AMS: USDA Agricultural Marketing Service

USDA APHIS: USDA Animal and Plant Health Inspection Service

USDA ARS: USDA Agricultural Research Service

USDA CEAH: USDA Center for Epidemiology and Animal Health

USDA ERS: USDA Economic Research Service

USDA FAS: USDA Foreign Agricultural Service

USDA FSIS: USDA Food Safety and Inspection Service

USDA NAHLN: USDA National Animal Health Laboratory Network

USDA NAHMS: USDA National Animal Health Monitoring System

USDA NASS: USDA National Agricultural Statistics Service

VCPR: Veterinarian-Client-Patient Relationship

Vet-LIRN: Veterinary Laboratory Investigation and Response Network

VFD: Veterinary Feed Directive

WGS: Whole Genome Sequencing

Background and Scope of this Report

Background

Antimicrobial drugs are a critical public health tool, used successfully to fight bacterial infections in humans and animals, as well as some crops and plants. However, the rapid emergence and spread of antimicrobial-resistant bacteria are widely acknowledged as major public and animal health challenges on a global scale. The loss of effective antimicrobials leads to increasingly limited options for treatment of life-threatening infectious diseases, including some healthcare-associated infections and foodborne illnesses in humans (CDC, 2019). The loss of effective therapies for bacterial diseases in animals threatens their health and may have negative effects on animal welfare and livestock production.

As a global problem with complex epidemiology, addressing antimicrobial resistance requires a broad and integrated One Health approach including research, surveillance, and interventions across human, animal, and environmental sectors. One Health is a collaborative, multisectoral, and transdisciplinary approach – working at the local, regional, national, and global levels with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment (CDC, 2021a). Since antimicrobial use is one driver among others in the development of antimicrobial resistance, implementation of good antimicrobial stewardship practices among all of these sectors is essential to help slow the emergence of resistance and preserve the effectiveness of antimicrobials.

Scope of this Report

This is the first report created by the United States (U.S.) Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) intended to describe and summarize data on antimicrobial use, stewardship, and resistance in animal agriculture, primarily as it relates to certain foodborne pathogens. The efforts described in this report highlight just some of the ongoing endeavors across multiple government agencies and stakeholders to promote antimicrobial stewardship in the animal agriculture sector. It is not intended to provide a complete picture of all efforts across the U.S. government and multiple stakeholders, but focuses on activities in which CVM plays a role. The objectives of this report are to describe:

- Current government monitoring and surveillance systems in place for antimicrobial sale, use, and antimicrobial resistance in animal agriculture and the related food chain;
- Publicly available data regarding antimicrobial sales, use, and resistance in U.S. animal agriculture and certain foodborne pathogens, with a focus on federal government systems collecting data for the years 2016 through 2019; and
- Recent progress made and continued plans for promoting and supporting antimicrobial stewardship in animal agriculture.

In general, the term "antimicrobial" refers broadly to all agents with activity against a variety of microorganisms including bacteria, viruses, fungi, and parasites. Antimicrobials that have specific activity against bacteria are

generally referred to as "antibacterial" or "antibiotic" drugs. Typically, the term "antibiotic" refers to substances produced by microorganisms that act against another microorganism. Thus, "antibiotics" do not strictly include antimicrobial substances that are synthetic (e.g., sulfonamides and quinolones), or semisynthetic (e.g., methicillin and amoxicillin). The term "antimicrobial" has a broader definition which includes any substance of natural, semisynthetic, or synthetic origin that kills or inhibits the growth of a microorganism (Giguere, 2013). This report may use the two terms interchangeably, but in most instances will use the term "antimicrobial."

While it is important to include humans, the environment, and all animal species in discussions about antimicrobial use and resistance to reflect a One Health framework, this report focuses on progress made in the four major food-producing species in U.S. animal agriculture (cattle, swine, chickens, and turkeys). Additional efforts are underway across multiple sectors, including government, academia, and industry, to address antimicrobial use, resistance, and stewardship for humans and other animal species, including minor food-producing species such as small ruminants (e.g., sheep and goats), farmed fish/aquaculture, and companion animals such as dogs, cats, and horses.

With regard to antimicrobial use and resistance in human health care, there are local, state, and national monitoring and surveillance programs in place, as well as ongoing antimicrobial stewardship programs, to support human healthcare providers and patients in their efforts to improve antimicrobial prescribing and use. The Centers for Disease Control and Prevention (CDC) most recently published the *2020 Update on Antibiotic Use in the United States: Progress and Opportunities*, which describes some of these efforts and their progress (CDC, 2021b). In addition, the CDC arm of the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) regularly publishes reports on antimicrobial resistance surveillance findings for foodborne and other bacterial pathogens of human health significance. While some data from the retail meat and food animal arms of the NARMS program will be presented in this report, the reader is referred to the CDC NARMS webpage and other reports for information specifically for antimicrobial resistance in humans.

Although not a focus of this report, the One Health concept also includes an emphasis on the environment. The natural background of antimicrobial resistance in different environments is not well understood, but strategies for monitoring and surveillance of antimicrobial resistance in the environment are being developed to provide data from sampling and testing programs for soil, water, and plants. For example, the U.S. Environmental Protection Agency (EPA) has conducted research and modeling activities to predict the occurrence of antimicrobial resistance genes in U.S. rivers and streams (US EPA, 2019). The National Antimicrobial Resistance Monitoring System (NARMS) recently published a new strategic plan for 2021-2025 which intends to explore possibilities for including environmental antimicrobial resistance monitoring, such as in surface waters (NARMS, 2020a). Ongoing research at the United States Department of Agriculture's Agricultural Research Service (USDA-ARS) strives to fill knowledge gaps in understanding the ecology of antimicrobial resistance in food animal production environments and to mitigate the spread of antimicrobial resistance across the farm-to-fork continuum (USDA-ARS, 2019).

Antimicrobial resistance is a priority for human and animal health. While much progress has been made, more work remains to be done to slow the emergence and spread of resistant bacteria and preserve the effectiveness of antimicrobials. As part of its regulatory mission, CVM is responsible for monitoring the safety and effectiveness of animal drugs, including antimicrobials. This report describes some of the important progress made to date and plans for continued advancement of antimicrobial stewardship in the animal agriculture sector.

CHAPTER 1

Introduction

1.1 Overview: Antimicrobials and Antimicrobial Resistance

1.2 Foodborne Illness and Antimicrobial Resistance in the Food Chain

1.3 Addressing the Threat of Antimicrobial Resistance – a One Health Approach

1.1 Overview: Antimicrobials and Antimicrobial Resistance

Sir Alexander Fleming, a Scottish physician and scientist, is credited with the landmark discovery of penicillin, a substance produced by fungi, in 1928. Within a few years, many other antimicrobials were discovered, followed by the development of semisynthetic and synthetic agents, including sulfonamides in the 1930s, which were the first clinically successful antibacterial agents brought to market (Aminov, 2010). With further developments, penicillin became commercially available in the 1940s. Thus began the so-called 'antibiotic revolution' which resulted in an increasingly powerful and effective variety of medicines available to treat infectious diseases. Drastic improvements in human health and life expectancy came about as the result of antimicrobial discovery. The use of antimicrobials in animals closely parallels their discovery and use in human medicine. Penicillin and sulfonamides were the first antimicrobials used in food animals in the 1940s, with the first reported uses for treatment of mastitis in dairy cows (Prescott, 2017). Subsequent discoveries led to therapeutic uses of antimicrobials for several types of infectious diseases in food animal species. The introduction and use of antimicrobials for animals brought major benefits to both animals and humans, for example: reduction in animal pain and suffering, protection of animal resources and human livelihoods, advancements in food production and feed efficiency, and decreases in potentially zoonotic infectious diseases that could result in loss of life, both human and animal.

Antimicrobial resistance, as it relates to bacteria, occurs when the bacteria are inherently resistant to the action of an antimicrobial, or when the bacteria change in some way that allows them to survive and reproduce in the presence of an antimicrobial. The emergence of antimicrobial resistance was not an unforeseen phenomenon and had been predicted by Alexander Fleming shortly after his initial discovery. He recognized that the bacteria exposed to antimicrobial agents quickly evolved strategies to survive them and warned in his Nobel Prize lecture in 1945 about the dangers of misuse of penicillin and resulting ineffectiveness (Fishman, 2012). Antimicrobial resistance is more recently understood to be an ancient phenomenon, and is the expected result of the interactions of many organisms within their environment (Munita and Arias, 2016). Studies of the natural history of antimicrobial resistance genes suggest their long-term presence in natural environments, well before the development and use of antimicrobial drugs began (Leisner et al, 2016).

Resistance can be intrinsic or acquired. Resistance which occurs naturally in bacteria, or intrinsic resistance, means that the bacterial organism is innately insensitive to a particular antimicrobial because of the structural or functional characteristics of the bacterium and the antimicrobial's mechanism of action, which is shared within a bacterial species. For example, the bacterium ***Pseudomonas aeruginosa*** is intrinsically resistant to many classes of antimicrobials because the structure of its outer membrane does not allow penetration of those antimicrobials into the bacterial cell. Resistance which results from genetic modification in bacteria, or acquired resistance, can occur through a number of different mechanisms. These include spontaneous chromosomal DNA mutations that confer to bacteria the ability to prevent a drug from binding to its target, the acquisition of enzymes that inactivate the drug, and energy-dependent efflux pumps that expel antimicrobials from bacterial cells. Many of these mechanisms are associated with mobile DNA elements, such as plasmids that are transferred between bacteria of the same or different species. This exchange of genetic elements between bacteria can occur readily in humans, animals, and the environment (Wright, 2012). The increased prevalence and propagation of resistance is a consequence of natural selection. In any population of bacteria, those that have the ability to survive in the presence of an antimicrobial will continue to reproduce, while those bacteria that are susceptible to the

antimicrobial are eliminated. Consequently, with continued exposure to an antimicrobial in a given environment, the resistant populations of bacteria eventually outnumber the susceptible. Resistance in these bacterial populations may sometimes persist after exposure to the antimicrobial has ended, but in some cases, susceptible populations of bacteria can return to dominance once the antimicrobial stimulus is removed (Boerlin, 2013). Infections caused by resistant bacteria are not as effectively treated.

Loss of antimicrobial effectiveness through the emergence, distribution, and persistence of antimicrobial resistance in many bacterial pathogens has become a serious threat to the successful therapy of infectious diseases in both humans and animals. Infections caused by resistant bacteria are often associated with higher morbidity and mortality than those caused by susceptible bacteria (Boerlin, 2013). Furthermore, bacteria may become resistant to several antimicrobials (multidrug resistance), making treatment of infections even more complicated. Recently, the CDC reported that in humans an estimated 2.8 million antimicrobial-resistant infections (due to both bacteria and fungi) occur in the U.S. each year, resulting in over 35,000 deaths (CDC, 2019). Similar data describing the impact of antimicrobial resistance on animal health is not available. Unfortunately, discovery and introduction of new classes of antimicrobials over the past 75 years has been steadily matched by the emergence of new bacterial resistance mechanisms. Thus, sustainable management and responsible use of currently available antimicrobials is vital to protecting human and animal health. While new antimicrobials could be developed for human use in the coming years, it is less likely that new antimicrobials will be developed for veterinary use. Improved utilization of current drugs, development of new (non-antimicrobial) alternatives, and improvements in disease prevention are essential.

Compared to resistance in human and foodborne bacterial pathogens, there is less information available about the emergence and dissemination of antimicrobial resistance occurring in animal pathogens (for the purposes of this report, referring to those bacteria that cause disease only in animals). For example, the development of widespread antimicrobial resistance in bovine respiratory disease (BRD) pathogens (such as ***Mannheimia haemolytica*** and ***Pasteurella multocida***), could be devastating to the cattle industry both economically and from an animal welfare standpoint, but it is not clear to what extent this may be occurring. The detection of emerging resistance in BRD pathogens, as well as pathogens affecting other food-producing species, has been somewhat hindered by the lack of a national routine surveillance program. In addition, there is a lack of understanding about some of the resistance mechanisms used by these pathogens against some classes of antimicrobials. There is a strong need for this type of data to be collected and reported on an ongoing basis since therapy of animal diseases caused by animal pathogens is the main driver for antimicrobial use in animals.

Since human, animal, and environmental health are interconnected, it is essential to consider the emergence and spread of antimicrobial resistance from a One Health perspective. While antimicrobial use and misuse in human clinical medicine is the major contributing factor to the development of antimicrobial resistance in humans, any use of antimicrobials (whether in humans, animals, or the environment) can potentially contribute to the emergence of resistant bacteria that may be transmitted between species and ecosystems (Holmes et al, 2016). Resistant bacteria arising in treated food-producing animals could be transferred to humans through direct contact or indirect contact, via food and environmental routes. Resistant bacteria arising in humans could also be transmitted to animals and the environment. Several recent examples of human disease outbreaks involving multidrug-resistant infections linked to food, or contact with animals, or the environment, demonstrate the complexities of disease transmission pathways (CDC, 2020a). Antimicrobial residues in wastes released from

human or animal healthcare settings, or from industrial processes (e.g., pharmaceutical manufacturing) may exert selection pressure on environmental bacteria (Kumar and Pal, 2018; Kotwani et al, 2021). Human travel as well as food and animal trade could have significant roles in the global spread of antimicrobial resistance by facilitating the movement of resistance genes (Bokhary et al, 2021; Magouras et al, 2017). Figure 1-1 illustrates how resistant bacteria can be transmitted between species and ecosystems.

Figure 1-1: Epidemiology of antimicrobial resistance: pathways of possible transmission of resistant bacteria between ecosystems

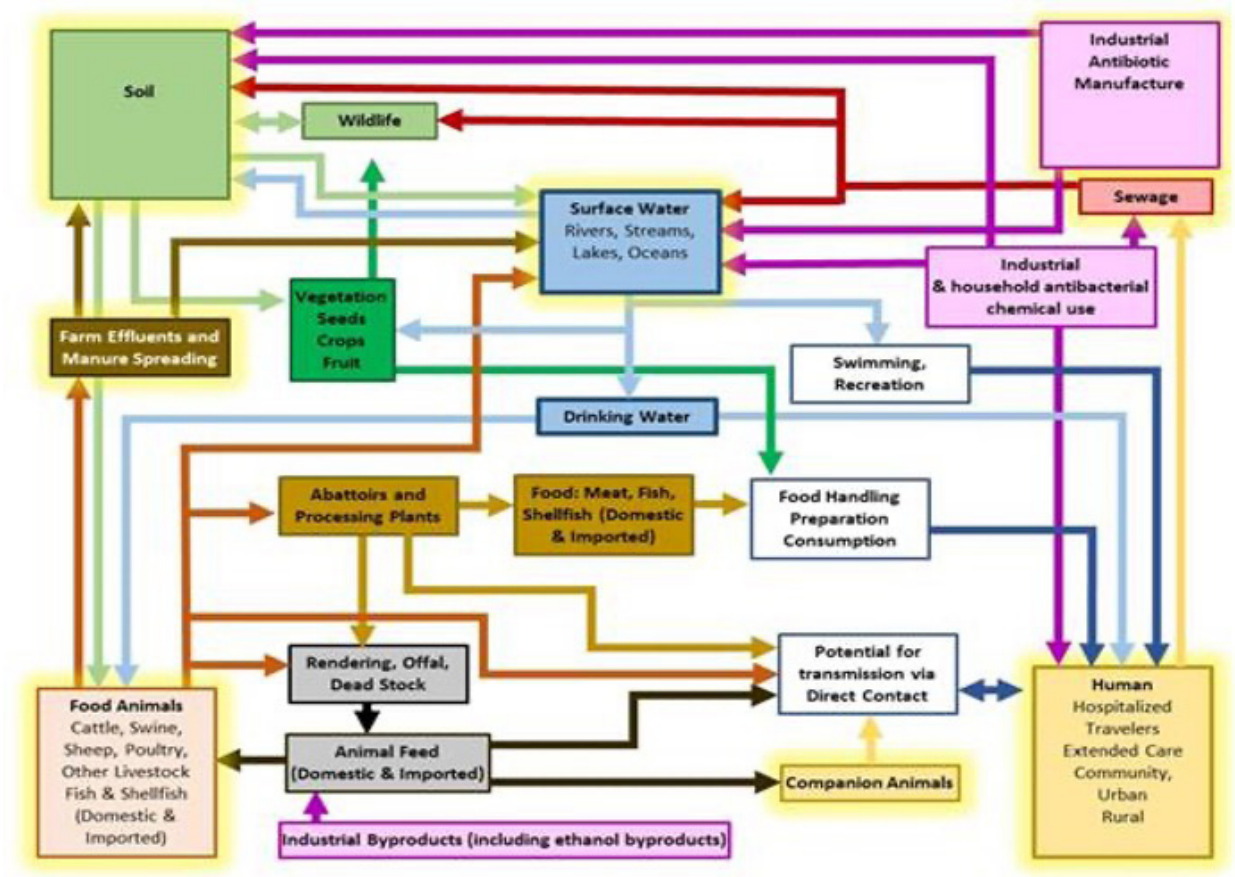


Figure used with permission, after Linton (1977), modified by RJ Irwin (2007), modified by L Durso (2019). From: One Health and antimicrobial resistance, a United States perspective (Bright-Ponte, et al. 2019)

1.2 Foodborne Illness and Antimicrobial Resistance in the Food Chain

Food of animal or plant origin may be contaminated with bacteria, some of which may be resistant to antimicrobials. As shown in Figure 1-1, antimicrobial-resistant bacteria may be found in soil, water, and in human or animal fecal material. Animal products may contain antimicrobial-resistant bacteria as a result of fecal contamination of carcasses during slaughter or other mechanisms, although much of this risk is mitigated through federal and state meat inspection programs, such as the Hazard Analysis and Critical Control Point (HACCP) programs for pathogen reduction (USDA-FSIS, 2017). During production, crops and plants may be irrigated using water contaminated with human and/or animal feces that contain antimicrobial-resistant bacteria. Food can also be contaminated with antimicrobial-resistant bacteria originating from other food sources during handling (i.e., cross-contamination) (Verraes et al, 2013).

Foodborne illness occurs when a pathogen, such as a virus or bacterium, is ingested with food and establishes itself (often multiplying), or when a pathogen produces a toxin which is ingested. In humans, over 200 different foodborne diseases have been identified. The most severe cases tend to occur in the very old, very young, and in those who have compromised immune system function. The CDC has estimated that each year in the U.S., 48 million people contract foodborne illness, 128,000 are hospitalized, and 3,000 people die (CDC, 2020b). The top five pathogens causing foodborne illness in the U.S. are norovirus, ***Salmonella enterica*** (henceforth referred to as ***Salmonella*** in this report), ***Clostridium perfringens***, ***Campylobacter***, and ***Staphylococcus aureus***. A number of other pathogens do not cause as many illnesses as the top five, but when they do occur, the illnesses are more likely to be severe and lead to hospitalization. These include ***Clostridium botulinum***, ***Listeria monocytogenes***, toxicogenic forms of ***Escherichia coli*** (***E. coli***), and ***Vibrio*** (CDC, 2020b). A proportion of foodborne pathogens are resistant to antimicrobials, and consequently, if treatment is necessary for an infected and ill human, it may be less effective if the usual treatment is the antimicrobial to which the pathogen is resistant (CDC, 2021c). In addition, antimicrobial resistance genes in commensal organisms (i.e., part of the normal bacterial flora) may be an indirect risk to public health, as they can increase the gene pool from which disease-causing pathogenic bacteria can acquire resistance traits (Brinkac et al, 2017). Some types of bacteria that contaminate food cause disease primarily by multiplying and producing toxins (e.g., ***Staphylococcus aureus*** and ***Clostridium botulinum***).

CDC's recent '*Antibiotic Resistance Threats in the United States, 2019*' report (2019 AR Threats Report) includes a list of 18 bacterial species of concern to human health at varying levels- urgent, serious, and concerning (CDC, 2019). Some of the bacterial species of concern may be foodborne, for example, ***Campylobacter***, ***Salmonella***, ***Enterococcus***, and ***E. coli***. Carbapenem-resistant ***Enterobacteriaceae*** (CRE) are considered an urgent threat (***Enterobacteriaceae*** are a family of gram-negative bacteria which includes ***Salmonella*** and ***E. coli***). Carbapenems are one of the few remaining antimicrobial drug classes that can treat infections caused by extended-spectrum beta-lactamase (ESBL)-producing bacteria. Antimicrobial-resistant ***Campylobacter*** and nontyphoidal ***Salmonella*** are classified as serious threats, as are ESBL-producing ***Enterobacteriaceae*** and vancomycin-resistant ***Enterococcus*** (VRE). While a full description of these pathogens is beyond the scope of this report, a brief summary is provided below.

Campylobacter may cause disease in humans and animals. Most human infections are caused by ***Campylobacter jejuni***, with typical symptoms of diarrhea, fever, and abdominal cramps. Unless severe, most infections do not require antimicrobial treatment. Occasionally, other symptoms and syndromes such as arthritis and temporary

paralysis may occur. ***Campylobacter*** causes an estimated 1.5 million human infections in the U.S. each year. Of these, 29% have decreased susceptibility to the fluoroquinolone or macrolide classes of antimicrobials, which are used to treat severe ***Campylobacter*** infections (CDC, 2019). ***Campylobacter*** spreads to humans most commonly through consumption of contaminated food or water, particularly raw or undercooked poultry or raw (unpasteurized) milk, and through direct contact with infected animals. Most species of domestic animals are susceptible to infection with ***Campylobacter***, and young animals are more severely affected. Animals can be infected through direct contact with other infected animals, ingestion of fecal-contaminated feed or water, or by ingestion of undercooked meat or other contaminated foods. Signs in animals are also usually gastrointestinal: diarrhea, fever, vomiting, and decreased appetite; however, in some species such as sheep and goats, ***Campylobacter*** infection is associated with abortion (Spickler and Larson, 2013a).

Non-typhoidal *Salmonella* (*S. enterica* serotypes) cause about 1.4 million human infections and 420 deaths in the U.S. each year, according to CDC estimates (CDC, 2021d). Most people who have illness due to ***Salmonella*** have diarrhea, fever, and abdominal cramps, and most recover without antimicrobial treatment. Antimicrobials such as fluoroquinolones, macrolides, or third generation cephalosporins may need to be used to treat severe illness. According to CDC data, 16% of nontyphoidal ***Salmonella*** infections are resistant to at least one antimicrobial considered essential for treatment (i.e., ciprofloxacin, azithromycin, ceftriaxone, ampicillin, and trimethoprim-sulfamethoxazole) (CDC, 2019). Humans may become infected with ***Salmonella*** by ingestion of contaminated food (e.g., meat, poultry, eggs, or produce) or drinking water, or by direct contact with infected animals or their environment. In animals, ***Salmonella*** infections mainly cause enteritis (inflammation of the intestines) and septicemia; however, many animal species carry ***Salmonella*** subclinically. ***Salmonella enterica*** subspecies ***enterica*** contains hundreds of different serovars, or serotypes, some with a very narrow host range, and others capable of infecting multiple species of animals. Signs in animals, when they occur, may include diarrhea, abdominal pain, fever, loss of appetite, and sometimes death in the case of septicemia (Spickler and Larson, 2013b).

Escherichia coli* (*E. coli*)** are coliform bacteria that normally reside in the intestines of healthy animals and humans, but some strains can cause infections in the intestines, urinary tract, and many other parts of the body. In humans, intestinal infections may occur by ingestion of contaminated food or water, or sometimes through direct contact with an infected animal. Intestinal infections typically cause diarrhea and abdominal pain. Certain strains of ***E. coli (e.g., O157:H7) produce toxins that can cause severe inflammation in the intestines and colon. Severe ***E. coli*** O157:H7 infections may lead to hemolytic uremic syndrome (HUS)**,** a complication causing kidney failure that develops in about 5 to 10% of cases (CDC, 2021e). Some ***E. coli*** infections, such as urinary tract infections, are treated with antimicrobials, but intestinal infections with certain strains such as O157:H7 are not, since antimicrobial therapy may increase the risk of HUS (CDC, 2021e). Many strains are resistant to ampicillin and tetracyclines, so other antimicrobials may be selected, such as carbapenems and fluoroquinolones (Bush and Vazquez-Pertejo, 2020). ESBL-producing ***Enterobacteriaceae*** are considered a serious threat (CDC, 2019). In animals, virulent strains of ***E. coli*** cause a variety of diseases; for example, diarrhea and sepsis may be especially critical in newborn or young animals. Other types of infections include acute mastitis in dairy cows and chronic respiratory disease in poultry. Most serotypes isolated from poultry are pathogenic only for birds; therefore, avian sources of ***E. coli*** do not seem to be important sources of infections in other animals. Animals do not seem to be clinically affected by ***E. coli*** O157:H7, but can serve as a reservoir and source of exposure for humans (Spickler, 2016).

Enterococcus (e.g., *Enterococcus faecium* and *Enterococcus faecalis*) often occur as normal gastrointestinal flora of humans and animals. Usually considered harmless commensals, they may occasionally cause opportunistic infections in humans, such as urinary tract infections, sepsis, and endocarditis (Hammerum et al, 2010); most of these infections are nosocomial (i.e., healthcare-associated) infections. Food products, such as meat, might be a vehicle for ***Enterococcus*** infections in humans (Tyson et al, 2017). Foodborne enterococci may also transfer resistance genes to other pathogens such as ***Campylobacter*** and ***E. coli***. About 30% of health-care associated enterococcal infections are resistant to vancomycin, which is an important glycopeptide class antimicrobial (CDC, 2019). Disease caused by ***Enterococcus*** in animals is uncommon.

1.3 Addressing the Threat of Antimicrobial Resistance – a One Health Approach

The science underlying the selection, transmission, and persistence of resistant bacteria is very complex. More research is needed to improve our understanding of all aspects of resistance, including what strategies centered on a One Health approach, will promote optimal health outcomes for humans and animals (and their environments) and preserve the effectiveness of antimicrobials. Cooperative, multisectoral efforts are under way in the U.S. to meet this challenge. In 2015, the U.S. government released a comprehensive plan that identified critical actions to be taken by federal departments and agencies to combat antimicrobial resistance. This National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) was developed by an interagency task force as a guide to implement the National Strategy on Combating Antibiotic-Resistant Bacteria (CARB, 2015). In October of 2020, an updated National Action Plan for 2020-2025 was published, building upon progress made with the first plan (CARB, 2020). This strategy outlines five interrelated goals, one of which is to strengthen national One Health surveillance efforts to combat antimicrobial resistance. Federal, state, and local government agencies work collaboratively towards this goal across human, animal, and environment sectors. Roles and responsibilities of the various federal departments and agencies vary. The table in Appendix 1 describes some of these roles, but it is not meant as an exhaustive representation of the breadth of U.S. government activities. This report focuses on CVM's roles and responsibilities, and describes some of the collaborations with federal partners and multiple stakeholders.

Antimicrobial stewardship describes measures that can be taken to help mitigate the risks associated with antimicrobial use, including the risk of antimicrobial resistance. Antimicrobial stewardship programs have been developed and implemented in human hospitals and outpatient settings, as well as in animal care and production settings. These types of programs aim to integrate infection prevention and control measures with approaches to encourage responsible use of antimicrobials. The CDC has defined antimicrobial stewardship in human healthcare as "***the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients***" (CDC, 2021f). The American Veterinary Medical Association (AVMA) has defined antimicrobial stewardship as "***actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health.***" The AVMA has also outlined core principles of antimicrobial stewardship in veterinary medicine (AVMA, 2018). Animal production industry and veterinary groups have implemented similar guidelines.

Many activities are ongoing across the One Health spectrum aimed at slowing the development of antimicrobial resistance and optimizing antimicrobial use. Important progress has been made and more work remains to be done. Ongoing surveillance and monitoring of both antimicrobial resistance and antimicrobial use across all sectors will help inform efforts to preserve the effectiveness of potentially life-saving antimicrobials. This report focuses on certain components of monitoring and surveillance of antimicrobial sales, use, and resistance as they relate to the four major food-producing species. It also describes some of the efforts and progress related to antimicrobial stewardship in animal agriculture. Cooperation and collaboration between U.S. government agencies, animal drug manufacturers, animal industry organizations, veterinary organizations, veterinarians, and producers are essential to continue building upon this progress. Chapter 2 describes some of the actions currently being taken by CVM and other stakeholders to support antimicrobial stewardship in veterinary settings. As part of its mission to protect human and animal health, CVM works to ensure the safety and effectiveness of animal drugs, including antimicrobials. Information about CVM and its organization and roles can be found at https://www.fda.gov/animal-veterinary.

CHAPTER 2

Efforts to Slow the Development of Antimicrobial-Resistant Bacteria

2.1 Introduction

2.2 FDA's 5-Year Plan for Supporting Antimicrobial Stewardship in Veterinary Settings

2.1 Introduction

The FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and animal drugs, biological products, and medical devices; ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation; as well as regulating the manufacturing, marketing, and distribution of tobacco products. FDA also plays a significant role in the Nation's counterterrorism capability, fulfilling this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats. The FDA website provides a wealth of information describing FDA's wide variety of regulatory and research activities.

CVM is the FDA Center responsible for ensuring the safety and effectiveness of animal drugs, including antimicrobials, and has been engaged in numerous activities to address the threat of antimicrobial resistance potentially arising from the use of medically important antimicrobials in food-producing animals. The term 'medically important antimicrobial' refers to antimicrobials that are considered important for therapeutic use in humans (US FDA, 2012).

This chapter is intended to describe FDA's 5-year plan for supporting antimicrobial stewardship in veterinary settings, with a summary of the activities planned through fiscal year 2023. Supplemental information describing the FDA's pre- and post-approval processes for animal drugs (including antimicrobials), and an overview of some of CVM's historical and recent activities aimed at reducing the threat of antimicrobial resistance that may arise as a result of the use of medically important antimicrobials in food-producing animals are included in Appendiices 2 and 3 of this report.

While this report focuses primarily on actions that CVM has taken and intends to take, some references will be made to collaborations and partnerships between CVM and other U.S. government agencies. The table in Appendix 1 briefly summarizes some of the key U.S. government activities aimed at combatting antimicrobial resistance. It is not intended to provide a comprehensive description of U.S. government activities related to antimicrobial resistance, but rather to provide some examples. For more details, the reader should consult agency websites.

2.2 FDA's 5-Year Plan for Supporting Antimicrobial Stewardship in Veterinary Settings (2019-2023)

In September of 2018, CVM published its 5-year action plan for supporting antimicrobial stewardship in veterinary settings. The plan builds on the success of complete implementation of FDA Guidance for Inustry (GFI) #213 (see Appendix 3) and supports the concept that medically important antimicrobials should only be used in animals when necessary for therapy of specific diseases. '*Supporting Antimicrobial Stewardship in Veterinary Settings: Goals for Fiscal Years 2019-2023*' is CVM's blueprint for activities during 2019 through 2023 to combat antimicrobial resistance and preserve the effectiveness of antimicrobials. The plan outlines a phased approach:

phase 1 covers fiscal years 2019 – 2021; phase 2 actions will be initiated between fiscal years 2022- 2023, provided adequate resources are available. The phased approach allows for adjustments based on science-based analyses, public health impacts, and feedback from stakeholders. CVM continues to engage stakeholders and the public as it develops and implements the strategies outlined in the plan.

The document organizes key activities under **three overarching goals**:

- Align antimicrobial drug product use with the principles of antimicrobial stewardship;
- Foster stewardship of antimicrobials in veterinary settings; and
- Enhance monitoring of antimicrobial resistance and antimicrobial drug use in animals.

Within each goal are objectives, along with actions planned for each objective. Below we briefly describe the objectives for each goal and some of the already initiated or planned actions. Progress on elements of the 5-year plan is provided in regular updates to FDA-TRACK, an agency-wide performance management system that monitors FDA Center activities through key performance measures and projects.

GOAL 1: ALIGN ANTIMICROBIAL DRUG PRODUCT USE WITH THE PRINCIPLES OF ANTIMICROBIAL STEWARDSHIP

- **Objective 1.1:** Revise, as necessary, the use conditions for approved medically important antimicrobials for food-producing animals
- **Objective 1.2:** Develop and implement a strategy for promoting antimicrobial stewardship in companion animals
- **Objective 1.3**: Enhance processes to support new product development

Some of the activities included under Goal 1 include, for example, a strategy for bringing all remaining dosage forms of medically important antimicrobials that are currently available over-the-counter (OTC) under veterinary oversight (i.e., Rx). GFI #263, described below, outlines the strategy. In addition, CVM has begun to address those medically important antimicrobials for food-producing animals that lack a defined duration of use, also described below. With regard to Objective 1.3, CVM recently described a potential revised process for ranking antimicrobials according to their relative importance in human medicine, and is also encouraging efforts to develop alternative therapies (e.g., alternative animal drug products) for addressing animal health needs that could be used in place of medically important antimicrobials. Objective 1.2 is specific to companion animals, and CVM has begun to engage with stakeholders to develop and implement a strategy to promote the judicious use of medically important antimicrobials in these species also.

GFI #263 ('OTC-to-Rx')

In June of 2021, CVM finalized GFI #263, entitled '*Recommendations for Sponsors of Medically Important Antimicrobial Drugs Approved for Use in Animals to Voluntarily Bring Under Veterinary Oversight All Products that Continue to be Available Over-the-Counter*.' GFI #263 explains the recommended process for drug sponsors to voluntarily bring the remaining approved animal drugs containing medically important antimicrobials under the oversight of licensed veterinarians by changing the approved marketing status from OTC to Rx. This guidance addresses the dosage forms that are not administered in feed or water, for example, injectables and oral dosage forms which were not the subject of GFI #213. The products addressed by GFI #263 include medically important antimicrobials for both food-producing and companion animals (i.e., dogs, cats, and horses). When GFI #263 has been fully implemented, all dosage forms of all approved medically important antimicrobials for all animal species can only be administered by or under the supervision of a licensed veterinarian. Full implementation is expected within two years of issuance of GFI #263, by approximately June of 2023.

Undefined Duration of Use

In GFI #213 and outreach related to the VFD final rule, CVM stated that, in addition to veterinary oversight, the antimicrobial should be administered for an appropriately targeted period, i.e., have a defined duration of use. Approximately 40% of approved medically important antimicrobial drug applications currently include at least one indication of use that does not have an appropriately defined duration. These antimicrobial drugs are now under veterinary oversight, but they may have undefined duration-related statements on their label such as "feed continuously" (with no other information provided), or the label may be silent regarding the approved duration(s) of use. As a continuation of FDA's antimicrobial stewardship efforts, CVM intends to develop and implement a specific strategy to ensure that all medically important antimicrobial drugs used in food-producing animals are labeled with an appropriately targeted duration of use.

CVM believes that updating the dosage regimens of affected animal drug products with defined durations of use should be based on science and available evidence. Recognizing that there are significant scientific and technical challenges to accomplish this, including the potential need to generate appropriate supporting information or data, CVM anticipates this initiative will require a substantial period of time to fully complete. At the time of this writing, the following activities have been completed:

- Publication of a Federal Register notice requesting comments on the establishment of appropriate durations of use for medically important antimicrobials. In that notice, FDA invited public comment on the establishment of appropriately targeted durations of use of medically important antimicrobials administered to food-producing animals in or on feed or in drinking water for those indications which a defined duration of use is not included on currently approved labeling. The comment period for that notice ended on March 13, 2017 and FDA received over 240 comments.
- Publication of a list of affected products that lack a defined duration of use (see https://www.fda.gov/

animal-veterinary/judicious-use-antimicrobials/list-approved-medically-important-antimicrobial-drugs-administered-feed-food-producing-animals-lack). All affected products are approved for use in or on medicated feed.

- Publication of two Funding Opportunity Announcements and Request for Applications (RFAs) for studies that can help target and define durations of use for affected medically important antimicrobials. For the first RFA, two grants were awarded in September of 2019 to investigators for projects related to the use of tylosin to reduce incidence of liver abscesses in feedlot cattle and the use of chlortetracycline for control of anaplasmosis in cattle. For the second RFA, a grant was awarded in 2020 related to the use of tylosin to reduce incidence of liver abscesses in beef cattle.
- Publication of a concept paper, "Potential Approach for Defining Durations of Use for Medically Important Antimicrobial Drugs Intended for Use In or On Feed." The purpose of this document is to provide CVM's initial thoughts and gather stakeholder feedback on establishing appropriately defined durations of use for medically important antimicrobials. Public comments were accepted through June 11, 2021. Feedback received will help inform CVM's final strategy and CVM will continue to engage with stakeholders and drug sponsors as a final strategy is developed.

Enhancing Processes to Support New Product Development

As part of the activities for Goal 1, CVM will continue to ensure that antimicrobial risks are addressed for new antimicrobial products approved for use in animals, and encourage the development of alternative therapies to address animal health needs.

CVM uses the concepts set out in GFI #152 (see Appendix 3) to assess antimicrobial risks associated with antimicrobial new animal drugs intended for use in food-producing animals. FDA recognizes that the list of drugs in Appendix A of GFI #152 is not static and should be periodically reassessed and revised as necessary. CVM, together with colleagues from the FDA Center that regulates human drugs (Center for Drug Evaluation and Research, or CDER) published a concept paper in 2020 describing a potential revised process for ranking antimicrobials according to their relative importance in human medicine, potential revised criteria to determine the medical importance rankings, and the list of antimicrobial drug medical importance rankings that would result if those criteria were to be used. The intent of the concept paper was to obtain public comment and input on the potential revised ranking process prior to issuing a draft guidance. A public meeting was held to discuss the potential approach in November of 2020, and written comments were accepted through April 22, 2021. FDA is considering all comments received as it prepares draft guidance for additional comment.

While medically important antimicrobials are valuable tools that veterinarians and animal producers require for addressing animal health needs, reducing reliance on such drugs by identifying alternatives for managing animal disease can help slow the development of resistance. Such alternatives can include changes in animal husbandry, biosecurity practices, vaccination programs, and other factors. As many of these factors are outside of CVM's regulatory authority, CVM is primarily focused on alternative drug products that could be used in place of medically important antimicrobials. CVM is seeking opportunities to collaborate on developing strategies to facilitate such product development and is focused on innovative approaches to consider new and novel methods for assessing alternatives to antimicrobials.

GOAL 2: FOSTER ANTIMICROBIAL STEWARDSHIP IN VETERINARY SETTINGS

- **Objective 2.1:** Support outreach and education by providing information on antimicrobial stewardship
- **Objective 2.2**: Strengthen CVM compliance program activities to support antimicrobial stewardship
- **Objective 2.3**: Support international outreach and collaboration to foster antimicrobial stewardship in veterinary settings

CVM is working with key stakeholders, including collaboratively with state and federal partners, to identify the most effective ways to develop, update, and disseminate information about antimicrobial stewardship. This may include information directed to veterinarians, veterinary students, academic institutions, animal producers, and consumers. CVM is also focusing compliance activities to ensure that medically important antimicrobials are being appropriately marketed and that their use is under veterinary oversight. For example, CVM published a summary assessment of VFD inspections conducted in fiscal years 2016-2018 (see below), and a VFD component for inspections associated with CVM's Drug Residue Inspection Program has been incorporated. CVM also collaborates with state organizations, such as the Minnesota One Health Antibiotic Stewardship Collaborative, among others, on stewardship initiatives. In addition to collaborations with state and federal partners, CVM supports international outreach and collaborations to foster antimicrobial stewardship. Given that antimicrobial resistance poses a worldwide public health challenge, it is essential that CVM engage international partners as policies related to antimicrobial stewardship are developed and implemented in the international arena. Some of CVM's activities related to international collaborations are described below.

Outreach and Education

It is critical that all affected stakeholders (e.g., veterinarians, animal producers, etc.) are informed and have access to the needed information to effectively implement antimicrobial stewardship practices in veterinary settings. CVM is committed to working with affected stakeholders to identify mechanisms for enhancing the availability and accessibility of relevant information. This includes, for example, enhancing access to label information for antimicrobial drug products as well as access to information from relevant guidance documents and regulations. Currently, Blue Bird labels (representative labeling for Type B and C medicated feed containing a new animal drug) are located on CVM's AnimalDrugs@FDA website and can be searched by various terms (e.g., species, active ingredient, etc.). A prototype application for handheld devices was recently developed and CVM is exploring possibilities for a publicly available version.

As part of Objective 2.1, CVM will work with other governmental departments and agencies such as USDA and CDC, veterinary organizations, and commodity groups to identify ways to develop and disseminate information on antimicrobial stewardship. In addition, CVM plans to work with academic institutions and federal partners to develop veterinary curricula or other educational materials that address antimicrobial stewardship in animals. CVM fosters antimicrobial stewardship in veterinary settings by staying engaged with veterinary practice associations and organizations that are leading the veterinary profession in advancing antimicrobial stewardship in practice, such as the AVMA and other industry and commodity group associations.

CVM Compliance Program Activities

CVM employed a phased-in enforcement strategy for the VFD final rule and GFI #213 implementation efforts (see Appendix 3). Inspection activities related to the VFD process are carried out by FDA's Office of Regulatory Affairs (ORA) and under contract by participating state feed regulatory programs. Initial focus for VFD inspections (2016-2017) was on education and outreach for affected stakeholders. Since then, CVM has transitioned toward an inspectional approach focused on compliance with VFD requirements and documenting violations. During inspections, field personnel examine VFD orders, requirements for the parties involved, and recordkeeping. A summary of VFD compliance activities conducted in fiscal years 2016-2018 was published by CVM in August of 2019. The summary assessment indicated that, in general, parties affected by the VFD final rule (i.e., producers, veterinarians, feed mills and distributors) were in compliance with it. Of the 456 total inspections included for 2016, 2017, and 2018, 91% were classified by inspectors as 'No Action Indicated', indicating no significant deficiencies. While the number of inspections conducted was limited, their findings have allowed CVM to respond to important stakeholder questions about implementation of the VFD final rule, gain a better understanding of industry practices related to the VFD final rule, and shape a broader inspection strategy to ensure ongoing compliance with the VFD regulation. The summary assessment report should be consulted for detailed information.

In addition to the VFD compliance strategy, CVM is developing strategies to identify and address inappropriate marketing of antimicrobials, for example, illegal marketing of unapproved animal drugs containing medically important antimicrobials.

Examples of CVM's Work on International Committees

Food safety experts at CVM collaborate with international regulatory bodies in the development of science-based regulations aimed at strengthening food safety systems and capacity at the global level. FDA subject matter experts contribute to the development and harmonization of global technical requirements for human and veterinary product registration, as well as data standards for detection of antimicrobial resistance such as whole genome sequencing technologies to advance their use in antimicrobial resistance surveillance. FDA's antimicrobial resistance mitigation and risk assessment guidelines (e.g., GFI #152) are often consulted for One Health projects developed by international organizations to improve global health. In addition, FDA experts currently contribute to several advisory committees within the World Health Organization, Food and Agricultural Organization, World Organisation for Animal Health (OIE), Codex ad hoc Intergovernmental Task Force on Antimicrobial Resistance, and Transatlantic Taskforce on Antimicrobial Resistance. CVM experts also collaborate globally with other countries' regulatory bodies to share knowledge and understanding of good regulatory practices and to promote close cooperation amongst a regional network of regulatory agencies, all while keeping with the broader aim of promoting animal health and its role in the One Health approach.

GOAL 3: ENHANCE MONITORING OF ANTIMICROBIAL RESISTANCE AND ANTIMICROBIAL DRUG USE IN ANIMALS

- **Objective 3.1:** Collect and analyze data on antimicrobial drug use in animals
- **Objective 3.2:** Enhance the collection and analysis of antimicrobial resistance data
- **Objective 3.3:** Increase data sharing and reporting to aid in the monitoring of antimicrobial drug use practices and resistance

In order to understand the drivers of resistance in veterinary settings and assess the impact of interventions designed to limit the development of resistance, it is essential to have scientifically-sound data on antimicrobial use and resistance, as well as animal health and management practices. To support this goal, CVM continues to explore new strategies to collect and analyze antimicrobial drug use data in food-producing animals and is enhancing the collection of antimicrobial resistance data. Through these actions, CVM seeks to reach a more comprehensive and science-based understanding of antimicrobial use and resistance in animal health and production settings.

Antimicrobial Use Data Collection

Antimicrobial use information is essential for assisting our understanding of the dynamics of animal health, production and management, specific use practices, their relationship with development of antimicrobial resistance, and how actions such as implementation of GFI #213 impact the development of resistance. CVM works closely with the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS) in support of ongoing data collection efforts to gather information on antimicrobial use and stewardship practices on farms through programs such as the USDA-APHIS National Animal Health Monitoring System (NAHMS). Since the NAHMS program conducts national surveys for specific commodities only on a periodic basis, detailed and ongoing information about antimicrobial use practices on farms is lacking. Based on knowledge of animal health and antimicrobial use information, specific on-farm management practices could be recommended or modified to help mitigate risks related to antimicrobial resistance. While CVM does collect and report annual sales data for antimicrobials approved for use in food-producing animals, the limitations of such data are recognized (see Chapter 3). To help address this, CVM funded two cooperative agreements in 2016 to support on-farm antimicrobial use and animal health data collection: one for poultry and swine and one for dairy cattle and feedlot cattle. These studies are expected to help identify prospects for sustainable methods to collect antimicrobial use data in food animal production settings. Initial results of the two cooperative agreements are presented in later chapters of this report. CVM also intends to publish a summary report of the information gathered through these agreements after they are completed.

Enhanced Antimicrobial Resistance Data Collection and Analysis

Enhanced collection and analysis of antimicrobial resistance data includes expanded sampling (including expansion of the types of food commodities and bacterial species) by NARMS, development of advanced approaches for resistance surveillance, targeted studies to assess the potential role of animal environments and feeds in the ecology of antimicrobial resistance, characterization of resistance in animal pathogens (including companion animals), and studies to document the role specific resistance genes may play in compromising clinical therapy. The NARMS program was reviewed by an FDA Science Board in 2017, which made several recommendations related to the expansion of current NARMS activities (FDA, 2017). Recommendations included expanding sampling and testing, as well as additional data collection capabilities intended to strengthen the scientific basis for regulatory decision-making. In 2018, NARMS began work on implementing some of the 2017 FDA Science Board recommendations, including launch of its first pilot to conduct surveillance on veal in nine retail meat sites (Tate et al, 2021). NARMS and CVM's Veterinary Laboratory Investigation and Response Network (Vet-LIRN) are also collaborating with USDA-APHIS National Animal Health Laboratory Network (NAHLN) laboratories to provide insight into the current state of antimicrobial resistance in bacterial pathogens from ill animals.

Continued use and expansion of advanced genomic technologies and bioinformatics tools for research and surveillance are also essential to improve understanding of antimicrobial resistance. In 2017, FDA launched Resistome Tracker, a tool that provides visually informative displays of antimicrobial resistance genes in bacteria. Currently, users can explore antimicrobial resistance genes present in the genomes of at least 295,000 ***Salmonella*** isolates submitted to the National Center for Biotechnology Information (NCBI), but future versions of the tool are intended to include data on other bacteria, such as ***E. coli*** and ***Campylobacter***. Resistome Tracker allows researchers to be alerted when new resistance genes emerge in a specified geographic region or sample source. The development of Resistome Tracker represented a major step forward in resistance monitoring that can assist in evaluation of the impact of antimicrobial use on the evolution and spread of resistance. NARMS continues to provide whole genome sequencing data to Resistome Tracker, and is also working towards accelerated data sharing, including genomic information.

In 2020, NARMS published its strategic plan for 2021-2025, more fully incorporating a One Health approach to surveillance, including piloting expansions for surveillance of antimicrobial resistance in animal pathogens and environmental water samples.

Increased Data Sharing and Reporting

CVM continues to advance the exchange of information among stakeholders to aid in monitoring of antimicrobial use practices and antimicrobial resistance. This includes engaging key stakeholders on data sharing and reporting strategies and ensuring that confidential information is appropriately protected. NARMS data are available to the public on-line. NARMS Now was launched in 2015 and provides downloadable data, as well as interactive graphs, tables, and maps. Data sharing and reporting objectives will be accomplished through the continued sharing of genomic information and data using improved interactive software tools and bioinformatics in the NARMS reports, as well as providing whole genome sequencing data to Resistome Tracker as already mentioned. In addition, CVM plans to publish information about the antimicrobial use cooperative agreements that characterize antimicrobial use in cattle, swine, and poultry.

CHAPTER 3

Surveillance and Monitoring of Antimicrobial Use and Resistance in Animal Agriculture

3.1 Introduction

3.2 Monitoring Antimicrobial Drug Sales and Distribution

3.3 Antimicrobial Drug Sales Adjusted by an Animal Biomass Denominator

3.4 Monitoring Antimicrobial Use

3.5 Antimicrobial Resistance Monitoring and Surveillance

3.1 Introduction

Data on the use of antimicrobials are particularly helpful when correlated with relevant data on antimicrobial resistance. A better understanding of antimicrobial use patterns is needed to support ongoing efforts to encourage the judicious use of antimicrobials in food-producing animals and to help ensure the continued availability of safe and effective antimicrobials for animals and humans. These data can also help measure the effectiveness of antimicrobial stewardship programs, and adherence to relevant policy or regulatory changes. Ongoing surveillance of antimicrobial resistance is essential for tracking changes in resistance in important bacterial commensal organisms and pathogens that can be acquired through the food chain by humans from animals and animal products. In addition, monitoring of antimicrobial resistance in animal pathogens is important for maintaining the health and welfare of animals.

In this chapter, we provide background information for some of the U.S. government programs and projects related to monitoring and surveillance of antimicrobial use and resistance in animal agriculture which are referenced later in species-specific chapters of this report. According to the World Organisation for Animal Health (OIE) Terrestrial Animal Health Code (OIE, 2019), '***monitoring***' is the intermittent performance and analysis of routine measurements and observations, aimed at detecting changes in the environment or health status of a population; while '***surveillance***' is the systematic and ongoing collection, collation, and analysis of information related to animal health and the timely dissemination of information for those who need to know so that action can be taken. Surveillance also provides information about the epidemiology of particular health threats, such as antimicrobial resistant infections, and their burden in a population.

This report is not intended to be an exhaustive review of all U.S. government programs and projects involved with surveillance and monitoring of antimicrobial use and/or resistance. For this report we focus on the following sources of data, primarily for the 2016-2019 time period:

- Antimicrobial sales and distribution data collected and reported by FDA on an annual basis, including species-specific estimates for the four major food-producing species (cattle, swine, chickens, turkeys) – see Section 3.2;
- Animal biomass-adjusted antimicrobial sales and distribution data for the four major food-producing species – see Section 3.3;
- Antimicrobial use information from U.S. feedlots and swine operations from surveys completed in 2017 by USDA-APHIS NAHMS – see Section 3.4;
- Antimicrobial use information from two FDA cooperative agreements designed to pilot methodologies for on-farm data collection for cattle, swine, chickens, and turkeys – see Section 3.4;
- Antimicrobial resistance data collected by the National Antimicrobial Resistance Monitoring System (NARMS) – see Section 3.5;
- Antimicrobial resistance information collected for the first two years (2018-2019) of the USDA APHIS National Animal Health Laboratory Network (NAHLN) Antimicrobial Resistance Pilot Project – see Section 3.5;
- Antimicrobial resistance information collected for the first year (2017) of an antimicrobial resistance pilot project in progress at the FDA's Veterinary Laboratory Investigation and Response Network (Vet-LIRN) – see Section 3.5.

In this chapter we provide general background and some information on methodologies used in each of these programs and projects. Data relevant to each of the food-producing species are presented separately in subsequent chapters.

3.2 Monitoring Antimicrobial Drug Sales and Distribution

3.2.1 Introduction

Antimicrobial sales and distribution data are one component that CVM utilizes to assess broad shifts in the amounts of antimicrobials introduced to the marketplace and intended for use in food-producing animals. Recognizing that national sales and distribution data do not reflect actual on-farm antimicrobial use practices, CVM is also developing strategies for collection of farm-level antimicrobial use data, which will be discussed later in this chapter. In addition, USDA- APHIS has collected some antimicrobial use data through the National Animal Health Monitoring System (NAHMS).

Since 2009, each year every sponsor of an approved or conditionally approved animal drug containing an antimicrobial active ingredient must report to CVM the amount of each such ingredient in these drug products sold or distributed for use in food-producing animals. CVM summarizes this information and makes it available to the public in annual summary reports. The first such report was published in 2010 and summarized antimicrobial sales data for 2009. The summary reports present the sales and distribution data for actively marketed antimicrobials approved for use in food-producing animals by antimicrobial drug class, medical importance, and route of administration. Beginning with reports covering calendar year 2016 and thereafter, drug sponsors have also been required to provide a species-specific estimate of the percentage of each product that was sold or distributed for use in cattle, swine, chickens, and turkeys, provided that these species appear on the approved drug label.

In this section, we review the background for the legislation requiring the reporting of antimicrobial sales and distribution data, the scope of reporting, as well as the uses and limitations of the data. Since the focus of this report is the years 2016-2019, we also present some of the key findings from the 2019 annual sales summary report (at the time of preparation of this report, 2020 sales data were not yet published). In Section 3.3, we review CVM's proposed methodology for applying a biomass denominator to adjust annual sales and distribution data, accounting for domestic animal populations and weights. Trends in the antimicrobial sales and distribution data and biomass-adjusted species-specific estimates for sales and distribution data for 2016 through 2019 are presented in later chapters.

3.2.2 Background and Scope of Reporting

The Animal Drug User Fee Act (ADUFA) was originally signed into law in 2003 and reauthorized in 2008, 2013, and 2018. It amended Section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), authorizing the FDA to collect fees for certain new animal drug applications and supplements, products, establishments, and sponsors of new animal drug applications and investigational new animal drug submissions. These resources support the FDA's responsibilities to ensure that new animal drug products are safe and effective for animals, as well as ensuring the safety of food from treated animals. When ADUFA was first reauthorized in 2008, Congress established additional reporting requirements for drug sponsors of antimicrobial drugs. Section 105 of the Animal Drug User Fee Amendments of 2008 requires that sponsors of approved animal drugs containing an antimicrobial active ingredient submit an annual report to FDA on the amount of each such ingredient in the drug that is sold or distributed for use in food-producing animals, including information on any distributor-labeled product. In May of 2016, FDA issued a final rule codifying annual reporting requirements under Section 105 of ADUFA and adding a new reporting provision to obtain estimates of sales broken down by major food-producing species (the 2016 final rule).

Information that must be submitted to FDA by the sponsor in each annual report is specified in the Code of Federal Regulations (21 CFR §514.87), and includes a listing of antimicrobial active ingredients in the drug product, description of drug product sold or distributed by unit (i.e., container size, strength, dosage form), a list of each target animal species that are specified on the drug product's label (including approved indications and animal production classes), and domestic and exported quantities of each drug product sold for each month of the reporting year. Each report must also provide a species-specific estimate of the percentage of each product that was sold or distributed domestically in the reporting year for use in any of the following animal species categories, but only for those species that appear on the approved label: cattle, swine, chickens, and/or turkeys. The total of the species-specific percentages reported for each product must account for 100% of its sales and distribution; therefore, a fifth category of "other species/unknown" must also be reported. The "other species/unknown" category includes a single combined estimate of product sales and distribution for: 1) other species listed on the approved label, including nonfood-producing animal species and minor food-producing species; 2) other species not listed on the approved label; and 3) unknown uses.

FDA makes annual summaries of the information reported by animal drug sponsors for each calendar year publicly available by December 31 of the following year. These reports include a summary of sales and distribution data and information by antimicrobial drug class and may include additional summary data and other information as determined by FDA. The annual summary reports include sales and distribution data of all antimicrobials that are specifically approved for antibacterial uses or are known to have antibacterial properties. As described elsewhere in this report, FDA has identified certain antimicrobial active ingredients as "medically important" based on their utility for treating disease in humans. Certain other drugs are not considered medically important; for example, drugs in the ionophore class are not considered medically important because they lack utility in human medicine and their use in animals does not pose any known cross-resistance concerns. Antifungal and antiviral drugs are not included in the summary report, and antiprotozoal drugs without antibacterial properties (e.g., amprolium) are also not included.

The annual summary reports are designed to provide useful information to the public while, at the same time,

meeting statutory requirements to report summary data in a manner consistent with protecting both national security and confidential business information. Under 21 CFR §514.87(f), annual sales and distribution data are summarized by antimicrobial drug class and only those antimicrobial drug classes and other categories with three or more distinct sponsors of approved and actively marketed animal drug products are independently reported. Antimicrobial drug classes with fewer than three distinct sponsors are reported collectively as "Not Independently Reported" (NIR). Following the same principle, for presentation of species-specific sales and distribution estimates, species categories (e.g., cattle) with fewer than three distinct sponsors are combined with the "other species/unknown" category and also reported collectively as NIR. If instances arise where two or more individual pieces of the summary data, when viewed together, could be used to derive other data that would reveal confidential business information, the categories are reported collectively as "other."

3.2.3 Uses and Limitations of Antimicrobial Sales and Distribution Data

There are certain inherent limitations on how antimicrobial sales and distribution data provided in the annual summary reports may appropriately be interpreted and used, including:

- The sales and distribution data submitted by animal drug sponsors are not indicative of how or if these antimicrobials were actually used in animals (e.g., for what indications, doses, or durations). With the exception of medicated feeds and certain drugs that are specifically prohibited from extralabel use, veterinarians can legally use approved animal drugs for species and therapeutic indications for which the drugs were not approved.
- Many of the applications are approved and labeled for use in multiple species, for multiple indications, and with multiple dosage regimens. This makes it difficult or impossible to determine which indications and/or dosage regimens are the most common.
- Animal drug sales data represent a summary of the volume of product sold or distributed through various outlets by the manufacturer intended for sale to the end user, not the volume of product ultimately purchased by the end user for administration to animals in a particular year. For example, veterinarians and animal producers may purchase drugs but never actually administer them to animals, or they may administer the drugs in later years.
- Regarding the collection and reporting of species-specific data, the percentages provided by the sponsors are their estimates of product sales and distribution. Sponsors are not required to provide information about how their estimates were determined. Therefore, there is an unquantifiable degree of uncertainty associated with these estimates.
- Sales data do not give any indication of the fluctuations of animal numbers within U.S. animal populations, the health of animals, or emergent animal disease trends for which antimicrobials may be required. Increases and decreases in sales can therefore be representative of population changes and/or changes in disease prevalence or incidence within an animal population just as readily as they could be related to changes in antimicrobial use. Other factors related to drug availability and cost, feed costs, and livestock market demands may influence shifts in antimicrobial sales and distribution in any given year.
- Sales data in kilograms do not take dose or drug potency into account. Certain antimicrobial classes might require more or less active ingredient to be considered one dose, compared to other classes. Therefore, while antimicrobial sales data may occasionally be presented as overall total amounts for summary purposes, displaying the data in this way is not of value when considering whether or not antimicrobials are being used judiciously.

In view of these and other potential limitations, antimicrobial sales and distribution data are not intended to be a substitute for actual on-farm antimicrobial use data. The usage of sales data as a sole indicator for the risk of development of antimicrobial resistance should also be viewed with these limitations in mind. Attempts to directly compare the species-specific sales estimates between species are also confounded by factors such as differences in population size, animal weights, animal health and lifespan, and drug metabolism. By the same token, comparison of animal antimicrobial drug sales and distribution data with similar data for humans poses many challenges. A number of differences in the circumstances in which antimicrobials are used in human and veterinary medicine must be considered, including differences in human and animal population numbers, weights, physiology, as well as drug metabolism.

3.2.4 Key Findings from the 2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals

The FDA's annual summary reports on antimicrobials sold and distributed for use in food-producing animals for the years 2009-2019 are posted on CVM's website (see https://www.fda.gov/industry/animal-drug-user-fee-act-adufa/adufa-reports). This section describes some of the sales and distribution data reported in the **2019** antimicrobial sales summary, the 2019 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals (2019 Annual Sales Summary report). The most recently published annual sales summary report (2020) is not covered in this report, since at the time of preparation of this report, the 2020 data had not been published yet.

The 2019 Annual Sales Summary report was published in December of 2020, the third year of reporting after complete implementation of GFI #213 on January 1, 2017 when all affected products that are medically important in human medicine (specifically, those medically important antimicrobials used in feed and water of food-producing animals) transitioned from OTC marketing status to either Rx or VFD marketing status and all production claims (e.g., uses for growth promotion and improved feed efficiency) were removed (see Appendix 3). Between 2016 and 2019, domestic sales and distribution of medically important antimicrobials showed an overall decrease of about 26%. Since other efforts across the animal production industry have also been ongoing to improve antimicrobial use and stewardship in food-producing animals, the reduction in sales is likely not solely due to GFI #213 implementation. CVM does not focus on setting overall targets for reductions in antimicrobial sales or use, but rather has focused on efforts to support judicious use of antimicrobials for therapeutic purposes that are necessary for the health of animals (i.e., not for production purposes) and used only under the oversight of veterinarians. Subsequent years may show increases or decreases in antimicrobial sales and use depending on multiple factors such as shifts in animal populations, changes in disease prevalence or incidence, and new or emerging diseases that may require the use of antimicrobials to ensure animal health and welfare.

A few key findings from the 2019 Annual Sales Summary report included:

- Overall domestic sales and distribution of medically important antimicrobials approved for use in food-producing animals:
  - increased by 3% from 2018 through 2019;
  - decreased by 36% from 2015 (the year of peak sales) through 2019; and
  - decreased by 19% from 2009 (the first year of reported sales) through 2019.

- Tetracyclines (accounting for the largest volume of domestic sales), increased by 4% from 2018 through 2019.

• Of the overall 2019 domestic sales and distribution of medically important antimicrobials approved for use in food-producing animals, tetracyclines accounted for 67%, penicillins for 12%, macrolides for 8%, sulfonamides for 5%, aminoglycosides for 5%, lincosamides for 2%, cephalosporins for less than 1%, and fluoroquinolones for less than 1%.

The annual summary reports feature a number of informative tables and graphs, presenting the data in several ways. In this section we include a portion of one of the summary tables from the 2019 Annual Sales Summary report. Species-specific estimates of antimicrobial sales and distribution data will be presented in subsequent chapters of this report. **Table 3-1** shows overall totals of domestic sales and distribution data for antimicrobials approved for use in food-producing animals and actively marketed by medical importance, antimicrobial drug class, and year for 2009 (the first year of reporting) and 2016 through 2019. Percent change between 2009 and 2019, 2016 and 2019, and 2018 and 2019 are shown in the last three columns. This is a portion of Table 2b published in the 2019 Annual Sales Summary report, which presents data for all years between 2010 and 2019. Antimicrobial classes for which there were fewer than three distinct sponsors actively marketing products domestically are not independently reported.

Table 3-1: Domestic sales and distribution data for antimicrobials approved for use in food-producing animals and actively marketed - in 2009 (first reporting year) and 2016-2019

Medical Importance	Drug Class	2009 Annual Totals (kg)[2]	2016 Annual Totals (kg)[2]	2017 Annual Totals (kg)[2]	2018 Annual Totals (kg)[2]	2019 Annual Totals (kg)[2]	% Change 2009-2019	% Change 2016-2019	% Change 2018-2019
Medically Important[3]	Aminoglycosides[1]	223,117	319,009	259,184	289,455	307,988	38%	-3%	6%
	Cephalosporins[1]	20,145	31,010	29,369	31,448	29,830	48%	-4%	-5%
	Fluoroquinolones	*	18,502	22,904	23,350	24,556	**	33%	5%
	Lincosamides[1]	93,330	142,458	152,497	125,514	134,962	45%	-5%	8%
	Macrolides[1]	562,062	554,714	468,794	473,038	488,082	-13%	-12%	3%
	Penicillins[1]	691,644	842,863	690,889	731,863	716,525	4%	-15%	-2%
	Sulfonamides[1]	505,880	369,826	274,112	278,562	304,327	-40%	-18%	9%
	Tetracyclines[1]	5,260,995	5,861,188	3,535,701	3,974,179	4,117,031	-22%	-30%	4%
	NIR[1,4]	329,391	216,771	125,761	104,888	65,958	-80%	-70%	-37%
	Subtotal	**7,686,564**	**8,356,340**	**5,559,212**	**6,032,297**	**6,189,260**	**-19%**	**-26%**	**3%**
Not Medically Important[5]	Ionophores	3,739,352	4,651,491	4,394,850	4,562,260	4,270,122	14%	-8%	-6%
	NIR[6]	1,161,541	1,018,305	979,306	968,524	1,008,976	-13%	-1%	4%
	Subtotal	**4,900,893**	**5,669,796**	**5,374,156**	**5,530,784**	**5,279,098**	**8%**	**-7%**	**-5%**
	Grand Total	**12,587,457**	**14,026,136**	**10,933,367**	**11,563,081**	**11,468,357**	**-9%**	**-18%**	**-1%**

[1] Includes antimicrobial drug applications which are approved and labeled for use in both food-producing animals and nonfood-producing animals.

[2] kg=kilogram of active ingredient. Antimicrobial class includes drugs of different molecular weights, with some drugs labeled in different salt forms. Antimicrobials that are labeled in International Units (IU) (e.g., penicillins) were converted to kg.

**Not reported because there were fewer than three distinct sponsors actively marketing product domestically.*

***Not calculated because there were fewer than three distinct sponsors actively marketing product domestically in 2009.*

[3] Guidance for Industry #213 states that all antimicrobial drugs and their associated classes listed in Appendix A of FDA's Guidance for Industry #152 are considered medically important in human medical therapy.

[4] NIR=Not Independently Reported. Antimicrobial classes for which there were fewer than three distinct sponsors actively marketing products domestically are not independently reported. These classes include the following: Amphenicols, Diaminopyrimidines, Fluoroquinolones (except 2016-2019), Polymyxins, and Streptogramins.

[5] Not Medically Important refers to antimicrobial classes approved for use in animals but not listed in Appendix A of FDA's Guidance for Industry #152.

[6] NIR=Not Independently Reported. Antimicrobial classes for which there were fewer than three distinct sponsors actively marketing products domestically are not independently reported These classes include the following: Aminocoumarins, Glycolipids, Orthosomycins (except 2009), Pleuromutilins, Polypeptides, and Quinoxalines.

3.3 Antimicrobial Sales and Distribution Adjusted by an Animal Biomass Denominator

3.3.1 Introduction

Animal biomass can be defined as the total mass of an animal species, determined by multiplying that species' population by their average weights in a given year. In the context of antimicrobial sales and distribution data, biomass may be considered a denominator – that is, it represents the animals that could potentially be exposed to antimicrobials. The goal of applying an animal biomass denominator to antimicrobial sales and distribution data is to provide estimates that represent trends in annual antimicrobial sales and distribution relative to the U.S. livestock population in which the antimicrobials may be used. These adjusted estimates are intended to provide insight into broad shifts in the amounts of antimicrobials sold for use in food-producing animals and to allow for a more nuanced view of how sales increase or decrease over time in a manner that is specific to U.S. animal production. In this section, CVM's proposed methodology is briefly reviewed. Full details of the proposal are found in the FDA's 2017 published report, *FDA's Proposed Method for Adjusting Data on Antimicrobials Sold or Distributed for Use in Food-Producing Animals Using a Biomass Denominator* (Biomass Denominator Technical Report). Animal biomass denominators for each species are presented for 2016 through 2019. Because the biomass denominator is only intended to be used with species-specific antimicrobial sales and distribution data, biomass-adjusted antimicrobial sales data will be presented separately in each species chapter of this report. Animal population and weight data used for the biomass denominator calculations are shown in **Appendix 4** along with references to the sources of this information.

Other countries and regions have used a biomass denominator or 'population correction unit' (PCU) to adjust antimicrobial sales data for use in food-producing animals, which are applicable to specific characteristics of animal production in those countries or regions (e.g., European Surveillance of Veterinary Antimicrobial Consumption; Canadian Integrated Program for Integrated Antimicrobial Resistance Surveillance (CIPARS), and others). CVM previously evaluated these methods and determined that they have significant limitations for the U.S. with respect to key components used in calculations of the biomass denominator. Examining the differences between countries and regions in animal populations, weights, management practices, and the number and types of antimicrobials approved led CVM to determine that a U.S.-specific biomass denominator method would be the most appropriate for the situation in the U.S.

The OIE produces an annual report which provides for a global perspective on antimicrobial agents intended for use in animals, the most recent of which was published in September 2021. The U.S. is a member country of the OIE and CVM is a Collaborating Centre. CVM responds to annual data requests from the OIE on the amount of antimicrobials sold or distributed in the U.S. The OIE annual reports include calculation of a biomass denominator for each reporting region, primarily using data from the OIE World Animal Health Information System (WAHIS) and the Food and Agriculture Organization Statistics database (FAOSTAT). The OIE report should be consulted for full details on methodology for that biomass denominator determination. The formulas chosen for calculation of the OIE denominator reflected the best fit estimations using the more general global animal

population data and were not necessarily intended to be used for monitoring of country-specific situations where more detailed information about animal species and production categories may be available.

3.3.2 FDA's Proposed Methodology for Application of a Biomass Denominator to Adjust Annual Antimicrobial Sales and Distribution Data

In 2017, CVM sought public comment (82 FR 38695) on the proposed methodology for applying a biomass denominator to annual data on approved antimicrobials sold or distributed for use in food-producing animals in the U.S. In the Biomass Denominator Technical Report describing the proposed method, CVM provided details of a U.S.-specific biomass denominator calculation that would account for domestic animal populations and weights to represent, reasonably accurately, trends in antimicrobial sales relative to the animal biomass of the livestock population in which the antimicrobials could potentially be used. The key elements of this biomass denominator method include:

1. Antimicrobial sales and distribution data reported annually to FDA;
2. Annually reported animal populations in the U.S.;
3. Annually reported animal weights in the U.S.;
4. Animal drug approvals in the U.S.; and
5. Limitations on the use of certain antimicrobial drugs and/or drug classes in the U.S.

CVM received feedback and 42 comments to the docket from various stakeholders, and in consideration of those comments conducted additional stakeholder outreach and consulted with epidemiologists and commodity specialists at USDA-APHIS to further refine the proposed method. Based on the feedback received and consultations with USDA, this section provides a summary of CVM's current method for using a U.S.-specific biomass denominator to adjust data on antimicrobials sold or distributed for use in food-producing animals and the resulting implementation of that method.

In addition to the key elements identified above, CVM proposed using percent change as the primary metric to analyze and compare annual trends in biomass-adjusted antimicrobial sales and distribution data for food-producing animals in the U.S. Percent change represents the relative change between two values and is also used to report trends in antimicrobial sales volume in the Annual Sales Summary reports. Relevant to the data for this report, the percent change between each year and between 2016 and 2019 are shown.

3.3.2.1 GENERAL METHOD

Biomass-adjusted species-specific estimated sales in milligram active ingredient per kilogram body weight (mg/kg) values are calculated for the antimicrobial drug classes that are important in human medicine and can be presented for species-specific estimated sales that are independently reported in FDA's Annual Sales Summary Reports. The numerator is the amount—expressed in mg—of a particular antimicrobial drug class sold for use in a given food-producing species as estimated and reported annually by animal drug sponsors to CVM. The denominator represents the estimated animal biomass—expressed in kg—of the given species.

Biomass denominators are calculated for each of the four major food-producing species—cattle, swine, chickens, and turkeys. The biomass denominator for each species, as it applies to the species-specific estimated sales for medically important drug classes, is referred to as a *target animal biomass* (TAB).

3.3.2.2 TARGET ANIMAL BIOMASS (TAB) DENOMINATOR COMPONENTS

Animal Population Data

CVM utilizes domestic livestock population data from USDA database reports from the National Agricultural Statistics Service (NASS) and U.S. data from the Global Agricultural Trade System (GATS) of the Foreign Agricultural Service to estimate annual livestock numbers for the biomass denominator. When referencing USDA's published reports, CVM uses the most recent data available in a publication.

To estimate the U.S. livestock population for a calendar year, CVM uses USDA reports that break down the animal population into subcategories for certain species that include:

- Annual totals of slaughtered animals;
- Annual inventory of animals kept longer than one year; and
- Numbers of animals imported to and exported from the U.S. in a calendar year to account for international trade of live animals.

Each of these subcategories of a species population is referred to in this report as an "animal category." Appendix 4 contains the list of animal categories utilized to calculate the biomass denominator and references to the sources of population data. Refer to the Biomass Denominator Technical Paper for a summary and detailed example of a TAB denominator calculation. Although the animal categories together represent a significant proportion of the U.S. livestock population for each species considered, they may not include 100% of the animals within that population that were potentially treated with antimicrobials sold in the U.S. CVM has made every attempt to include animal categories applicable to each TAB denominator. In cases where an animal category was excluded from label indications on all animal drug approvals within an antimicrobial drug class, that animal category was not included in the TAB denominator for that species. For example, for the lincosamide drug class, all approvals for chickens are limited to broiler chickens and chicks up to 7 days of age, and approved lincosamide drugs are not approved for use in layers or breeders. Therefore, the chicken TAB denominator for lincosamides only includes the population and estimated weight of young chickens from the USDA Poultry Slaughter Summary reports, which define 'young chickens' as commercially grown broilers-fryers and other immature birds and 'mature chickens' as birds from breeder and market egg flocks.

CVM recognizes that in an effort to most accurately represent the U.S. livestock population in a calendar year using publicly available data, there may be some occurrences of "double reporting" of animals. For example, the TAB denominator for cattle may include culled dairy cows in the total number of cattle slaughtered as well as the inventory of livestock dairy cows. Due to variations in the length of animal life cycles and the limitations of publicly available data sets for animal populations, CVM has determined that minor occurrences of double reporting that are relatively consistent from year to year will have minimal impact on annual trend analysis.

Animal Weight Data

CVM's biomass denominator method uses annual livestock weights that will be reevaluated on an annual basis to capture shifts in animal demographics that may result from changing management practices or other factors, such as infectious disease outbreaks and changes in disease prevalence or incidence.

As with the animal population data, CVM relies primarily on data from USDA's NASS and GATS to calculate annual average weights of livestock populations. Average weights at slaughter are used to represent animal populations slaughtered annually. Weights for animals imported to or exported from the U.S. are based on weight categorizations used in the GATS database on livestock and meat international trade. For livestock kept longer than one calendar year (e.g., dairy cows, sows, and beef cows), CVM calculated annual average weights using information from USDA's periodic species-specific reports (e.g., reports by USDA's National Animal Health Monitoring System) or other sources. In cases where annual average weights were unavailable from USDA sources, CVM calculated average weights based on academic resources and industry publications. Where animal weights are reported in pounds (lb), those values are converted to kilograms (kg) for the TAB calculations using a conversion factor of 1 lb = 0.453592 kg. If animal weights were reported in kilograms, the reported value was used. Refer to Appendix 4 for the list of animal categories and corresponding average weights used to calculate the biomass denominators, including references.

To maintain consistency across animal categories and species for the purposes of annual trend analysis, average live weight at slaughter, maximum live weight, or maximum value of import/export weight categorizations are used as representative average weights for target animal categories. Note that these will likely result in high-end estimates of biomass for the U.S. livestock population and are not intended to represent the biomass of treated animals at the time of treatment. CVM also understands that not all animals in the U.S. livestock population are treated with antimicrobials. However, the biomass denominator is intended to represent the annual U.S. livestock population that could possibly be treated with antimicrobials sold in a calendar year according to the drug label indications. Since these average weight data are collected and reported annually, CVM believes that these will allow for the most representative annual trend analysis of sales and distribution of antimicrobials relative to annual U.S. livestock population biomass. If nationally representative data on animal weights at the time of antimicrobial treatment for the four major food-producing species become available in the future, CVM will consider how this could be incorporated into a biomass denominator adjustment method or other methods used to analyze antimicrobial sales and distribution data or data on antimicrobial use in food-producing animals.

3.3.3 Target Animal Biomass for 2016 - 2019

Target animal biomass is a summation of the biomass of each animal category within a species group; this will then be the denominator in the biomass-adjusted sales data calculations. The biomass of the animal category is determined by multiplying the enumerated population of a given animal category by the previously defined average weight of an animal within that animal category.

Target Animal Biomass (TAB) is calculated for the four major food-producing species using the following general formula:

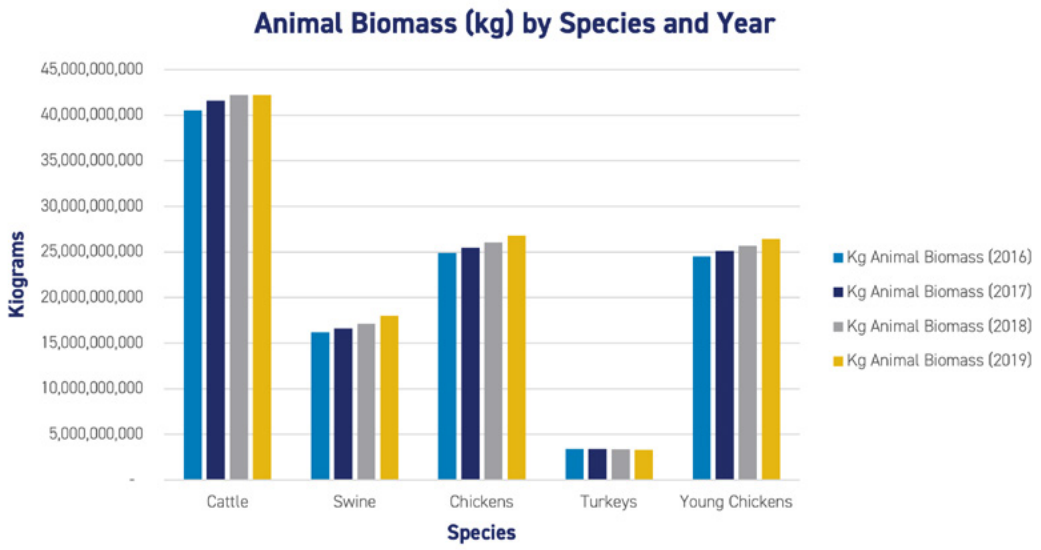
> **TAB = sum of (estimated number of animals in the given animal category * estimated average weight, in kg, of an animal in this animal category) for each target animal species**

Refer to the Biomass Denominator Technical Paper for the detailed calculation method. TAB values are calculated using animal weights, in kilograms. The biomass and mg/TAB values presented in this report may differ slightly from what can be calculated directly from the individual data elements due to rounding of values as indicated. **Table 3-2** shows the animal biomass (in kg) for each of the four major food-producing species for 2016 through 2019 and represents the biomass for all of the animal categories identified for each species in Appendix 4. In addition, the biomass for young chickens was calculated since the lincosamide drug class is only approved for this category of chickens and is therefore the only biomass denominator applied to lincosamide sales for chickens. **Figure 3-1** represents the same data shown graphically. Between 2016 and 2019, cattle, swine, and chickens have had variable increases in total biomass each year while turkeys have had a small decrease.

Table 3-2: Animal biomass, by species and year and percent change, 2016-2019

Species	Animal Biomass (kg)				% Change 2016 to 2017	% Change 2017 to 2018	% Change 2018 to 2019	% Change 2016 to 2019
	2016	2017	2018	2019				
Cattle	40,543,058,336	41,606,395,144	42,204,117,708	42,203,819,532	2.6%	1.4%	-0.001%	4.1%
Swine	16,201,398,108	16,620,621,732	17,118,873,912	17,971,526,756	2.6%	3.0%	5.0%	10.9%
Chickens	24,905,080,747	25,465,862,951	26,022,566,702	26,784,266,991	2.3%	2.2%	2.9%	7.6%
Young chickens only	24,512,262,854	25,087,277,922	25,633,638,644	26,454,579,125	2.4%	2.3%	3.1%	7.9%
Turkeys	3,385,185,854	3,387,385,140	3,338,092,481	3,305,504,799	0.06%	-1.5%	-1.0%	-2.4%

Figure 3-1: Animal biomass, by species and year, 2016-2019



3.3.4 Target Animal Biomass-Adjusted Antimicrobial Sales and Distribution Data

The numerator in CVM's biomass-adjusted sales data (in mg/TAB) represents the sum of all antimicrobial sales and distribution data estimated for a single species across an antimicrobial drug class as reported in the Annual Sales Summary Report. Based on statutory requirements to report sales summary data in a way that protects confidential business information, CVM is limited in how antimicrobial sales and distribution data can be summarized and reported. This limitation extends to how CVM can report antimicrobial sales adjusted by a biomass denominator.

CVM will apply TAB denominators to species-specific estimated drug sales by antimicrobial drug class for each of the four major food-producing species only where these class data can be "independently reported" in the Annual Sales Summary Reports. A biomass denominator is applied to the grouping of "not independently reported" (or "NIR") drug classes utilizing the species total biomass denominator, but any potential exclusions of animal categories cannot be utilized for these NIR groupings even if an exclusion would otherwise have been applicable. As indicated in the Biomass Denominator Technical Paper, CVM cannot calculate a mg/TAB value for the "other species/unknown" category or "all species" summarized data. This is because the "other species/unknown" category may include sales for minor food-producing species such as sheep, goats, and fish, and companion animals, as well as any extralabel uses in any species (including extralabel uses in cattle, swine, chickens, and turkeys), and the "all species" summarized data include data for more than one type of food-producing species (i.e., for some drug classes the "all species" summarized data may include combined data for cattle, swine, and chickens, etc.). Therefore, finding appropriate values for estimating associated animal population numbers and weights for the wide variety of indications and animals in these "other species/unknown" and "all species" summarized data categories is not feasible for all antimicrobial drug classes.

Antimicrobial sales and distribution data represent the amount of product entering the distribution chain in one calendar year, but not necessarily the total amount of product purchased by the end user to administer to animals in the same year. This biomass denominator method assumes a generally consistent lag in sales and distribution of antimicrobials relative to their use in the annual population and would therefore not impede the ability to follow trends over time. When additional years of species-specific estimated sales data are available, CVM may consider reporting the trends in species-specific estimated sales for a calendar year relative to animal biomass for the following year to account for lag time between sales, distribution, and use in the animals.

Target Animal Biomass (TAB) is used to adjust antimicrobial sales data to the drug class level according to species-specific estimates using the following formula:

> **mg/TAB = (the sum of all sales of an antimicrobial drug class, in mg, estimated for a given target animal species)/ [sum of (estimated number of animals in the given animal category * estimated average weight, in kg, of an animal in this animal category) for each target animal species]**

Note that where TAB is used to adjust species-specific estimated antimicrobial sales data, only the animal categories applicable to the approved indications on marketed antimicrobial products will be included in the denominator (with the exception of drug classes included within the "NIR" category that cannot be reported independently, so no specific exclusions are made for the denominator for these).

CVM proposed percentage change as the primary metric for assessing mg/TAB trends within a single species and for showing the effect of adjusting the sales data relative to animal biomass. The formula used to calculate percent change is: [(value for year 2 – value for year 1)/value for year 1] * 100.

In tables showing biomass-adjusted antimicrobial sales data for each species (see subsequent chapters of this report), trends are shown (percent change) for the years 2016 through 2019. As additional years of species-specific estimated sales data become available, CVM can use animal biomass denominator adjustments to better interpret the amount of drugs sold or distributed for use in food-producing animals relative to shifts in animal weights and populations over time.

Two key elements of this U.S.-specific biomass denominator method refer to animal drug approvals in the U.S. and limitations on the use of certain antimicrobial drugs and/or drug classes in the U.S. The level of detail to which CVM can independently report species-specific estimated sales data may create limited instances where TAB includes less than all of the animal categories for a species. If additional levels of detail in species-specific estimated sales are provided in Annual Sales Summary Reports in the future, CVM will consider what animal categories are appropriate for each TAB calculation based on the approved indications for antimicrobial products included in the numerator.

As previously described, there are limitations to this biomass denominator method such as statutory reporting requirements for antimicrobial sales and distribution data (e.g., restrictions on reporting of certain confidential business information) and lack of nationally-representative publicly available data on average weights of food-producing animals by production class (e.g., average live weight or weight at time of treatment). As such, CVM's method for adjusting data on antimicrobials sold or distributed for use in food-producing animals using a biomass denominator may be subject to refinement as additional information becomes available.

3.4 Monitoring Antimicrobial Use in Animal Agriculture

3.4.1 Introduction

Knowledge about antimicrobial selection pressures is important to understand potential risk factors for development of antimicrobial resistance in bacteria. Since antimicrobial use in food-producing animals is one contributing factor towards these selection pressures, information about antimicrobial use in animals is needed to further understand its role in the development of resistance. Antimicrobial use information is also needed to assist in the development of strategies to optimize antimicrobial use so that their effectiveness can be preserved for both humans and animals.

Nationally-representative and continuously collected data for on-farm antimicrobial use in livestock and poultry in the U.S. are not currently publicly available. Some information from specific studies or surveys may be

available in scientific literature, but a comprehensive literature review was beyond the scope of this report. Private enterprises that may collect this type of information generally do not make such data available publicly. Much of the published literature which does mention antimicrobial use in agriculture is focused on understanding if there are linkages between such use and antimicrobial resistance in humans. Similarly, much of the literature published about antimicrobial resistance is focused largely on antimicrobial resistance in foodborne pathogens rather than on antimicrobial resistance of pathogens important to veterinary medicine.

Both qualitative and quantitative antimicrobial use data are needed for a number of reasons; for example:

- To assist in the investigation of associations between antimicrobial use and resistance;
- To design and conduct appropriate analyses of the human and animal health risks associated with antimicrobial use in animals;
- To aid in the development and evaluation of programs and policies designed to contain antimicrobial resistance; and
- To inform antimicrobial stewardship programs through identification of changes in prescribing or use patterns over time and determination of the impacts of various interventions.

Ideally, for antimicrobial use data to have the most relevance to studying resistance development patterns, these data should be collected from a representative sample of farms along with the indications for use, the route of administration, the dose and duration, and any other information that provides context for the use, such as animal health and management factors and disease prevalence or incidence. Collection of such detailed data at a national level is challenging due to the intensive resources it requires and is also complicated by the variety in structure of the various livestock industries. For example, the poultry and swine industries are often vertically integrated to varying degrees, whereas the cattle industry is more segmented, resulting in differences across species in the routine usage of standardized health record systems which are an important component of any large-scale data collection effort.

Data obtained through nationally representative monitoring of antimicrobial use practices could help provide useful information about the most common reasons for antimicrobial use, identify more optimal patterns of antimicrobial use, and design educational programs to improve prescribing practices. In the U.S., a program of long-term and sustained antimicrobial use data collection is needed to determine how and why antimicrobials are being used in animals. USDA APHIS, through the NAHMS program, has gathered some limited information about antimicrobial use practices as part of their periodic commodity surveys. APHIS also recently conducted two surveys specifically to collect information about antimicrobial use practices in feedlot cattle and swine operations in the U.S. While these studies collected the information during on-farm surveys conducted in 2017, they were designed to gather data regarding representative antimicrobial use practices on farms in 2016, prior to implementation of GFI #213. As noted in Chapter 2, CVM also announced a funding opportunity in 2016 and requested applications for projects to pilot antimicrobial use data collection methodologies for the four major food-producing species in the U.S. One of the requirements for applicants was that the data collection design would include antimicrobial use data for 2016 to serve as a baseline for comparison after implementation of GFI #213 was completed. Two grants were awarded in the form of cooperative agreements in July of 2016 and these projects are ongoing at this time. This section describes the background for these USDA and FDA data collection efforts. Information obtained about antimicrobial use for each of the four major food-producing species will be described in the relevant species chapters later in this report.

3.4.2 USDA APHIS National Animal Health Monitoring System (NAHMS)

3.4.2.1 BACKGROUND

APHIS initiated the NAHMS program in 1983 to collect, analyze, and disseminate data on animal health, management, and productivity across the U.S. The NAHMS program conducts national studies by combining the efforts of government agencies, producers and other industry representatives, academic institutions, as well as public and animal health professionals. These efforts are organized by the Center for Epidemiology and Animal Health (CEAH), a program within APHIS.

NAHMS national studies generally focus on one animal commodity or production type (such as swine production or beef cow-calf operations). Studies typically consist of surveys of animal producers and might include collection of animal biological samples (e.g., blood, feces, milk) related to the study objectives. To be considered national in scope, each study is designed to include the states that represent at least 70% of the targeted animal population and at least 70% of operations with the target animal species in the U.S. The interval between studies for each commodity or production type depends on information needs. In general, swine, dairy, and beef commodities are studied about every five years, while other commodities (such as sheep, goats, horses, and catfish) are studied at longer intervals. **Table 3-3** shows the commodity groups for which NAHMS has conducted multiple national studies since 1990. In addition, NAHMS has conducted multiple small-scale studies and more recently, antimicrobial use studies specifically for beef feedlots and swine operations in 2017. According to NAHMS, beef feedlot and swine studies conducted in 2021 will also collect antimicrobial use and stewardship information.

Table 3-3: NAHMS studies by commodity group and year

Commodity Group	Year(s)
Aquaculture	1997, 2003, 2010
Beef Feedlot	1994, 1999, 2011, 2021 (current)
Beef Cow-Calf	1993, 1997, 2008, 2017
Bison	2014
Cervids	2014
Dairy	1992, 1996, 2002, 2007, 2011, 2014
Equine	1998, 2005, 2015
Goats	2009, 2019
Poultry	1999, 2004, 2007, 2010, 2013
Sheep	1996, 2001, 2011
Swine	1990, 1995, 2000, 2006, 2007, 2012, 2021 (current)

Source: USDA NAHMS: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/monitoring-and-surveillance/nahms

3.4.2.2 NAHMS GENERAL STUDY PROCESS

From initial planning to full reporting of results, each NAHMS study takes about four years to complete. A new study begins about every year, so several studies are in progress at any given time. The cycle for each study generally consists of several steps including an information needs assessment, questionnaire development and sampling design, implementation of data collection in the field, data entry and analysis by CEAH epidemiologists and commodity specialists, and report preparation and publication. Detailed information about conduct of NAHMS studies can be found in a brochure on the NAHMS website.

Participation by producers in NAHMS national studies is voluntary. Producer identities and other proprietary data (e.g., location, inventory, etc.) are treated as confidential business information. No information is released that would enable the identification of individual producers.

Data obtained through NAHMS studies provide essential information on U.S. livestock and poultry health and management for decision makers including producers, researchers, and policymakers. National estimates generated from each NAHMS study are used to provide up-to-date and trend information needed to monitor animal health, support trade decisions, assess research and product development trends, answer questions for consumers, and set policy.

3.4.2.3 NAHMS STUDIES REFERENCED IN THIS REPORT

Some of the previous and current NAHMS commodity studies included information pertaining to antimicrobial use in U.S. livestock and poultry, and some have also collected biological samples for antimicrobial resistance testing. Published studies can be accessed on the NAHMS website. NAHMS recently published reports for feedlot cattle and swine operations in the U.S. which focused on antimicrobial use practices during 2016. The data from these two antimicrobial use and stewardship studies are summarized in the cattle and swine chapters of this report.

3.4.3 FDA Cooperative Agreements for Collection of On-farm Antimicrobial Use Data for Food-Producing Animals

One objective of the National Action Plan for Combating Antibiotic-Resistant Bacteria is to strengthen the national infrastructure for antimicrobial use monitoring across the One Health spectrum, including the use of antimicrobials in food-producing animals on farms. Gathering information on the way medically important antimicrobials are used in food-producing animals is also essential to measuring the initial impacts of GFI #213. Data from multiple sources are needed to provide a comprehensive and science-based picture of antimicrobial drug use and resistance in animal agriculture.

In March of 2016, FDA announced the availability of fiscal year 2016 funds to support the collection of data on antimicrobial use in animal agriculture (Funding Opportunity Announcement RFA-FD-16-046). The funded data collection efforts are intended to provide needed information on antimicrobial use practices in various animal

production settings (i.e., cattle, swine, and poultry) and to provide important information on data collection methodologies to help optimize long-term strategies for collecting and reporting such data. This funding, in the form of cooperative agreements, is intended to collect data that will help assess the rate of adoption of changes outlined in GFI #213 and help gauge the success of antimicrobial stewardship efforts.

FDA's stated goals and objectives for the funding opportunity were the following:

- Applicants (for the funding opportunity) should develop a methodology to collect detailed information on antimicrobial drug use in one or more of the major food-producing species (cattle, swine, chickens, turkeys). Information collected could include such information as antimicrobial drug name, dose, duration of use, purpose of use, and quantity/extent of use;
- Applicants' methodology should provide for annual collection and reporting of antimicrobial use information, including for the 2016 calendar year;
- Applicants should characterize the extent to which the collected data is representative of the particular food-producing species/ industry segment in the U.S.;
- Applicants should collect data in a manner that protects disclosure of farm/production unit identifying information or other confidential business information; and
- Applicants should produce an annual summary report of the data collected, including a detailed description of the data collection methodology.

In addition to these goals and objectives, FDA specifically requested proposals that would:

- Provide detailed antimicrobial drug use data that accurately reflects actual on-farm use;
- Provide "baseline" data on antimicrobial use (i.e., data prior to the implementation GFI #213);
- Pilot methodologies for collecting, summarizing, and reporting antimicrobial use data;
- Foster public-private partnerships/collaboration;
- Leverage existing data systems and minimize burden and disruption to animal producers; and
- Incorporate strategies for protecting farm/producer identity and other confidential information.

After careful evaluation by an objective review panel of the applications received, two grants were awarded in August of 2016. The two projects awarded were:

- *Characterization of Antimicrobial Use in Beef Feedlots and Dairies* (Grant number 5U01FD005868)
- A*ntibiotic Use Data Collection in U.S. Poultry and Swine Production* (Grant number 5U01FD005878)

Currently, the investigators are in the final year of the cooperative agreements. To assist with process validation for data collection and analysis procedures, project investigators consulted with the USDA APHIS Center for Epidemiology and Animal Health (CEAH). Primary investigators have submitted annual progress reports as required by the terms of the agreement. In December of 2018, the investigators also submitted initial reports describing the first two years of data (2016 and 2017) collected, which will be summarized in this report within each species chapter. At the end of the five year projects, a final report will be published to summarize the results and determine next steps. It is expected that the results of these pilot projects will help to inform the development of future long-term and sustainable antimicrobial use data collection plans.

3.5 Antimicrobial Resistance Monitoring and Surveillance

3.5.1 Introduction

Antimicrobial resistance monitoring and surveillance across the One Health spectrum are necessary to estimate the degree, patterns, and human and animal health burden of antimicrobial resistance at national, regional, and international levels to assist in detection of emerging resistance, and to evaluate the impact of various interventions. Accurate and reliable antimicrobial susceptibility testing (AST) is essential for human and animal health care providers to select appropriate antimicrobials for treatment of patients with bacterial infections. This section focuses on antimicrobial resistance surveillance designed to provide a national-level foundation for assessing the burden of antimicrobial resistance in the food chain in the U.S., as well as some programs that conduct surveillance on bacterial pathogens important to animal health.

There are a number of commonly used laboratory AST methods each with advantages and disadvantages; for example, broth microdilution tests, antimicrobial gradient diffusion methods, disc diffusion, as well as a variety of automated instrument systems (Reller et al, 2009). Some testing methods provide more quantitative results (e.g., minimum inhibitory concentration, or MIC), whereas others provide more qualitative results (e.g., disc diffusion). Detailed descriptions of the test methods are published by national and international organizations, such as the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), among others. Categorization of susceptibility of an organism to an antimicrobial drug (e.g., as resistant, intermediate, or susceptible) depends on breakpoints set by various international agencies, such as the CLSI and EUCAST. Both of these organizations publish breakpoint guidelines used in AST programs worldwide. Interpretive cutoffs set by the CLSI are determined by MIC distributions, pharmacokinetic-pharmacodynamic (PK-PD) properties, and mechanisms of resistance, while EUCAST bases its breakpoints on epidemiological MIC cut-offs (ECOFFS) and PK-PD properties. Currently, there is a lack of completely harmonized AST methodologies across all surveillance programs, and different clinical breakpoints and/or different epidemiological cut-off values are listed in various guidance documents. In order to compare data collected through different surveillance programs, it is important to know the methods used and interpretive criteria to classify the bacteria as susceptible, intermediate, or resistant. If the data are used to direct therapeutic choices of antimicrobials in a clinical setting, clinical breakpoints are used. ECOFF values are used to describe changes in MIC distributions over time. They are valuable in a surveillance system where incipient resistance may become evident first as deviations from "wild type" among susceptible bacterial populations. Since not all surveillance programs define resistance in the same way, it is best to compare the laboratory values using a single set of breakpoints rather than simply comparing resistance rates across national or international programs.

There are disadvantages to using the AST methods including the lack of harmonization that can hinder interlaboratory comparisons, the absence of valid methods for some organisms, shifting interpretive criteria (McDermott et al, 2016), and lack of established breakpoints for many animal species and tissues. In addition, for public health surveillance systems charged with evaluation of foodborne antimicrobial resistance risks, AST data alone may not be sufficient in some circumstances. Additional information gained from genetic testing, such as whole genome sequencing (WGS), may be needed for incorporation in risk assessments; for example, information on alleles and strain types among isolates from different environments in the farm-to-fork continuum. With the advent of more affordable WGS technology, the entire DNA sequence of a bacterium can be determined in just

a few days. WGS is therefore rapidly gaining popularity in public health surveillance programs because it can provide quick and comprehensive information on resistance determinants. A number of studies have shown that WGS can predict resistance phenotypes for some antimicrobials, such as in ***Salmonella*** (Zankari et al, 2013, McDermott et al 2016), ***Campylobacter*** (Zhao et al, 2016), and other foodborne bacteria (Tyson et al, 2015). WGS can also be used in detection and epidemiologic investigations of outbreaks including identification of outbreak sources and trace-back studies. As the use of WGS gains momentum, additional guidelines and standards for interpretation and reporting of these data will be needed. In addition, there is currently limited understanding as to how WGS can guide therapy in clinical situations. A potential limitation of WGS methods is that they only detect previously identified resistance mechanisms; therefore, some form of phenotypic AST will continue to be needed for clinical isolate testing and surveillance as well as for regulatory purposes.

In the U.S., Goal 2 of the National Action Plan for Combating Antibiotic-Resistant Bacteria is to 'strengthen national One Health surveillance efforts to combat resistance.' Specifically, it calls for enhancements and integration of data from surveillance systems that monitor human pathogens (e.g., the National Health Surveillance Network, the Emerging Infections Program, and NARMS) with data from surveillance systems that monitor animal pathogens (e.g., the USDA-APHIS NAHMS program and the National Animal Health Laboratory Network, and the FDA Veterinary Laboratory Investigation and Response Network). These activities will provide high-quality data, including detailed genomic data, and other information necessary to track resistant bacteria in diverse settings in a timely fashion. Given the complex interplay of humans, livestock, pets, wildlife, and the environment, the adoption of a One Health approach to addressing resistance has gained consensus worldwide.

Much of the focus on antimicrobial resistance in food animals concerns the potential hazards to human health, but antimicrobial resistance is also a problem for animal health and welfare. National or regional surveillance programs that monitor antimicrobial resistance in animal production systems are often limited to human enteric and sentinel indicator species of bacteria. In the next few sections, information is presented on the background of some of the antimicrobial resistance surveillance programs in the U.S.: the National Antimicrobial Resistance Monitoring System (NARMS), the USDA-APHIS National Animal Health Laboratory Network (NAHLN), and the FDA's Vet-LIRN. Background is provided for these programs because some of the data they collect will be described in subsequent species-specific chapters of this report.

3.5.2 National Antimicrobial Resistance Monitoring System

The National Antimicrobial Resistance Monitoring System (NARMS) was established in 1996 as the result of recommendations of an expert panel convened by the FDA in 1994 to establish a national system to monitor resistance among certain enteric bacteria transmitted in meat products. NARMS is a collaborative effort of three federal agencies: the Centers for Disease Control and Prevention (CDC), the USDA Food Safety and Inspection Service (FSIS), and FDA CVM, along with state and local health departments in all 50 states. **Table 3-4** shows the general organization of the NARMS program including sample types and bacteria tested.

Table 3-4: Summary of NARMS surveillance

	Humans	Food Animals	Retail Meats
Lead federal agency	CDC	USDA (FSIS)	FDA (CVM)
Geographic coverage	Nationwide[1]	Nationwide	24 States
Sample sources	Ill humans in all 50 States	From slaughter plants: Chickens, turkeys, cattle, and swine (carcass and cecal samples[2])	From grocery stores: chicken parts, ground turkey, ground beef, and pork chops
Year initial testing began	1996	1997	2002
Bacteria tested	Non-Typhi *Salmonella* *Campylobacter* *Escherichia coli* O157 *Salmonella* Typhi *Shigella* *Vibrio*	Nontyphoidal *Salmonella* *Campylobacter* *Escherichia coli* *Enterococcus*	Nontyphoidal *Salmonella* *Campylobacter*[3] *Escherichia coli*[4] *Enterococcus*[4]

[1] *Campylobacter* human surveillance is limited to 10 states.
[2] Cecal sampling was added in 2013.
[3] Testing is limited to chicken parts and ground turkey since 2008.
[4] Testing is conducted at four selected sites.

The human isolate component of NARMS started in 1996 testing non-Typhi *Salmonella* and *E. coli* O157 isolates. In 1997, testing of *Campylobacter* began followed by *Salmonella* serotype Typhi and *Shigella* in 1999 and *Vibrio* in 2009. The food animal component of NARMS started in 1997 with monitoring of nontyphoidal *Salmonella* isolated from chicken, turkey, cattle, and swine carcasses (conducted under the USDA's Pathogen Reduction/ Hazard Analysis and Critical Control Point, or PR/HACCP, program), and later expanded to include *Campylobacter* (1998), *E. coli* (2000), and *Enterococcus* (2003) from chickens. The food animal component was expanded in 2013 to include cecal samples collected from individual animals at the time of slaughter. The retail meat component of NARMS started in 2002, with testing of *Salmonella*, *Campylobacter*, *E. coli*, and *Enterococcus* isolates from chicken, ground turkey, pork, and ground beef sold in retail stores. Antimicrobial susceptibility testing for generic *E. coli* and *Enterococcus* isolates broadly indicates resistance to antimicrobials that are active against Gram-negative and Gram-positive bacteria.

NARMS reports minimum inhibitory concentrations (MICs) for a panel of antimicrobials tested for each isolate. The antimicrobials selected for testing are based on their importance in human and veterinary medicine and for their utility as epidemiological markers for the movement of resistant bacteria and genes between environments. For retail meat and food animal isolates, antimicrobial agents tested depend on the organism. For *Salmonella* and *E. coli* isolates, antimicrobial drug classes tested include aminoglycosides, β-lactam/ β-lactamase inhibitor combination agents, carbapenems, cephalosporins, folate pathway inhibitors, macrolides, penicillins, phenicols, quinolones, and tetracyclines. For *Campylobacter* isolates, antimicrobial classes tested include aminoglycosides, lincosamides, macrolides, phenicols, quinolones, and tetracyclines. For *Enterococcus*, antimicrobial classes tested include aminoglycosides, glycopeptides, glycylcyclines, lincosamides, lipopeptides, macrolides, nitrofurans, oxazolidinones, penicillins, phenicols, quinolones, streptogramins, and tetracyclines. The specific sampling, laboratory, and data management methodologies for food animal and retail meat components of the NARMS program are published in detail on the FSIS and FDA websites. Where available, the NARMS program uses human clinical breakpoints established by CLSI to interpret AST results for *E. coli*, *Salmonella* and *Enterococcus*. EUCAST-established epidemiological cutoff values are used to interpret AST results for

Campylobacter. Where no CLSI clinical breakpoints are established, NARMS-established epidemiological cutoffs are used. For example, azithromycin interpretive standards used for nontyphoidal ***Salmonella*** and ***E. coli*** isolates are reported by NARMS as 'decreased susceptibility to azithromycin' for isolates with a NARMS-established epidemiological cutoff value. For interpretations of ciprofloxacin MIC data for ***E. coli*** and ***Salmonella***, NARMS assigns isolates with MICs in the CLSI intermediate and resistant categories as having 'decreased susceptibility to ciprofloxacin.' The NARMS websites should be consulted for full details about interpretive criteria used to report antimicrobial susceptibility for each of the organisms tested.

According to the new NARMS Strategic Plan (2021-2025), NARMS' mission is to provide scientifically reliable data to help reduce the human, animal, and environmental health burden caused by antimicrobial-resistant bacteria. To accomplish this, NARMS conducts the following activities:

- Monitors trends in antimicrobial resistance among enteric bacteria from humans, retail meats, and animals at the time of slaughter;
- Disseminates timely information on antimicrobial resistance in pathogenic and commensal microorganisms to stakeholders in the U.S. and abroad to promote interventions that reduce resistance among foodborne bacteria;
- Conducts research to better understand the emergence, persistence, and spread of antimicrobial resistance;
- Provides timely antimicrobial resistance data for outbreak investigations; and
- Provides data that assist the FDA in making decisions related to the approval of safe and effective antimicrobials for animals.

The NARMS program utilizes an integrated One Health approach for surveillance of resistance in foodborne bacteria advancing food safety, animal health, and public health in several ways. NARMS provides data on the emergence of drug-resistant enteric bacteria; movement of bacterial populations among humans, food animals, and other sources; genetic mechanisms of resistance; and risk factors for and outcomes of resistant infections. Data collected through the NARMS program also provide information about the prevalence of pathogens in food categories under surveillance, the types of strains predominant in foods, and shifts in serotypes among ***Salmonella*** isolates from foods and food-producing animals over time. Isolates are subtyped by WGS and the data are uploaded to the National Center for Biotechnology Innovation (NCBI), which is part of the U.S. National Library of Medicine. NCBI maintains a public database of microbiological data including biomedical and genomic information. WGS data uploaded to NCBI are an important source that can be used in outbreak investigation and response as well as other research activities.

Since it began in 1996, NARMS has adapted and expanded the various elements of surveillance including geographical areas, new isolate sources, bacteria, sampling schemes, and antimicrobial agents tested. Karp, et al recently published a comprehensive review of two decades of NARMS surveillance (Karp et al, 2017). The NARMS program undergoes periodic reviews by external experts, the most recent of which was conducted in 2017 by a subcommittee of the FDA Science Board. The published report provides details about several recommendations made for NARMS regarding commodities sampled, sampling methodologies, and reporting of data. The 2021-2025 NARMS Strategic Plan addresses these recommendations and describes future work within a One Health paradigm including an environmental surveillance component.

In addition to surveillance, NARMS scientists conduct epidemiologic and microbiologic research aimed at characterizing resistant infections and bacteria and to better understand how resistance spreads. NARMS laboratories and databases hold specimens and data for more than 200,000 bacterial strains from humans, food animals, and retail meats (Karp et al, 2017). NARMS scientists and collaborators have used NARMS isolates for bacterial genetic studies that have improved understanding of the nature, behavior, and sources of antimicrobial resistance, as well as the genes, mobile DNA elements, and mutations responsible for resistance. Since 2014, NARMS has used WGS to characterize strains under surveillance and to identify antimicrobial resistance genes. WGS makes it possible to quickly distinguish genetic determinants of resistance, improving the ability to compare bacterial strains from different sources and consequently assist with outbreak investigations.

CVM uses NARMS data to assist with pre-approval risk assessments for antimicrobial drugs intended for use in food-producing animals where human food safety implications are considered (see Appendix 3). NARMS data are also utilized by FDA in post-approval monitoring to help ensure the continued safe use of approved drugs. Two examples were described in Appendix 3 of this report - the withdrawal of approval for fluoroquinolone use in poultry and the extralabel use prohibition of cephalosporins in food-producing animals. These actions were taken by FDA partially as a result of data collected through the NARMS program indicating emergence of resistance and potential threats to public health.

The NARMS program produces periodic integrated summary reports; the most recent (at the time of this report) was published in 2020, the *2018 NARMS Integrated Summary*. These reports summarize trends in the prevalence of resistance to antimicrobials important in human and veterinary medicine. NARMS data, including genomic data, are available to the public online and interactive graphs and other data visualization tools are also available on the NARMS Now website.

NARMS data presented in this report are focused on animals at slaughter (cecal) and retail meat sources. Highlights of the recent NARMS data for ***E. coli***, ***Salmonella***, ***Campylobacter***, and ***Enterococcus*** for each of the four major food-producing species are shown in the relevant species chapters of this report. Line charts for trends (2015-2019) in NARMS AST data for these four organisms are shown in Appendices 5 through 8. The NARMS website should be consulted for complete details about current trends (including preliminary data for 2020-2021) in antimicrobial resistance of the enteric pathogens tracked in the program for retail meat, animal sources, and humans.

3.5.3 USDA APHIS Veterinary Services National Animal Health Laboratory Network (NAHLN) Antimicrobial Resistance Pilot Project

The USDA APHIS Veterinary Services (VS) National Animal Health Laboratory Network (NAHLN) is a nationally coordinated network and partnership of federal, state, and university-associated animal health laboratories. The network of over 60 NAHLN laboratories provide animal health diagnostic testing, methods research and development, and expertise for education and extension to detect biological threats to U.S. animal agriculture, thereby protecting the nation's food supply as well as animal and human health. NAHLN laboratories provide the capability to diagnose both endemic and high-consequence livestock pathogens in animals, food, and environmental samples and are likely to be the first-line laboratories for recognition of an intentionally or

accidentally introduced agent in animals. The USDA's National Veterinary Services Laboratories (NVSL) serves as the national diagnostic reference and confirmatory laboratory.

As part of a USDA-funded collaboration with the American Association of Veterinary Laboratory Diagnosticians (AAVLD), CLSI, Vet-LIRN, and the USDA APHIS Center for Epidemiology and Animal Health, NAHLN began a pilot project in 2018 to develop a sampling stream to monitor antimicrobial resistance profiles in animal pathogens routinely isolated by veterinary clinics and diagnostic laboratories across the U.S. A joint working group made up of representatives from these organizations and government agencies developed recommendations for a standardized antimicrobial susceptibility testing and data collection plan to leverage data from veterinary diagnostic laboratories. A centralized data collection and reporting process across all of these laboratories would be useful to monitor trends in antimicrobial resistance phenotypes and genotypes to identify new or emerging resistance profiles, to help monitor the continued effectiveness of antimicrobials over time, and to provide information back to stakeholders about observed trends.

For the first year of the project, 19 laboratories contributed AST data from 3,213 veterinary bacterial isolates. For the second year of the project, 24 laboratories contributed AST data from 5,430 isolates. Both livestock and companion animal species were included. Bacterial isolates surveyed in the first year were ***E. coli*** from all species, ***Salmonella enterica*** from all species, ***Mannheimia haemolytica*** (cattle only), and ***Staphylococcus intermedius*** (dogs and cats only). In 2019, ***Salmonella enterica*** isolates were for cattle only (due to insufficient numbers of isolates from all species in 2018) and additional isolates surveyed were ***Streptococcus suis*** (swine only), ***Pasteurella multocida*** (poultry), and ***Streptococcus equi*** and ***S. equi*** ssp. ***zooepidemicus*** (horses only). The initial animal pathogens were identified for monitoring in 2018 based on a joint APHIS-AAVLD working group recommendation which used several criteria, including the impact of the disease on each animal commodity or industry, its impact on public health, and whether antimicrobials used to treat the disease were also on the WHO and OIE lists of antimicrobials of critical importance to human and veterinary medicine, respectively. Isolates for the surveyed organisms were selected by participating laboratories for inclusion in the pilot project based on the criteria that the isolates were identified at the genus and species level (and serotype level for ***Salmonella***), associated with clinical disease or diagnostic findings, and from unique animal sources (no more than one isolate from the same herd, flock, farm, or household). Selection of bacterial species to monitor for 2019 was adjusted based on the 2018 results. One of the challenges highlighted by this pilot project was the fact that veterinary clinical breakpoints have not been established for many of the antimicrobial/bacterial combinations in most animal species or tissues within species.

Details regarding methodologies as well as full results can be found in the published NAHLN reports for Year 1 (2018) and Year 2 (2019). In subsequent chapters of this report, we briefly present results for ***E. coli***, ***Salmonella enterica***, ***Mannheimia haemolytica***, ***Streptococcus suis***, and ***Pasteurella multocida*** for relevant species.

3.5.4 Veterinary Laboratory Investigation and Response Network (Vet-LIRN) Antimicrobial Resistance Pilot Project

The Veterinary Laboratory Investigation and Response Network (Vet-LIRN) is managed and organized by FDA CVM. Vet-LIRN's mission is to promote human and animal health by collaborating with veterinary diagnostic laboratories in order to provide scientific information, build laboratory capacity for routine and emergency response, and to train scientists. The program coordinates facilities, equipment, and professional expertise of government and veterinary diagnostic laboratories across the U.S. and Canada to respond to high priority chemical and microbial feed and drug contamination events. The network provides the means for rapid response to reports of animal injury and establishes protocols to facilitate veterinary diagnostic reporting to FDA. Vet-LIRN works with the veterinary diagnostic laboratories to document, investigate, and diagnose animal feed or drug related illnesses. These efforts can contribute to overall food safety as animal feed events could signal potential issues in the human food system. Vet-LIRN also works with referring veterinarians and pet owners to investigate cases of potential foodborne illness in pets. Currently there are 45 Vet-LIRN network laboratories across the U.S. and Canada (Guelph).

In 2015, the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) specifically charged the Vet-LIRN program with developing, expanding, and maintaining capacity in veterinary and food safety laboratories to conduct standardized AST and characterize priority animal pathogens through WGS. Other partners in this effort include the USDA's NAHLN and NARMS. Representatives from Vet-LIRN and these programs, as well as the AAVLD, formed a working group (the AAVLD Antimicrobial Resistance Working Group) to address the tasks outlined by the CARB initiative. The working group conducted a survey of veterinary diagnostic laboratories in the U.S. to identify which bacteria are most frequently obtained in veterinary clinical laboratories and to develop a list of priority pathogens for surveillance (Dargatz et al, 2017). The laboratories responding to the survey listed ***E. coli*** as the most common pathogen on which AST was performed followed by ***Pseudomonas aeruginosa***, ***Staphylococcus*** spp., ***Salmonella*** spp., and ***Pasteurella multocida***. Using this and other information from the survey and based upon the recommendations of the AAVLD working group, CVM developed a pilot program to assess the feasibility of using veterinary diagnostic laboratories in the Vet-LIRN network to monitor the antimicrobial susceptibility of select veterinary pathogens.

The four key objectives of this pilot project were to:

- develop the laboratory infrastructure for a collaborative project with multiple participating veterinary diagnostic laboratories;
- confirm laboratory proficiency for AST and WGS;
- develop technology for sharing data across the network; and
- make the information publicly available.

The working group subsequently recommended ***E. coli***, ***Salmonella enterica***, and ***Staphylococcus pseudintermedius*** for resistance monitoring for the pilot project based on frequency of culture, importance of the pathogen in veterinary practice, and availability of standardized AST methods for these pathogens. Vet-LIRN collected ***Staphylococcus pseudintermedius*** and ***E. coli*** isolates from dogs, and ***Salmonella enterica*** isolates

from all species. Ceric and colleagues recently published the results of the first year of data collection (2017) (Ceric et al, 2019). They reported on the prevalence of antimicrobial resistance genes in the study population and performed WGS on a subset of isolates to identify genetic determinants associated with antimicrobial resistance and the potential genetic relatedness of human and animal strains.

In 2017, a total of 1,968 isolates were collected (691 ***E. coli***, 691 ***S. pseudintermedius***, and 586 ***Salmonella enterica***), and 200 of these were sequenced. Eight isolates were excluded from the initial 200 sequenced isolates, leaving a total of 192 isolates being sequenced for the project. Isolates were collected from 20 Vet-LIRN veterinary diagnostic laboratories ("source laboratories"), each of which were partnered with one of four laboratories which could perform WGS. Source laboratories collected the first four isolates each month from each of the three selected pathogens. U.S. laboratories serotyped all ***Salmonella*** isolates either in-house or by referral to the USDA NVSL; Canadian isolates were serotyped by the Public Health Agency of Canada National Microbiology Laboratory. Details regarding sampling and testing methods can be found in the published report (Ceric et al, 2019).

Results for 2017 indicated that 67% of ***Salmonella*** isolates had no known resistance genes. Several isolates from both companion animals and food-producing animals did show genetic relatedness to isolates from humans. For pathogenic ***E. coli***, no resistance genes were identified in 60% of the isolates. Where resistance was detected, diverse resistance patterns were observed, and one isolate had predicted resistance to fluoroquinolones and cephalosporins. For ***Staphylococcus pseudintermedius,*** a bimodal distribution of resistance genes was observed with 32% of isolates having a wide range of resistance mechanisms, including the ***mecA*** gene. The study emphasized the importance of performing antimicrobial resistance surveillance of bacteria from veterinary diagnostic laboratories as a part of any national surveillance program. Inclusion of companion animals helps address a key gap in national antimicrobial resistance surveillance as part of a One Health model. Vet-LIRN continues to support network laboratory participation in antimicrobial resistance monitoring of animal pathogens as part of fulfilling its mission to advance human and animal health. Animal pathogen data collected through the Vet-LIRN pilot project are now included with the NARMS Integrated Summary and 2017-2018 data are available on the website (data published for 2018 are for dogs only).

During 2018, the pilot was continued with the same bacterial strains, collecting over 2,900 isolates and sequencing over 900 isolates. In 2019, the Vet-LIRN Antimicrobial Monitoring Project grew with the addition of five source and one WGS laboratories in the U.S. and a WGS laboratory in Canada, which is receiving isolates from laboratories from four additional Provinces. The program thus consists of 30 source laboratories and six WGS laboratories. Additional bacteria were added to the scope of the project to include ***Klebsiella pneumoniae***, ***Pseudomonas aeruginosa***, ***Enterococcus faecalis*** or ***faecium,*** and ***Streptococcus group*** (***canis, equis, suis, zooepidemicus***) from any animal host in addition to the original bacteria (***S. pseudintermedius*** and ***E. coli*** from dogs and ***Salmonella*** from any host). Vet-LIRN also started a pilot project with six laboratories collecting and testing fish pathogens. Results regarding ***Salmonella*** isolates collected in 2017 as part of this Vet-LIRN pilot project from food-producing species will be included later in this report in each species chapter. Companion animal results and more information about the relatedness of human and animal strains can be found in the published report (Ceric et al, 2019) and 2018 data for dogs are the most recent available data on the NARMS website.

PREFACE TO CHAPTERS 4 - 7

In Chapters 4 through 7, species-specific information is presented for each of the four major food-producing species. In each species chapter, the following information is included:

- Brief background information about animal production and animal health;
- Species-specific antimicrobial sales estimates and biomass-adjusted sales estimates;
- Antimicrobial use;
- Antimicrobial resistance with a focus on foodborne pathogens monitored by NARMS and animal pathogens; and
- Examples of antimicrobial stewardship activities in the sector.

Brief summaries describing animal production and some important bacterial diseases are included with the intent of providing context for animal populations that may be exposed to antimicrobials and some examples of the diseases for which they may receive therapy with antimicrobials. It is acknowledged that there are differences within species groups between the various production segments (e.g., breeding stock, young/nursery animals, laying hens vs. broiler chickens, etc.), but detailed information about these segments is not always available. Therefore, the chapters focus mostly on animals that are in production.

Some general comments about animal health and judicious antimicrobial use applicable to all species groups follow.

Animal Health and Disease – General Comments

Many animal diseases have a multifactorial etiology. In addition to pathogenic (disease-causing) organisms such as bacteria, viruses, and parasites, animal-related conditions such as age and immune status, as well as environmental factors (e.g., temperature, transportation/movement) and certain feeding/management practices may contribute to the occurrence of disease. Disease may result in decreases in productivity, animal suffering, and sometimes death. Some infectious diseases may exist at subclinical levels, meaning signs are not readily observable. If infection is not detected and treated early in the course of disease, more severe or chronic infections may arise (Casewell et al, 2003; Hao et al, 2014). Some diseases spread rapidly within a herd or flock, so preventing and controlling spread of infections is critical to ensure animal health and productivity, and to avoid large losses (Robertson, 2020). This may occasionally involve the judicious administration of antimicrobials to animals which are not yet exhibiting clinical signs, but which are at imminent risk of developing infection due to

exposure to ill animals or other pathogen sources, or environmental factors (Nickell and White, 2010). Vaccination and disease prevention and control programs may vary depending on the type of operation and disease incidence specific to geographic areas. Veterinarians work with producers to design and implement herd and flock health programs appropriate to the location and situation.

While livestock operations may have developed health programs specific to their operations or geographic area, there is a general lack of animal health monitoring at the national level aimed at capturing information about relatively common diseases on an ongoing basis. Current animal health surveillance systems, such as the USDA APHIS National Animal Health Surveillance System (NAHSS) are focused only on certain reportable and notifiable diseases, as well as certain zoonotic and emerging diseases. The National Animal Health Reporting System (NAHRS) is the reporting system for OIE-reportable diseases in the U.S. The USDA APHIS NAHMS program (see Chapter 3) conducts periodic surveys of animal health and production representative of the U.S. on a periodic basis (usually every 5 to 10 years). Ideally, ongoing surveillance systems could be developed to obtain more regular and frequent data on general animal health and disease conditions so that information could be used by producers, veterinarians, and animal health officials to detect areas of concern and implement disease prevention and management programs.

Judicious Antimicrobial Use – General Comments

Antimicrobials are an important management tool for therapy (treatment, control, and prevention) of bacterial infections in animals. Producers, veterinarians, educators, and government agencies share the responsibility for promoting judicious use of antimicrobials in food-producing animals, in particular those that are used for both animal and human infections. One component of judicious use is to administer them only when needed for treatment, control, or prevention of specific diseases. Disease prevention practices focused on improved farm management, proper nutrition and weaning programs, adequate biosecurity, and vaccination programs may help reduce the overall incidence of disease, thus reducing the need for antimicrobials. Veterinarians are the best source of animal health information when considering the appropriate disease prevention programs for any particular production situation. Veterinarians also possess the necessary knowledge and expertise to provide oversight for judicious use of antimicrobials in animals. Animal industry and academic groups have played a pivotal role in encouraging and promoting the judicious use of antimicrobials in animal agriculture. FDA is supportive of efforts that encourage the judicious use of antimicrobials, including such uses that are necessary for maintaining the health and welfare of animals.

CHAPTER 4

Antimicrobial Use and Resistance in U.S. Cattle Production

4.1 Introduction

4.2 Cattle Production in the U.S.

4.3 Cattle Health: Examples of Bacterial Diseases

4.4 Antimicrobial Sales and Biomass-Adjusted Antimicrobial Sales Estimates for Cattle

4.5 Antimicrobial Use in Feedlot and Dairy Cattle

4.6 Antimicrobial Resistance in Cattle and Retail Ground Beef

4.7 Antimicrobial Stewardship in Cattle Production

4.1 Introduction

In the U.S., cattle may be raised as livestock for meat (e.g., beef, veal), for milk and dairy products, and for hides used to make leather. Domesticated for several thousand years, cattle are ruminants, meaning their digestive system is highly specialized to utilize poorly digestible plants as food. Due to this ability, cattle primarily consume various types of forage and convert that energy into high-protein edible products for human consumption. Cattle production is one of the most important agricultural enterprises in the U.S. The U.S. has an established beef industry that is largely separate from its dairy sector. Worldwide, beef production is the third largest meat industry, behind poultry and swine (FAO, 2021a), and the U.S. is the largest producer and consumer of beef in the world (USDA-ERS, 2021a). The beef cattle industry is roughly divided into two main production segments: cow-calf operations and cattle feeding operations. Cow-calf operations mostly focus on maintaining a herd of beef cows for the purpose of raising calves. These operations are located throughout the U.S. and the animals raised mostly on pasture. Animals on cattle feeding operations are generally those that have entered a feedlot and are fed a ration of grain, silage, and hay until they reach market weight. Cattle feeding operations in the U.S. are concentrated in the Great Plains, but are also located throughout the "Corn Belt", Southwest, and Pacific Northwest. The industry has been shifting towards a smaller number of large specialized feedlots focused on raising cattle for particular markets, such as conventional or organic.

In the last three decades, world milk production has increased by nearly 60% and according to data from the Food and Agriculture Organization, the U.S. is the second largest milk producer after India (FAO, 2021b). Milk is produced in all 50 states with the majority of production in the western and northern areas of the country. Dairy farms, many of which are family-owned and managed, are usually members of producer cooperatives. Major trends in U.S. milk production include a fairly steady increase in milk production and a consistent decline in the overall number of operations, but with increased numbers of cows per operation (USDA-ERS, 2021b). Veal calves are usually male calves produced in the dairy industry. Veal consumption has drastically decreased in the U.S. over the last several years to less than 0.25 pounds per capita in 2019 (USDA-ERS, 2021c). Currently, there is a general lack of publicly available information about antimicrobial use and resistance in veal so this sector will not be covered in this report. A recent article did report on the prevalence of bacterial contamination and antimicrobial resistance in various retail veal meats collected during a 2018 NARMS survey in nine states (Tate et al, 2021). Future reports may include information on veal antimicrobial use and resistance as more becomes available.

4.2 Cattle Production in the U.S.

Detailed information about cattle populations, production practices, and economic indicators are routinely or periodically published by USDA agencies including the USDA Economic Research Service (ERS), the USDA National Agricultural Statistics Service (NASS), and the USDA Animal and Plant Health Inspection Service (APHIS), which conducts studies through the National Animal Health Monitoring System (NAHMS). In this section, we briefly summarize recent published information about U.S. production in the beef and dairy sectors to provide some context for populations and antimicrobial use practices discussed later in the chapter.

4.2.1 Beef Cattle Production

The U.S. is the world's leading producer of beef followed by Brazil (USDA-FAS, 2021). As of January 1, 2020, the inventory of all cattle and calves in the U.S. totaled 94.4 million head, below the 94.8 million head inventory on January 1, 2019 (USDA-NASS, 2020a). Cattle and calves on feed for the slaughter market for all feedlots totaled about 14.3 million head as of December 1, 2019. Most cattle on feed were in feedlots with capacity of 1,000 or more head. In 2019, the three states with the largest inventory of cattle on feed were Texas, Nebraska, and Kansas (USDA-NASS, 2020b). Beef cows, at about 31.3 million head as of January 1, 2020, were down about 1% from the previous year (USDA-NASS, 2020b). Beef production in the U.S. totaled 27.2 billion pounds in 2019, up 1% from the previous year (USDA-NASS, 2020c). According to the most recent food availability data published by USDA-ERS, the availability (a proxy measure for consumption) of beef to consumers in the U.S. was just over 55 pounds per capita in 2019 (USDA-ERS, 2021c).

Beef cattle production principally consists of three stages or types of operations, which may specialize in one or more of these stages. The first stage is cow-calf operations, where calves are born and raised until weaning (usually around 6 to 9 months of age), when they weigh between 450-700 pounds. After weaning, in the second stage calves may go to a stocker or backgrounder operation. At these operations calves get over the stress of weaning, gain weight, and are managed to promote health and immunity prior to arriving at the feedlot. Calves may also go directly from the cow-calf operation to a feedlot (often with an intermediate stop at a sale barn). The third stage is the finishing or feedlot period, where steers and heifers are fed a combination of forage and grain to reach a slaughter weight of 1,000 to 1,500 pounds. After being fed to market weight, cattle are sent to beef packers which harvest and process cattle, and the finished meat products are then sent to retailers and distributors (USDA-ERS, 2015). An additional component of beef production is that related to breeding stock, which involves the production of genetically superior females and herd bulls that commercial cow-calf producers will ultimately use to improve their stock.

The beef industry as a whole is less integrated than the pork and poultry industries owing primarily to the large number of small-scale beef producers and the longer production cycle for beef cattle (USDA-ERS, 2015). Ownership of cattle often changes over the animals' lifecycles as they move through each stage of production. Cattle may be transported long distances to feedlots, with potential commingling with other cattle before reaching the feedlot. Feedlots are often quite large; for example, cattle and calves on feedlots with a capacity of 1,000 or more head represented 81.5% of all cattle and calves on feed in 2019 (USDA-NASS, 2020d).

4.2.2 Dairy Cattle Production

In 2019, milk production in the U.S. was 218 billion pounds, a 0.4% increase from 2018. The rate of milk production per cow, at 23,391 pounds, was 241 pounds greater than individual production in 2018. The annual average number of milk cows on farms in 2019 was 9.3 million head, down 62,000 head from 2018 (USDA-NASS, 2020e). According to the most recent food availability data published by USDA ERS, the availability (a proxy measure for consumption) of fluid milk to consumers in the U.S. was about 142 pounds per capita in 2019 (USDA-ERS, 2021c).

In dairy production systems, birthing of calves and milk production are interrelated, so lifecycle stages not usually combined in beef production systems are combined. Some farms may keep dairy bulls onsite for breeding purposes, but most rely on artificial insemination of cows. Milk cows typically give birth to calves on the dairy farm once each year and then provide milk for about 300 days before being "dried off" in preparation for the next calving. The dry period is an important resting period for the dairy cow when udder tissue is allowed to repair and rejuvenate before the next lactation. Male calves are usually sold and raised for veal or beef, while female calves are usually raised to be replacement heifers in the milking herd or sold to other dairies as replacement heifers. Heifers (milk cows that have not yet calved) are often raised on the dairy farm, or some may be raised on another farm until they are ready to enter the milking herd at around 24 months of age (USDA-ERS, 2015). Most U.S. dairy cows are Holsteins, a breed that tends to produce more milk per cow than other breeds.

Similar to other livestock industries, dairy production has shifted toward larger operations. Major trends in U.S. milk production include a fairly steady increase in milk production, a steady decline in the number of dairy operations, and an increase in the number of cows per operation (USDA-ERS, 2021b). A large number of small farms with dairy cows exist, but these account for a small percentage of overall U.S. milk production. The top 5 milk production States in 2019 were California, Wisconsin, Idaho, New York, and Texas. These States collectively produced more than 50% of the U.S. milk supply (USDA-NASS, 2020e). Most dairies do not operate under production contracts, but many dairy farmers belong to producer-owned national cooperatives. The cooperatives collect milk from members and transport it to processors and manufacturers, or some cooperatives operate their own processing and manufacturing plants.

4.3 Cattle Health: Examples of Bacterial Diseases

Bacterial diseases in cattle may affect any body system, but often affect the respiratory, enteric (intestinal), and reproductive systems. An extensive review of these is beyond the scope of this report; however, **Table 4-1** shows some examples of bacterial pathogens of cattle and associated disease processes – it is not intended to be an exhaustive list of all potential bacterial diseases of cattle. Veterinary and cattle health references can be consulted for detailed information about bacterial diseases of cattle including disease epidemiology, risk factors, diagnosis, prevention, and therapeutic management. Also shown in Table 4-1 are examples of antimicrobials which are currently approved for use in cattle for therapy of these infections. Some of the drugs are approved only for certain production classes (e.g., dairy cattle, feedlot cattle, calves, etc.). Table 4-1 is not intended to be an exhaustive list of all bacterial pathogens of cattle and all approved antimicrobials for cattle, but rather to provide examples. AnimalDrugs@FDA can be searched to find specific drug products with approved label information. Not all approved drugs are currently marketed in the U.S. Animal drug sponsors (i.e., pharmaceutical companies) decide what products they will manufacture and market at any given time. As discussed in Appendix 3, veterinarians may legally prescribe extralabel uses of approved animal drugs under specific conditions. Table 4-1 is not intended to capture legal extralabel use of approved antimicrobials.

Table 4-1: Examples of bacterial pathogens of cattle and examples of FDA-approved antimicrobials for therapy of these infections

Bacterial Pathogen(s)	Disease Process(es)	Examples of FDA-Approved Therapeutic Antimicrobials[1,2]
Actinobacillus lignieresii	Wooden Tongue	Oxytetracycline
Anaplasma marginale	Anaplasmosis	Chlortetracycline; Oxytetracycline
Bacillus anthracis	Anthrax	Oxytetracycline
Bacteroides melaninogenicus	Infectious pododermatitis/ Foot Rot	Ceftiofur; Florfenicol
Clostridium chauvoei	Blackleg	Penicillin
Escherichia coli	Enteritis/Septicemia; Mastitis	Ampicillin; Ceftiofur (mastitis); Chlortetracycline; Neomycin; Oxytetracycline; Streptomycin; Sulfabromomethazine; Sulfachloropyridazine; Sulfaethoxypyridazine; Sulfamethazine; Tetracycline
Eimeria spp.[3]	Coccidiosis	Lasalocid[4]; Monensin[4]; Sulfamethazine; Sulfaquinoxaline
Fusobacterium necrophorum	Infectious Pododermatitis/ Foot Rot; Calf Diphtheria; Liver Abscesses	Amoxicillin; Ceftiofur; Florfenicol; Oxytetracycline; Sulfabromomethazine; Sulfadimethoxine; Sulfaethoxypyridazine; Sulfamethazine; Tulathromycin; Tylosin
Histophilus somni	Respiratory Disease/Pneumonia	Amoxicillin; Ceftiofur; Enrofloxacin; Florfenicol; Gamithromycin; Tildipirosin; Tilmicosin; Tulathromycin
Klebsiella spp.	Respiratory Disease/Pneumonia	Ampicillin; Chlortetracycline; Oxytetracycline; Tetracycline
Leptospira pomona	Reproductive Disease/Abortions	Dihydrostreptomycin; Oxytetracycline
Mannheimia haemolytica	Respiratory Disease/Pneumonia	Amoxicillin; Ceftiofur; Danofloxacin; Enrofloxacin; Florfenicol; Gamithromycin; Oxytetracycline; Tildipirosin; Tilmicosin; Tulathromycin
Moraxella bovis	Infectious Keratoconjunctivitis/ Pinkeye	Gentamicin; Polymyxins; Oxytetracycline; Tulathromycin
Mycoplasma bovis	Respiratory Disease/Pneumonia	Enrofloxacin; Florfenicol; Gamithromycin; Tulathromycin
Pasteurella multocida	Respiratory Disease/Pneumonia	Amoxicillin; Ampicillin; Ceftiofur; Chlortetracycline; Danofloxacin; Enrofloxacin; Erythromycin; Florfenicol; Gamithromycin; Oxytetracycline; Penicillin; Sulfabromomethazine; Sulfaethoxypyridazine; Sulfadimethoxine; Sulfamethazine; Tetracycline; Tildipirosin; Tilmicosin; Tulathromycin; Tylosin
Salmonella spp.	Enteritis	Ampicillin; Chlortetracycline; Oxytetracycline; Streptomycin; Tetracycline
Staphylococcus aureus	Mastitis; Other	Amoxicillin; Ceftiofur; Cephapirin; Cloxacillin; Dihydrostreptomycin + Penicillin; Erythromycin; Novobiocin[4]; Penicillin; Pirlimycin
Streptococcus agalactiae	Mastitis	Amoxicillin; Cephapirin; Cloxacillin; Erythromycin; Novobiocin[4]; Penicillin; Pirlimycin
Streptococcus dysgalactiae	Mastitis	Ceftiofur; Erythromycin; Novobiocin[4]; Penicillin; Pirlimycin
Streptococcus uberis	Mastitis	Ceftiofur; Erythromycin; Novobiocin[4]; Penicillin; Pirlimycin
Streptococcus spp.	Respiratory Disease; Metritis; Other	Oxytetracycline; Penicillin; Sulfabromomethazine; Sulfamethazine
Trueperella (formerly Actinomyces and Arcanobacterium) pyogenes	Upper Respiratory/Pharyngitis; Metritis; Liver Abscesses	Penicillin; Tylosin

1 See AnimalDrugs@FDA for information about approved antimicrobials including specific indications, dose, duration, approved production classes, limitations, and approved combination products.
2 Not all antimicrobials are currently marketed.
3 *Eimeria* spp. are protozoal organisms, not bacteria, but are a common infection in cattle for which certain antimicrobials are used for therapy.
4 Not currently considered a medically important antimicrobial according to Appendix A of GFI #152.

4.4 Antimicrobial Sales and Biomass-Adjusted Antimicrobial Sales Estimates for Cattle

4.4.1 Introduction

In this section, information is presented about antimicrobial sales and distribution estimates for cattle. These data are not necessarily indicative of how the antimicrobials were actually administered to or used in cattle (e.g., for what indications, doses, or durations). Antimicrobial use information (i.e., record of on-farm administration) is helpful to determine what disease pressures exist and could help inform stewardship practices, as discussed later in this chapter. The overall amount of antimicrobials sold and used in cattle is expected to change from year to year and will depend on several factors, including cattle populations and disease pressures faced each year.

In order to further characterize the species-specific antimicrobial sales and distribution estimates, a biomass denominator adjustment is also included in this section. This allows for a representation of trends in annual antimicrobial sales and distribution relative to the estimated cattle population in the U.S. in which the antimicrobials could be used.

4.4.2 Medically Important Antimicrobial Sales and Distribution Estimates for Cattle

Table 4-2 shows the annual species-specific sales and distribution estimates, by medically important antimicrobial class, reported by antimicrobial drug sponsors for cattle for 2016 through 2019, as well as the percent change in these estimates between time periods. Only the following antimicrobial classes can be shown for all four years because they had at least three drug sponsors and had species-specific estimates for cattle: aminoglycosides, cephalosporins, macrolides, penicillins, sulfonamides, and tetracyclines. Fluoroquinolones are shown for 2019 only, because prior to that time, fluoroquinolone sales were not independently reportable for cattle. Other medically important drug classes that may have had drug sales for cattle include amphenicols, diaminopyrimidines, lincosamides, polymyxins, and streptogramins. However, these are not independently reported classes for cattle (due to lack of three or more drug sponsors), so data cannot be shown in order to protect confidential business information of drug sponsors.

The majority of medically important antimicrobial sales estimated by drug sponsors for cattle each year for 2016 through 2019 were for tetracyclines. **Figure 4-1** contains the same sales information as Table 4-2, but visually demonstrates the magnitude of the tetracycline class compared to the other medically important antimicrobial classes. As noted in Appendix 3, GFI #213 was completely implemented as of January 1, 2017. Between 2016 and 2017, total medically important antimicrobial sales estimated for cattle decreased by about 35%. With the exception of macrolides, there were overall decreases in all classes for which data can be shown between 2016 and 2017. Between 2017 and 2018, there were small increases in most medically important antimicrobial classes (except penicillins and sulfonamides, which showed decreases), with a small increase (about 8%) in the overall total. Between 2018 and 2019, cephalosporins, penicillins, and the sum of not independently reportable classes decreased, while other classes increased a small amount. The percent change in sales comparing 2016 and 2019 still indicates an overall decrease of about 30% in total estimated sales for cattle. Since the requirement for drug sponsors is only to provide estimated species-specific antimicrobial drug sales and distribution for the four major

food-producing species, it is not possible to further break down the sales and distribution estimates into the various cattle production classes (e.g., beef cattle, dairy cattle, calves, etc.).

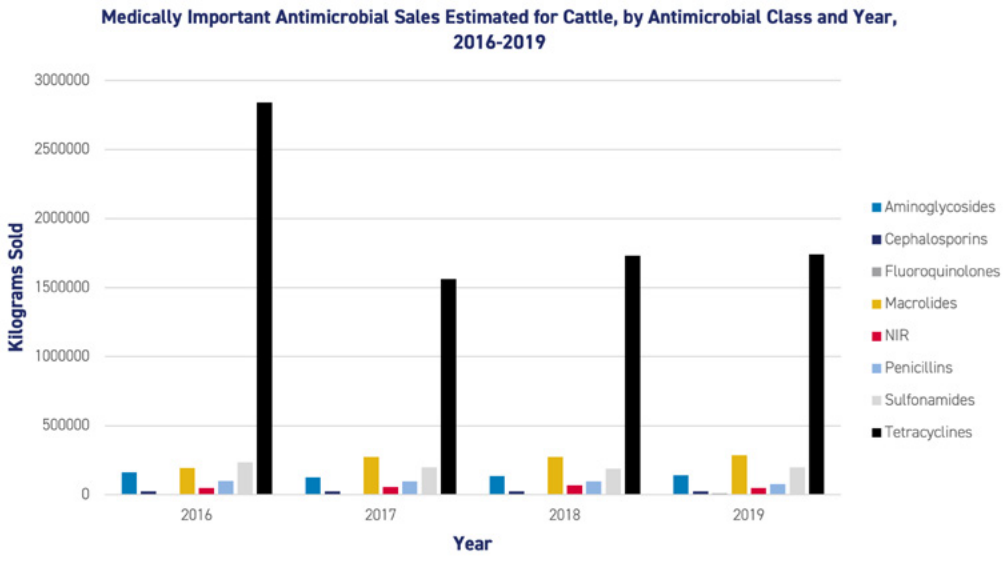
Table 4-2: Medically important antimicrobial sales and distribution estimates for cattle by reportable drug class, 2016-2019

Medically Important Antimicrobial Drug Class	2016 Estimated Annual Sales Totals for Cattle (kg)	2017 Estimated Annual Sales Totals for Cattle (kg)	2018 Estimated Annual Sales Totals for Cattle (kg)	2019 Estimated Annual Sales Totals for Cattle (kg)	Overall Percent Change in Sales from 2016 to 2017	Overall Percent Change in Sales from 2017 to 2018	Overall Percent Change in Sales from 2018 to 2019	Overall Percent Change in Sales from 2016 to 2019
Aminoglycosides	161,646	124,675	133,842	139,445	-22.9%	7.4%	4.2%	-13.7%
Cephalosporins	24,677	23,512	25,337	24,158	-4.7%	7.8%	-4.7%	-2.1%
Fluoroquinolones	*	*	*	12,560	---	---	---	---
Macrolides	194,811	274,479	274,837	286,438	40.9%	0.1%	4.2%	47.0%
Penicillins	99,935	96,936	96,591	78,887	-3.0%	-0.4%	-18.3%	-21.1%
Sulfonamides	234,955	196,902	187,603	197,486	-16.2%	-4.7%	5.3%	-15.9%
Tetracyclines	2,840,519	1,560,542	1,732,416	1,741,883	-45.1%	11.0%	0.55%	-38.7%
NIR[1]	49,000	56,793	66,760	48,424	15.9%	17.5%	-27.5%	-1.2%
Total	3,605,543	2,333,839	2,517,386	2,529,281	-35.3%	7.9%	0.47%	-29.9%

1 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For cattle, drug classes which cannot be shown in order to protect confidential business information are Amphenicols, Diaminopyrimidines, Fluoroquinolones (except for 2019), Lincosamides, Polymyxins, and Streptogramins. The value of sales for the NIR category was therefore calculated as the overall annual sales total for cattle minus the sum of all reportable classes for that year. The individual drug classes within the NIR category may or may not have had actual sales in any given year. Fluoroquinolone sales may be included in the NIR category for 2016-2018.

*Fluoroquinolones were only reportable as a class beginning in 2019; therefore, percent change calculations cannot be shown.

Figure 4-1: Medically important antimicrobial sales and distribution estimates for cattle, by antimicrobial class and year, 2016-2019



*NIR: Antimicrobial classes for cattle which are not individually reportable in order to protect confidential business information – may or may not include amphenicols, diaminopyrimidines, fluoroquinolones (2016-2018 only), lincosamides, polymyxins, and streptogramins.

4.4.3 Biomass-Adjusted Medically Important Antimicrobial Sales and Distribution Estimates for Cattle

Appendix 4 shows the estimated annual population and weight in kilograms (kg) for each category of cattle for 2016 through 2019. Using these data, the biomass total calculated for cattle (including all categories) was approximately 40.5 billion kg in 2016, approximately 41.6 billion kg in 2017, and approximately 42.2 billion kg in 2018 and 2019, representing about a 4.1% increase in estimated U.S. cattle biomass between 2016 and 2019.

Using the estimated annual total sales for medically important antimicrobials by drug class (in mg) for cattle and estimated annual cattle biomass (target animal biomass [TAB], in kg), **Table 4-3** shows the biomass-adjusted medically important antimicrobial sales and distribution data for cattle, by drug class and year. Table 4-3 also indicates the percent change for each reportable drug class between time periods. While the majority of antimicrobial classes which can be reported showed a decreased mg/TAB value comparing 2016 to 2019, the macrolides indicated an increase of about 41%.

Table 4-3: Biomass-adjusted medically important antimicrobial sales and distribution estimates for cattle, by reportable drug class, 2016-2019

Medically Important Antimicrobial Drug Class	2016 Estimated mg/TAB for Cattle	2017 Estimated mg/TAB for Cattle	2018 Estimated mg/TAB for Cattle	2019 Estimated mg/TAB for Cattle	Percent Change[1] in mg/TAB 2016 - 2017	Percent Change[1] in mg/TAB 2017-2018	Percent Change[1] in mg/TAB 2018-2019	Percent Change[1] in mg/TAB 2016-2019
Aminoglycosides	3.99	3.00	3.17	3.30	-24.8%	5.8%	4.2%	-17.1%
Cephalosporins	0.61	0.57	0.60	0.57	-7.2%	6.2%	-4.7%	-6.0%
Fluoroquinolones	*	*	*	0.30	---	---	---	---
Macrolides	4.81	6.60	6.51	6.79	37.3%	-1.3%	4.2%	41.3%
Penicillins	2.46	2.33	2.29	1.87	-5.5%	-1.8%	-18.3%	-24.2%
Sulfonamides	5.80	4.73	4.45	4.68	-18.3%	-6.1%	5.3%	-19.3%
Tetracyclines	70.06	37.51	41.05	41.27	-46.5%	9.4%	0.6%	-41.1%
NIR[2]	1.21	1.37	1.58	1.15	12.9%	15.9%	-27.5%	-5.1%
Total[1]	88.93	56.09	59.65	59.93	-36.9%	6.3%	0.5%	-32.6%

1 Calculations of the totals and the percent change were performed using the raw (unrounded) data for estimated mg/TAB. Calculations using the rounded numbers in this table will not yield exactly the same result.

2 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For cattle, drug classes which cannot be shown in order to protect confidential business information may be Amphenicols, Diaminopyrimidines, Fluoroquinolones (except 2019), Lincosamides, Polymyxins, and Streptogramins. The value of sales for the NIR category was therefore calculated as the overall annual sales total for cattle minus the sum of all reportable classes. The individual drug classes within the NIR category may or may not have had actual sales in any given year. The cattle biomass denominator is applied to the NIR category as a whole; therefore does not account for potential exclusions of cattle categories for the denominator that may otherwise apply to individual NIR classes.

*Fluoroquinolones were only reportable as a class beginning in 2019; therefore, percent change calculations cannot be shown.

Table 4-4 shows the comparison of percent change in species-specific estimated sales volume (kg) and the percent change in biomass-adjusted species-specific estimated sales (mg/TAB) between 2016 and 2019 for cattle. With the approximately 4.1% increase in estimated cattle biomass between 2016 and 2019, the biomass denominator adjustment resulted in a variable degree of difference in the percent change in mg/TAB relative to the percent change in species-specific estimated sales volume (kg) for antimicrobial drug classes which can be reported. Application of the cattle biomass denominator to total sales of medically important antimicrobials for cattle indicates that there was a nearly 33% decrease in sales between 2016 and 2019.

Table 4-4: Percent change in estimated sales and distribution data for cattle in sales volume (kg) and adjusted by a biomass denominator (mg/TAB), between 2016 and 2019

Medically Important Antimicrobial Drug Class	Percent Change in Species-Specific Estimated Sales Volume (kg) from 2016 to 2019	Percent Change in Biomass Adjusted Species-Specific Estimated Sales (mg/TAB) from 2016 to 2019
Aminoglycosides	-13.7%	-17.1%
Cephalosporins	-2.1%	-6.0%
Macrolides	47.0%	41.3%
Penicillins	-21.1%	-24.2%
Sulfonamides	-15.9%	-19.3%
Tetracyclines	-38.7%	-41.1%
NIR[1]	-1.2%	-5.1%
Total	-29.9%	-32.6%

1 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For cattle, drug classes which cannot be shown in order to protect confidential business information are Amphenicols, Diaminopyrimidines, Fluoroquinolones, Lincosamides, Polymyxins, and Streptogramins. The individual drug classes within the NIR category may or may not have had actual sales in any given year. The cattle biomass denominator is applied to the NIR category as a whole; therefore does not account for potential exclusions of cattle categories for the denominator that may otherwise apply to individual NIR classes.

4.5 Antimicrobial Use in Cattle

4.5.1 Introduction

Nationally-representative and continuously collected data on antimicrobial use in cattle in the U.S. are not currently publicly available. Some information about antimicrobial use in cattle has been collected and published by USDA APHIS through periodic studies conducted by the National Animal Health Monitoring System (NAHMS). Feedlot cattle studies were conducted by NAHMS in 1994, 1999, and 2011. NAHMS also conducted studies for the beef cow-calf sector in 1993, 1997, 2007-08, and 2017. Dairy cattle studies were conducted by NAHMS in 1996, 2002, 2007, and 2014. Complete reports from these studies, including questionnaires, survey methodology and results, are available on the USDA APHIS NAHMS website.

In this section we present data from two recent efforts that the U.S. government undertook to obtain antimicrobial use and stewardship information: the USDA NAHMS Antimicrobial Use and Stewardship on U.S. Feedlots study conducted in 2017 (for collection of 2016 antimicrobial use information from feedlots), and FDA cooperative agreements which were awarded in 2016 to pilot methodologies for collection of on-farm antimicrobial use information for feedlot and dairy cattle.

4.5.2 USDA APHIS NAHMS Antimicrobial Use and Stewardship on U.S. Feedlots, 2017

In 2017, USDA NAHMS, in collaboration with the USDA National Agricultural Statistics Service (NASS), conducted a national study focusing on how antimicrobials are used on feedlots in the U.S. (USDA-APHIS, 2019a). The study represented the first time that NAHMS conducted a targeted study on antimicrobial use and stewardship, and it was also the first time that NAHMS collected detailed information on antimicrobial use in feed and water in feedlots with a capacity of 50-999 head of cattle. As part of past national feedlot studies conducted in 1999 and 2011, NAHMS collected information on antimicrobials used in feed and water only from feedlots with a capacity of at least 1,000 head.

The 2017 study focused on how antimicrobials were used in 2016, before FDA completed implementation of GFI #213 on January 1, 2017. As such, some medically important antimicrobials were still used for production purposes (i.e., growth promotion and increased feed efficiency) in 2016. These data may be useful as part of a baseline for comparison in future studies of antimicrobial use on feedlots. The planned NAHMS Feedlot 2021 study on cattle health and management practices is expected to incorporate some information about antimicrobial use and stewardship and may provide additional data to analyze trends in antimicrobial use and animal health in this sector.

The 2017 study was conducted in 22 top cattle-producing states. Feedlots were categorized for this study based on their capacity: small feedlots (50-999 head) were selected from 13 of the 22 participating states, and large feedlots (1,000 or more head) were selected from 16 of the 22 participating states. The 13 states from which small feedlots were selected represented 91.3% of national feedlots with a capacity of 50-999 head, and the 16 states from which large feedlots were selected represented 92.3% of national feedlots with capacity of 1,000 or more head.

Antimicrobials used in feed and water were the main focus of the 2017 NAHMS study, although limited information about injectable antimicrobials was also reported. **Table 4-5** shows the percentage of feedlots in the study that gave cattle medically important or non-medically important antimicrobials in 2016, by route of administration and by feedlot capacity. Some of the main findings from this study are provided below the table.

Table 4-5: Antimicrobial administration by route and feedlot capacity, 2016

Route of Administration	Feedlot Capacity (number head)					
	Percent Small Feedlots (50-999)		Percent Large Feedlots (1,000 or more)		Percent All Feedlots (50-1,000 or more)	
	Percent	Standard error	Percent	Standard error	Percent	Standard error
Feed – medically important antimicrobials	53.8	(6.0)	77.8	(3.6)	55.6	(5.5)
Feed – only non-medically important antimicrobials[1]	15.6	(4.6)	9.3	(2.5)	15.2	(4.2)
Feed – any antimicrobial (either or both medically and non-medically important)	69.5	(4.8)	87.1	(2.8)	70.8	(4.5)
Water[2]	9.1	(3.2)	1.1	(0.7)	8.5	(2.9)
Injection (group)[2]	12.8	(3.8)	39.3	(3.4)	14.8	(3.5)
Injection (individual)[2]	78.5	(4.9)	97.9	(1.0)	80.0	(4.6)
Any antimicrobials, any route	86.6	(4.0)	99.5	(0.5)	87.5	(3.7)

Source: USDA NAHMS: Antimicrobial Use and Stewardship on U.S. Feedlots, 2017 (Table B.1.)
1 Ionophores were the only antimicrobials used by feedlots in this report that are not considered medically important by FDA.
2 All antimicrobials used in water or by injection in this report are considered medically important by FDA.

Some key findings of this NAHMS study (for 2016 antimicrobial use) included:

- 55.6% of all feedlots in the study administered medically important antimicrobials in feed and 8.5% of all feedlots administered medically important antimicrobials in water.
- A higher percentage of large feedlots (77.8%) gave cattle medically important antimicrobials in feed compared with small feedlots (53.8%).
- Of feedlots that administered antimicrobials in feed or water, the most common reason for use was for therapy of respiratory disease.
- Chlortetracycline was the most commonly used medically important antimicrobial in feed. Sulfadimethoxine was the most frequently used medically important antimicrobial in water.
- Ionophores were the most commonly used non-medically important antimicrobials in feed, and were primarily used for growth promotion and for prevention or control of coccidiosis.
- 14.8% of all feedlots in the study administered an injectable antimicrobial to groups of cattle (e.g., for control of respiratory disease outbreaks), while 80% of feedlots reported administration of an injectable antimicrobial to individual animals. Oxytetracycline was the most frequently reported antimicrobial administered via injection to groups of cattle.
- Criteria that feedlots reported were important when determining whether to administer injectable antimicrobials to groups of cattle were the occurrence of respiratory disease in some of the cattle of the group or pen and previous respiratory disease problems in cattle from the same source. Other common criteria included known lack of preconditioning and/or vaccines, season of the year, and length of shipping distance.

Details of the conduct, methodology, and complete results of the study can be found in the published report (USDA-APHIS, 2019a).

4.5.3 FDA Cooperative Agreement: Characterizing Antimicrobial Use in Feedlot and Dairy Cattle

Chapter 3 described the Funding Opportunity Announcement that FDA issued in 2016, announcing the availability of grants in the form of cooperative agreements to develop and pilot methodologies for collecting and reporting antimicrobial use data in the four major food-producing species at the farm level. One of the grants (5U01FD005868) was awarded for the collection and reporting of antimicrobial use data in cattle. Given the differences in production practices and disease challenges between feedlot and dairy sectors, this project was divided into two segments.

The primary goal of the overall project was to explore options for antimicrobial use monitoring in cattle production systems, with a long-term goal of informing and supporting the continued advancement of antimicrobial stewardship within U.S. cattle production systems. Specific aims of this project included:

1. Collect antimicrobial use data from beef feedlots and dairies and document available record systems;
2. Establish a scalable system to create an aggregate report of antimicrobial use in participating facilities using multiple metrics, and provide benchmark reports back to each facility;
3. Develop estimates for resources required to expand the program to a representative sample of the industries on a yearly basis; and
4. Identify optimal record system formats and explore ways to expand their use in the beef and dairy industries.

Detailed measurement of antimicrobial use in cattle systems to achieve a representative sample across the industry is challenging for a number of reasons; for example, differences in record-keeping and technology, logistical difficulties involving data collection and transfer, analytical needs for converting disparate datasets into a uniform reporting platform, and data availability barriers related to concerns about the confidentiality of producer participants' data. Thus, the focus of this project was to pilot methodologies for antimicrobial use data collection, management, and analysis on beef feedlots and dairies, and to explore antimicrobial use metrics which could be useful in the development of long-term data collection platforms. For this project, the study investigators summarized various types of numerators and denominators that have been used to measure and report antimicrobial use and included a discussion of their advantages and disadvantages. A number of factors may affect the various metrics chosen to describe antimicrobial use. For example, a denominator utilizing animal weights is affected by factors which contribute to that weight, such as animal sex, breed, marketing strategy, and feeding strategy, among others.

Antimicrobial use measures which report only the total values of antimicrobials (without further describing by antimicrobial class and reason for use) are not well-suited to assessing whether or not a particular use is judicious. Such assessments require detailed understanding of the entire production system being evaluated, including disease detection methods and prevention measures, as well as treatment outcomes. From this standpoint, the investigators concluded that it is also not particularly practical or useful to set arbitrary reduction targets for measures of use without considering all of the factors that contribute to decisions regarding antimicrobial use which vary within and between production systems. Rather, efforts to reduce use are likely more appropriately directed towards decreasing disease incidence through improving availability and accuracy of diagnostic tools (i.e., pathogen detection, antimicrobial susceptibility testing and reporting), and implementing disease prevention measures appropriate to a particular production system.

The next sections summarize some of the results for the feedlot and dairy antimicrobial use data collected during the first two years (2016-2017) of the cooperative agreement project. Recently, investigators published detailed reports about the results for the first two years of data collection, along with an in-depth comparison of antimicrobial use metrics (Hope et al, 2020; Schrag et al, 2020). Data collection is ongoing, and CVM expects to publish a more complete summary of the cooperative agreement results after the conclusion of the projects. In addition, CVM will use information gained from the cooperative agreement pilot projects to help inform development of a long-term strategy to support continued antimicrobial use data collection.

4.5.3.1 FEEDLOT ANTIMICROBIAL USE DATA (2016-2017)

Feedlots were recruited by study investigators through state beef producer organizations, feedlot consulting veterinarians, and by direct contact of feedlots known to the study investigators; thus, this pilot project utilized a convenience sample design and does not represent a random sample of feedlot cattle in the U.S. Therefore, the antimicrobial practices described may not necessarily be representative of the entire U.S. beef/feedlot industry. A combination of farm records and surveys was used to collect antimicrobial use data, which were then converted into a uniform database by study investigators for analysis. Agreements signed with participating feedlots prohibit the public reporting of individual feedlot values even when identity is masked. This serves to maintain confidentiality and is consistent with stated program goals for the FDA cooperative agreements.

Twenty-two feedlots agreed to participate, all located in one of the five highest reported feeder cattle production states: Texas, Nebraska, Kansas, Colorado, and Iowa. For 2016, the total head of cattle closed out by participating feedlots was 599,289 representing approximately 2.4% of the USDA-reported annual steer and heifer slaughter in 2016. For 2017, there were 667,295 head, representing 2.6% of USDA-reported steer and heifer slaughter for that year. The size of individual feedlots ranged from less than 2,500 head closed-out per year to more than 100,000 head (closed out indicates the end of the feeding period and sale of cattle). The majority of feedlots in the study were in the 10,000 to 50,000 head size.

Methods – Data Collection from Feedlot Records

Farm and feedlot record systems are quite varied in the amount of information collected, the method of recording data, and the structure of reports. Electronic systems and software programs or handwritten records may be used. On participating feedlots for this project, at least three different electronic systems were utilized. In some instances, components of different systems were combined, or components of a system were combined with manual entry. The electronic systems had different capabilities with regard to what specific data were captured; for example, information may be captured at the animal lot level, individual animal level, or both. Animal lot data may include information such as the number of head entering and leaving a specific lot, weights at entry and exit, total days on feed, and daily feed consumption by type of feed ration. A few of the feedlots had only purchase records for antimicrobials used. In these instances, investigators captured reported days on feed, animal weights, inclusion rates of antimicrobials in feed, labeled doses, and amounts charged from purchase records to determine the amounts of antimicrobials used. Additional information recorded may include antimicrobials used for control of bovine respiratory disease at the lot level and/or antimicrobials used for treatment of individual animals. Treatment records contained variable levels of detail about antimicrobial use, such as specific

indication, dose of drug administered, duration of administration, and animal weight at treatment. For this project, information for in-feed antimicrobial use (macrolides and tetracyclines) was captured for all 22 of the participating feedlots. Individual animal treatment records were captured for 18 of the feedlots, and 16 feedlots provided injectable antimicrobial use information for control of bovine respiratory disease in groups of cattle.

Due to the wide variation of feedlot record formats, study investigators spent significant amounts of time organizing the data into a usable form for analysis. Details regarding specific data capture methods, data management, and data standardization are beyond the scope of inclusion in this report. Data management and standardization involved multiple steps prior to analysis. Quality assurance protocols were incorporated at multiple steps to assure that data management and standardization did not introduce errors.

Methods – Data Collection from Feedlot Surveys

Collecting data through surveys requires fewer resources than those required for collection of actual use data from treatment records. The investigators sought to determine how closely the information obtained through survey data would agree with the data from actual treatment records in this project. Surveys were administered and recorded in person by a single experienced feedlot veterinarian who recorded all responses. Surveys were administered within six months of the end of the calendar year. A full description of the content and conduct of the survey can be found in the investigators' published report (Hope et al, 2020).

Measurements of Antimicrobial Use in Feedlot Cattle

Numerators evaluated and considered for inclusion by the investigators for this project included treatment regimen and weight of active drug substance in milligrams (mg). Treatment regimens were defined by six parameters: the drug product, route of administration, total amount administered (in mg), mg per administration, number of administrations, and time frame (amount of time between the first and last administrations). Total mg of antimicrobial use were calculated by drug class for antimicrobials for three main categories – in-feed use of medically important antimicrobials (macrolides and tetracyclines) and non-medically important antimicrobials (lasalocid and monensin), control of bovine respiratory disease for groups of animals, and individual animal treatments.

Denominators considered were kilogram (kg) of animal liveweight sold and animal years. It should be noted that kg of animal liveweight sold does not account for animals that may have been exposed to antimicrobials but later died. Animal years were calculated using total head days or days on feed and dividing by 365 days.
The study investigators selected two primary metrics by which to report the antimicrobial use on feedlots:

- Milligrams of antimicrobial drug per kilogram of cattle liveweight sold (mg drug/kg liveweight sold); and
- Number of treatment regimens per animal year (regimens/animal year)

The study investigators for this pilot project reported initial results for antimicrobial use values using the two primary metrics (mg/kg liveweight and regimens/animal year) at both the study level and feedlot level. The study level combined individual lot data across all feedlots in the study and calculated one value for each metric. The feedlot level calculated values for each feedlot and expressed the metrics as means (with standard deviations) and medians. Comparison of the data obtained through surveys and that obtained through records

was also performed. The investigators also reported results by increasing levels of granularity for each metric, including overall antimicrobial totals, antimicrobials by drug class, and antimicrobials by three specific use categories (in-feed use, control of bovine respiratory disease, and individual animal treatments). Differences in potency of the various antimicrobial classes is an important consideration when determining which use metrics to report. For purposes of this report, only study level results are shown. Feedlot level results are very detailed and may be provided in summary reports after the projects are completed.

Results – Study Level

The initial study level results for 2016 and 2017 for all medically important antimicrobial use on participating feedlots are shown in **Table 4-6**. The principal finding from these data indicates a reduction in the overall (i.e., all medically important antimicrobials combined) mg/kg liveweight values and essentially no change in the number of regimens per animal year. This particular metric is not useful for purposes of assessing antimicrobial stewardship because no information is included about antimicrobial class or reason for use.

Table 4-6: Mg/kg liveweight and regimens/animal year at study level, for all uses of medically important antimicrobials, 2016 and 2017

Year	Mg/kg Liveweight	# Regimens/Animal Year
2016	44.65	3.65
2017	30.18	3.17

Table 4-7 shows the mg/kg liveweight values and number of regimens per animal year at the antimicrobial class level. Since not all feedlots use the same antimicrobials, the number of feedlots contributing information for a particular antimicrobial class is also shown. The most notable numerical change occurred in the tetracycline class between 2016 and 2017 with a numerical decrease from about 22.2 to 9.7 mg/kg liveweight.

Table 4-7: Mg/kg liveweight and regimens/animal year at study level, by antimicrobial class and year, 2016 and 2017

Antimicrobial Class	Feedlot Count[1]	Mg/Kg Liveweight		# Regimens/Animal Year	
		2016	2017	2016	2017
Aminoglycosides	2	0.03	0.03	0.007	0.004
Cephalosporins	20	0.21	0.14	0.14	0.10
Fluoroquinolones	20	0.16	0.14	0.07	0.06
Macrolides	22	21.33	19.31	2.34	2.39
Penicillins	13	0.05	0.07	0.01	0.01
Phenicols	21	0.40	0.45	0.06	0.05
Sulfonamides	9	0.27	0.31	0.01	0.01
Tetracyclines	21	22.21	9.73	1.02	0.56

Source: Hope, et al. Antimicrobial use in 22 U.S. beef feedyards: 2016-2017. *Zoonoses and Public Health* 2020; 67 (Suppl. 1): 94-110.
1 Feedlot count indicates the number of feedlots reporting use of the antimicrobial class.

Table 4-8 shows the mg/kg liveweight data at the study level by antimicrobial class, year, and further stratified by category of use: medically important antimicrobials for in-feed use (macrolides and tetracyclines only), control of BRD for groups of cattle, and individual treatments for any disease. Overall, the total for all three categories of these uses for 2016 and 2017 decreased from about 44.6 to 30.2 mg/kg liveweight, with the most notable decrease in the in-feed uses, in particular tetracyclines. The overall total number of regimens per animal year for all three types of use essentially remained the same, decreasing slightly from about 3.6 to 3.2 regimens per animal year. Overall numerical mg/kg values and regimens/animal year also decreased for use for control of BRD, but increased by a small amount for individual treatment of animals.

Table 4-8: Mg/kg liveweight and regimens/animal year at study level, by antimicrobial class, year, and category of use, 2016 and 2017

Category of Use	Antimicrobial Class	Mg/Kg Liveweight		Regimens/ Animal Year		Feedlot Count
		2016	2017	2016	2017	
In-Feed	Macrolides	20.859	18.984	1.999	2.058	18
	Tetracyclines	21.563	8.999	0.907	0.430	13
	Total	**42.421**	**27.984**	**2.906**	**2.489**	
Control of BRD (Groups of Cattle)	Aminoglycosides	0.025	NR	0.006	NR	1
	Cephalosporins	0.167	0.099	0.112	0.067	8
	Fluoroquinolones	0.019	0.0001	0.012	0.00002	3
	Macrolides	0.374	0.230	0.265	0.239	16
	Penicillins	0.029	0.045	0.008	0.009	3
	Phenicols	0.114	0.002	0.029	0.0001	4
	Sulfonamides	0.010	0.008	0.0003	0.0002	1
	Tetracyclines	0.367	0.421	0.067	0.080	12
	Total	**1.105**	**0.805**	**0.499**	**0.395**	
Treatment of Any Disease (Individual Animals)	Aminoglycosides	0.004	0.025	0.0004	0.004	2
	Cephalosporins	0.043	0.045	0.028	0.029	20
	Fluoroquinolones	0.138	0.139	0.055	0.055	20
	Macrolides	0.095	0.099	0.080	0.089	22
	Penicillins	0.020	0.022	0.003	0.004	13
	Phenicols	0.286	0.451	0.030	0.047	21
	Sulfonamides	0.259	0.300	0.005	0.005	9
	Tetracyclines	0.279	0.306	0.045	0.050	21
	Total	**1.124**	**1.387**	**0.246**	**0.284**	
Types of Use Combined	**Total**	**44.650**	**30.176**	**3.651**	**3.168**	

Source: Hope, et al. Antimicrobial use in 22 U.S. beef feedyards: 2016-2017. *Zoonoses and Public Health* 2020; 67 (Suppl. 1): 94-110.

Results – Regimen Descriptions

Additional information was obtained for antimicrobial regimens used on feedlots. Regimen descriptions are essential for understanding the pharmacokinetic and pharmacodynamic components of drug exposures. The contribution of various aspects of regimens (e.g., duration of treatment, amount given per dose and/or treatment course, and the number of times a drug product is administered) to the overall pressure exerted relative to antimicrobial resistance selection is unknown. Regimens were described for each of the three main use

categories (Table 4-9). The investigators summarized specific regimen information at a drug class level for 2016 and 2017 data combined. A few of the notable points are included here:

- In-feed uses contributed the most to the percent of total regimens by use category. In-feed uses represented 79.1% of total regimens compared to 13.1% for control of BRD in groups of cattle and 7.8% for individual treatments.
- Regimen timeframes (time between first and last administration) were largest for macrolide in-feed use (mean for all feedlots, 134 +/- 70 days). Tetracyclines (i.e., chlortetracycline) in-feed had a mean regimen timeframe of about 4 days.
- As would be expected for in-feed uses, this category had the greatest number of administrations per regimen. For control of BRD, the number of administrations per regimen was one, while for individual treatments the mean was between one and two administrations depending on antimicrobial class. Antimicrobials used for control of BRD and treatment of individual animals are typically injectable products.
- The number of milligrams per administration varies depending on drug class and is typically based on label doses and animal weights. The lowest milligrams per administration was for macrolide use for control of BRD. The highest milligrams per administration were for sulfonamides, although sulfonamides represent less than 1% of all regimens. This demonstrates the importance of considering the differences in potency of the various drug classes when determining which antimicrobial use metrics to report.

Results – Survey

Eighteen of the 22 feedlots were included in the comparison of treatment records and surveys. Considering the 18 feedlots together and all categories of use (in-feed, control of BRD, and individual treatments) at the study level, the agreement between treatment records and surveys for regimens per animal year was very close (overall total regimens/animal year from treatment records were 2.98, compared to 3.75 from survey responses). For mg/kg liveweight data, surveys tended to overestimate the amount used (overall total mg/kg from treatment records was 31.84, compared to 41.67 mg/kg from survey responses). Much of the variation in the mg/kg liveweight from surveys was due to overestimated uses of in-feed tetracyclines and macrolides, although sulfonamides for individual animal treatments were also overestimated in surveys. **Table 4-9** shows the differences in mg/kg liveweight and regimens/animal year between treatment records and surveys by use category, at the study level (Hope et al, 2020).

Table 4-9: Mg/kg liveweight and regimens/animal year comparing treatment records and surveys for 18 feedlots, at study level and by use category

Use Category	Mg/Kg Liveweight		Regimens/Animal Year	
	Records	Survey	Records	Survey
In-feed use	30.15	36.38	2.43	2.90
Control of BRD in groups of animals	0.60	0.38	0.32	0.36
Individual animal treatments	1.09	4.91	0.23	0.49
Total all uses	31.84	41.67	2.98	3.75

Source: Hope, et al. Comparison of surveys and use records for quantifying medically important antimicrobial use in 18 U.S. beef feedyards. *Zoonoses and Public Health* 2020; 67 (Suppl. 1): 111-123.

The investigators evaluated the correlations between survey and treatment record data and from a statistical standpoint determined that the study lacked sufficient power to clearly indicate that treatment record vs. survey data were different. Additional studies would be required to further delineate these correlations. While surveys are useful tools to provide insight into antimicrobial use trends and practices on feedlots, using survey-collected antimicrobial use data to rank feedlots by amount of use for purposes of benchmarking or regulatory programs is not likely to be a useful approach.

4.5.3.2 DAIRY ANTIMICROBIAL USE DATA (2016-2017)

Dairies were recruited through their veterinarians with whom the study investigators had a previously established relationship; thus, this pilot project also utilized convenience sampling, is not a random sample of dairy cattle or operations in the U.S., and the antimicrobial practices described here are not necessarily representative of the entire U.S. dairy industry. Study investigators indicated the established relationships with the participating veterinarians and the veterinarians' relationships with their dairy clients were pivotal to the success of this pilot project. Data were collected from multiple sources including farm treatment protocols, drug purchase records, surveys, and treatment records. Due to the wide variability in treatment recording and other aspects of the electronic systems used, investigators spent substantial time converting the records into a standard format to analyze the data adequately.

The study was originally designed to capture all uses of antimicrobials within the dairy systems. However, upon analysis of the initial data collected it was recognized by the investigators that gathering data on some uses was too resource intensive to capture in the initial years of the project. Examples include topical hoof treatments, treatments for young stock, and feed uses for dairy cattle. Topical hoof treatments were often for sole ulcers and digital dermatitis and it was found that records of individual animal hoof treatments rarely indicated which drug or amount of drug was used for treatment. Regarding young stock and calves, available records were very incomplete or did not exist. If treatments were recorded, they were often in a temporary format and/or mixed with records of multiple farms due to the farm's use of a contracted heifer grower. Records from heifer growers did not allow allocation of calves to dairy farms, so expenditure of time and resources to estimate use in calves was not feasible for this project. Regarding feed use records, the study investigators determined that most of the dairies were using ionophores (not medically important) in the feed of lactating cows, but the record systems for feed were entirely separate from treatment records for medically important antimicrobials, so time and other resources did not permit collection and analysis of these data.

Thirty-two (32) dairy farms, ranging in size from 180 to 6,000 adult cows, agreed to participate. Efforts were made to include dairies from multiple regions of the U.S., and there were no restrictions for participation other than a willingness to work with the investigators on the data collection and to allow publication of summarized data. Data were collected for calendar years 2016 and 2017. Data for three of the initial 32 dairies are not included due to changes in management or ownership, or due to lack of sufficient retrospective data. The published article provides full details and results of the study (Schrag et al, 2020).

Methods – Data Collection from Dairy Farm Records

Treatment data included multiple record system types. The 29 dairies in this project utilized one of four electronic data record systems, with the majority of the dairies using the same system. However, the dairies differed in their utilization of the systems to record treatment data. For example, some farms used electronic records for all treatments administered, other farms used them only for a subset or certain type of treatment, and still other farms recorded all treatments on paper and utilized the electronic systems only for management of tasks unrelated to cow treatments. A variety of methods were used by farm staff for recording animal treatments. For example, some farms may have recorded one treatment 'event' as an antimicrobial drug given once daily for five days, whereas others may have recorded treatments given as a separate entry for each day.

Data from treatment records were manually entered by study investigators into a standard format, which included the disease being treated, drug product, route of administration, dose, number of administrations, interval between administrations, and detected disease incidence. Diseases were grouped into nine syndrome categories: digestive, displaced abomasum, lameness, metritis, mastitis, metabolic, respiratory, other, and unknown. Both grams of drug and regimens (including information about drug, dose, route, frequency, and duration) administered were stratified by disease syndrome. When the details for the standard treatment record format were not explicitly listed in the original treatment record, other sources were used to determine the appropriate values specific to the individual farm and animal treated; for example, protocols, purchase records, and survey information may have been used.

Methods – Data Collection from Dairy Farm Surveys

Collecting data through the use of surveys requires fewer resources than those required for collection of actual use data from treatment records. The investigators sought to determine how closely the information obtained through survey data would agree with the data from actual treatment records in this project, similar to the evaluation done for feedlots (see above). Surveys were administered in person by a single experienced veterinarian who recorded all responses. Surveys were administered to participating farms within the first year of the project. A full description of the content and conduct of the survey are beyond the scope of this report, but the survey was designed to provide information that would result in the ability to calculate the same metrics as those from the treatment records.

Measurements of Antimicrobial Use on Dairy Farms

Numerators evaluated and considered for inclusion by the investigators for the dairy project included treatment regimens and weight of active drug substance in grams. Treatment regimens were defined by five parameters: the drug product, route of administration, mg per administration, number of administrations, and time frame (amount of time between the first and last administrations). In cases where there were multiple administrations of the same drug product for the same disease, that course of therapy was counted as one regimen, provided there was not a gap of more than five days between administrations.

All measures were reported using a denominator of cow-years. Cow-years were calculated from the average count of adult dairy cows present on each dairy during a calendar year, essentially representing a space on a farm occupied by an adult cow for one year. Due to variations in calving intervals and lactation status that occur during any given year, that space is not necessarily occupied by the same cow for the entire year. The use of milk (pounds produced) was considered as a denominator, but since meat is also a product from dairy systems, allocation of use to one or both products was problematic.

The study investigators selected two primary metrics by which to report the antimicrobial use on dairies:

- Grams of antimicrobial (active drug substance) per cow-year; and
- Number of antimicrobial treatment regimens per cow-year

All values were reported as composite values for total use by year, as well as stratified by disease and drug class. These stratifications were further subdivided by three major therapeutic use categories: dry cow therapy, clinical mastitis therapy, and other treatments. Dry cow therapy is intramammary (i.e., administered through teats into the udder) treatment administered at the end of lactation aimed at treating chronic or subclinical infections and preventing new infections. Some farms treat all cows ("blanket" dry cow therapy), while others select cows for treatment based on milk quality and treatment history ("selective" dry cow therapy). Clinical mastitis therapy means the intramammary treatment of cows diagnosed with mastitis according to the farm definition. Other treatments were all other non-intramammary treatments for all diseases.

The study investigators reported initial results for antimicrobial use values using the two primary metrics (grams/cow-year and regimens/cow-year) at both the study level and dairy level. The study level summarized total antimicrobial use in each therapeutic use category across all dairies combined. The dairy level calculated values for each dairy and expressed the metrics as means (with standard deviations) and medians. Comparison of data obtained through surveys and that obtained through farm records was also performed. For purposes of this report, only study level results are shown. Individual dairy level results are very detailed and may be provided in summary reports after the projects are completed.

Results – Study Level

The initial study level results for 2016 and 2017 for 29 participating dairies are shown in **Table 4-10**. The principal finding from these data indicates an essentially stable number of regimens per cow-year and overall grams of antimicrobial per cow-year. As with the feedlot study, this particular metric is not useful for purposes of assessing antimicrobial stewardship because no information is included about antimicrobial class or reason for use.

Table 4-10: Grams of antimicrobial/cow-year and regimens/cow-year at study level, for all uses of medically important antimicrobials, 2016 and 2017

Year	Grams/Cow-Year	# Regimens/Cow-Year
2016	8.25	1.43
2017	8.25	1.40

Table 4-11 shows the grams per cow-year values and number of regimens per cow-year at the antimicrobial class level, and reason for use category. Since not all dairies use the same antimicrobials, the number of dairies contributing information for a particular antimicrobial class is also shown. No particular notable numerical changes occurred between 2016 and 2017. When measured by regimens, cephalosporin use is highest, but when measured by grams of active ingredient, penicillin use is highest. Results shown in Table 4-11 indicate that dry cow therapy for mastitis is the primary driver of use when measured by regimens, whereas when measured by grams, the 'other treatments' category is highest. These differences serve to illustrate how the choice of metric affects potential conclusions drawn about antimicrobial use.

Table 4-11: Grams/cow-year and regimens/cow-year at study level, by antimicrobial class, reason for use category, and year, 2016 and 2017

Antimicrobial Class	Reason for Use Category	Grams/Cow-Year		# Regimens/Cow-Year		Dairy Count[1]
		2016	2017	2016	2017	
All Classes	All Reasons	8.25	8.25	1.434	1.403	29
Aminocoumarins	Dry Cow Therapy	0.044	0.031	0.014	0.010	2
Aminoglycosides	Dry Cow Therapy	0.236	0.138	0.030	0.017	3
Amphenicols	Other Treatments[2]	0.005	0.002	0.0003	0.0003	4
Cephalosporins	Dry Cow Therapy	0.897	0.818	0.542	0.486	20
	Clinical Mastitis	0.168	0.136	0.260	0.233	29
	Other Treatments	1.191	1.234	0.250	0.256	28
Lincosamides	Clinical Mastitis	0.004	0.005	0.025	0.025	17
Macrolides	Other Treatments	0.0004	N/A	0.0001	N/A	2
Penicillins	Dry Cow Therapy	0.455	0.456	0.142	0.178	13
	Clinical Mastitis	0.003	0.006	0.017	0.034	13
	Other Treatments	4.033	4.055	0.125	0.127	28
Sulfonamides	Other Treatments	0.957	1.050	0.014	0.013	5
Tetracyclines	Other Treatments	0.255	0.320	0.016	0.023	19

Source: Schrag et al. Antimicrobial use quantification in adult dairy cows-Part 3- use measured by standardized regimens and grams on 29 dairies in the United States. *Zoonoses and Public Health* 2020; 67 (Suppl. 1): 82-93.

1 Dairy count indicates the number of dairies reporting use of the antimicrobial class.

2 Other Treatments included disease syndromes such as respiratory disease, metritis, metabolic diseases, lameness, systemic treatments for mastitis, digestive disorders, displaced abomasum, and other/unknown.

Results – Regimen Descriptions

Further information was also provided to describe regimens. Regimen time frame calculations indicated that intramammary ceftiofur and injectable (parenteral) penicillin had the longest regimen time frames (mean, 3.7 days and 3.4 days, respectively) and the most administrations per regimen (mean, 4.7 and 4.4 administrations, respectively). Parenteral sulfadimethoxine had the largest grams per regimen (mean, 79.4 grams), but accounted for less than 1% of all regimens administered. Intramammary ceftiofur accounted for the largest percentage of regimens administered , but had very low grams administered (Schrag et al, 2020).

Results - Survey

Surveys gathered numerator data on the number of regimens administered by disease syndrome, as well as denominator data (number of cow-years). They also gathered information about clinical mastitis cases; all but one respondent indicated they routinely used 'blanket' dry cow therapy routinely in 2016 and that dairy used selective dry cow therapy. Two additional dairies began using selective dry cow therapy in 2017. Surveys also gathered information about the use of antimicrobials in foot baths. Foot baths are routinely used to control digital dermatitis. All dairies reported that foot baths were used, with frequency varying from one to seven times per week. No dairies reported using medically important antimicrobials in foot baths.

Results from surveys and treatment record data were compared, where data were complete enough to allow for an adequate comparison. Results were compared only for the disease syndromes of mastitis, metritis, lameness, and digestive disorders because of the very low incidence of other disease syndromes on responding dairies. Denominator data (calculated cow-years) from surveys were found to correlate well with the data from treatment records. However, in general, survey estimates of number of treatment regimens were not well correlated to treatment records. Recall bias may account for some of the lack of correlation, and respondents reportedly struggled to answer some of the survey questions at times due to the extreme variation in disease pressure that occurs at various times throughout the year. For example, some diseases vary seasonally, while others vary with the percentage of cows entering lactation at any given time point. Investigators hypothesized that conducting a pilot survey and modification of the survey might improve correlation between survey and treatment record data.

4.6 Antimicrobial Resistance in Cattle and Beef

4.6.1 Introduction

In this section, some of the available information about antimicrobial resistance specific to bovine pathogens is described. This is limited to information recently collected through the first two years of the USDA APHIS NAHLN Antimicrobial Resistance Pilot Project (2018-2019) and results from the first year of an FDA CVM Vet-LIRN collaborative antimicrobial resistance pilot project with veterinary diagnostic laboratories (2017). Some historical information has also been published as part of periodic USDA APHIS NAHMS cattle studies, available on the NAHMS website.

In addition, some of the 2019 antimicrobial resistance information is highlighted for bacterial isolates collected from retail ground beef samples and cecal (intestinal) contents at the time of slaughter for beef and dairy cattle, collected through the FDA (retail meat) and USDA FSIS (cecal) components of the NARMS program. Preliminary real-time genotypic data are available on the NAHMS website, but not included here since the focus of this report is on 2016-2019.

4.6.2 Antimicrobial Resistance in Bovine Pathogens

4.6.2.1 USDA APHIS NAHLN ANTIMICROBIAL RESISTANCE PILOT PROJECT – CATTLE RESULTS (2018-2019)

As part of the USDA APHIS NAHLN Antimicrobial Resistance Pilot Project (see Chapter 3), pathogens tracked from cattle included ***E. coli***, ***Salmonella enterica,*** and ***Mannheimia haemolytica***. For the pilot project, information regarding cattle production class and age was not collected. The full reports should be consulted for information on methodologies used and complete results for this project, including minimum inhibitory concentration (MIC) data for the isolates (USDA-APHIS, 2019b and USDA-APHIS, 2019c).

E. coli

Only two antimicrobials have bovine-specific clinical breakpoints established by the Clinical Laboratory Standards Institute (CLSI) for ***E. coli*** – ampicillin and ceftiofur (CLSI, 2018). Ampicillin only has breakpoints established for metritis and ceftiofur only has breakpoints established for mastitis.

A total of 372 ***E. coli*** isolates from cattle were submitted in 2018 for the pilot project. Of the 372 isolates, only three were associated with a diagnosis of metritis – one was susceptible to ampicillin and the other two were resistant. For mastitis, only five isolates were recovered, and all were susceptible to ceftiofur. Overall, the most common clinical symptom or diagnoses associated with ***E. coli*** infections in cattle were diarrhea (58.3%), septicemia (10.8%), and pneumonia (9.7%).

In 2019, there were a total of 626 ***E. coli*** isolates from cattle submitted. Only 10 of these 626 isolates were associated with mastitis cases and nine of those were susceptible to ceftiofur. One of the 626 ***E. coli*** isolates was from a metritis case and it was susceptible to ampicillin. Overall, the most common clinical symptom or diagnosis associated with ***E. coli*** infections in cattle for 2019 submissions were again diarrhea (64.1%), septicemia (9.6%), and pneumonia (7.7%).

Salmonella spp.

Currently no antimicrobials have bovine-specific CLSI clinical breakpoints established for ***Salmonella*** spp.; thus, percentage resistance was not reported. MIC data are available in the report published by NAHLN, as well as additional data for other serotypes not mentioned below.

A total of 349 ***Salmonella*** spp. isolates were submitted for cattle in 2018; 37 different serotypes were identified among these isolates. Overall, the four most prevalent serotypes were Dublin (33.2%), Cerro (18.6%), Typhimurium (10.9%), and Montevideo (8.6%). These four serotypes were also the most commonly associated with diarrhea in cattle, while Dublin was the most common serotype for pneumonia and septicemia.

In 2019, there were a total of 380 ***Salmonella*** spp. isolates from cattle submitted. Forty-eight different serotypes were reported, with serotypes Dublin (38.2%), Cerro (10.5%), Montevideo (10.0%) and Typhimurium

(8.4%) again the most frequently identified. Serotype Dublin was the most common serotype associated with clinical submissions; diagnoses reported in association with these submissions included diarrhea, septicemia, pneumonia, and abortion/neonatal death.

Mannheimia haemolytica

Twenty-one antimicrobials were tested, 12 of which have bovine-specific CLSI breakpoints established for ***M. haemolytica*** (CLSI, 2018).

There were 380 isolates of ***M. haemolytica***, one of the most common cattle respiratory pathogens, submitted in 2018. Of the 380 isolates, 65.3% were susceptible to all 12 antimicrobials for which a breakpoint is established. Thirty-nine isolates (10.3%) demonstrated resistance to one antimicrobial class and 22 isolates (5.8%) were resistant to two antimicrobial classes. Multidrug resistance (MDR, i.e., defined in the NAHLN report as non-susceptibility to at least one agent in three or more antimicrobial classes) was observed in 18.7% of isolates. One MDR isolate was resistant to 10 of the 12 antimicrobials tested on one type of antimicrobial susceptibility testing plate.

In 2019, there were 612 isolates of ***M. haemolytica*** submitted for cattle. As expected, all isolates were associated with respiratory disease or pneumonia. Of the 612 isolates, 69.4% were pan-susceptible, slightly higher than the pan-susceptible percentage in 2018 isolates, indicating a slight downward trend in resistance for ***M. haemolytica*** isolates. Sixty-seven isolates (10.9%) demonstrated resistance to one antimicrobial class and 19 isolates (3.1%) were resistant to two classes. Multidrug resistance was observed in 16.5% of the isolates. Seventeen of the MDR isolates were resistant to 11 of the 12 antimicrobials tested with bovine breakpoints.

Table 4-12 shows the percentage resistance in *Mannheimia haemolytica* isolates from 2018 and 2019 for antimicrobials which have breakpoints established.

Table 4-12: Percentage resistance – *Mannheimia haemolytica* isolates from cattle in 2018 and 2019

Antimicrobial Class	Antimicrobial Drug	2018 % Resistance (n=380 isolates)[1]	2019 % Resistance (n=612 isolates)[2]
Aminoglycosides	Spectinomycin	16.6	14.1
Amphenicols	Florfenicol	11.3	9.3
Cephalosporins	Ceftiofur	0.3	0
Fluoroquinolones	Danofloxacin	21.8	17.0
	Enrofloxacin	19.7	15.2
Macrolides	Gamithromycin	13.0	16.3
	Tildipirosin	1.1	14.4
	Tilmicosin	23.2	19.1
	Tulathromycin	18.4	15.4
Penicillins	Ampicillin	20.8	14.9
	Penicillin	20.8	13.6
Tetracyclines	Tetracycline	20.7	24.3

Source: USDA-APHIS National Animal Health Laboratory Network (NAHLN) Antimicrobial Resistance Pilot Project Year 1 Report: 2018 and Year 2 Report: 2019.
1 The number of isolates tested for gamithromycin, tildipirosin, and tetracycline was 92 in 2018.
2 The number of isolates tested for gamithromycin, tildipirosin, and tetracycline was 473 in 2019.

4.6.2.2 FDA CVM VET-LIRN COLLABORATIVE PROJECT WITH VETERINARY DIAGNOSTIC LABORATORIES, ANTIMICROBIAL RESISTANCE PILOT – CATTLE RESULTS (*SALMONELLA* ONLY)

As part of the collaborative project with veterinary diagnostic laboratories in the U.S. and Canada, Vet-LIRN collected *Salmonella* isolates from veterinary diagnostic source labs from any host animal (see Chapter 3). In 2017, 586 *Salmonella enterica* isolates were collected, 69 of which were whole genome sequenced. Of these 69 isolates, 25 were of bovine origin. The serovars for these 25 isolates were Dublin (6), Cerro (3), Typhimurium (2), Mbandaka (2), Montevideo (2), Uganda (2), and one each for serovars Saintpaul, Muenster, Muenchen, Kentucky, Enteriditis, Heidelberg, Meleagridis, and Senftenberg. Thirteen of the 25 isolates carried at least one resistance gene. Five of the six Dublin isolates carried multiple resistance genes, including *strA* and *strB*, $bla_{\text{CMY-17}}$, $bla_{\text{TEM-214}}$, *floR*, *sul2*, and *tet(A)*, conferring resistance to antimicrobials in the aminoglycoside, βlactamase, amphenicol, sulfonamide, and tetracycline classes, respectively. The one Heidelberg isolate carried 14 resistance genes, including the plasmid-mediated quinolone resistance gene *qnrB5*. None of the isolates had fluoroquinolone resistance mutations in *gyrA* (Ceric et al, 2019).

4.6.3 Antimicrobial Resistance in Cattle at Slaughter and Retail Beef

This section highlights antimicrobial resistance information for 2019 for generic *E. coli, Salmonella*, *Campylobacter*, and *Enterococcus* isolates collected from retail ground beef samples and cecal (intestinal) contents at the time of slaughter for beef and dairy cattle. This information was collected through the FDA (retail meat) and USDA FSIS (cecal) components of the NARMS program. The CDC NARMS website should be consulted for information about bacteria isolated from humans that are monitored for antimicrobial resistance. For purposes of this report, antimicrobial susceptibility testing (i.e., phenotypic) data are described, including some information about multidrug resistance (MDR, defined by the NARMS program as resistance to three or more antimicrobial classes). The NARMS program websites and most recent integrated report (2018 NARMS Integrated Summary) can be consulted for more information, including whole genome sequencing data. **Appendix 5** provides line graphs depicting some of the resistance trends (from antimicrobial susceptibility testing) for a five-year period (2015-2019). Genotypic real-time data are published at NARMS Now and includes 2018-2021 data.

P-values, where reported in this section, were obtained using Fisher's exact test for comparing proportions (McDonald, 2014). P-values help assess statistical significance when comparing two or more sets of numerical data. In this case the proportions compared were the percentages of resistance (for a given bacteria and sample source) between 2018 and 2019, and the significance level was set at $p \leqslant 0.05$.

4.6.3.1 *E. COLI* – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL GROUND BEEF AND CATTLE CECAL SAMPLES

Recovery of *E. coli* from retail ground beef samples collected in the NARMS program was 38.2% in 2019, down from about 47% in 2015. Recovery of *E. coli* from beef cattle and dairy cattle cecal samples also decreased compared to 2015. *E. coli* is a common commensal organism of the intestinal microbiota, so high prevalence levels are not unusual in animal cecal samples. **Tables 4-13 and 4-14** show the annual number of samples collected and number of *E. coli* isolates from the NARMS retail meat and cecal sampling programs for 2015

through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the cecal and retail sampling programs, as well as changes in sampling over the years.

Table 4-13: Number of retail ground beef samples collected by year (2015-2019), and percent positive for *E. coli* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Ground Beef					
Number of samples	480	427	713	911	748
Number of isolates	227	174	271	260	286
Prevalence (%)	47.3	40.7	38.0	28.5	38.2

Table 4-14: Number of beef and dairy cattle cecal samples collected by year (2015-2019), and percent positive for *E. coli* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Beef Cattle Cecal					
Number of samples	600	819	1031	1166	872
Number of isolates	556	738	936	1029	759
Prevalence (%)	94.3	90.1	90.8	88.2	87.0
Dairy Cattle Cecal					
Number of samples	334	483	506	515	508
Number of isolates	325	450	446	415	422
Prevalence (%)	97.3	93.2	88.1	80.6	83.1

Appendix 5 shows resistance trends (2015 to 2019) for *E. coli* isolated from retail ground beef and beef and dairy cattle cecal samples, for antimicrobials selected from the 10 antimicrobial drug classes tested. Cattle source *E. coli* isolates are generally most resistant to tetracycline and streptomycin compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing results) in *E. coli* isolates from cattle samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- In 2019, no *E. coli* isolates from retail ground beef were resistant to ceftriaxone, compared to 0.6% in 2016 and zero in 2018. For beef and dairy cattle cecal samples, ceftriaxone resistance in *E. coli* isolates were stable (beef cecal) or decreased (dairy cecal) between 2018 and 2019, remaining below 1% in beef cattle cecal samples and decreasing below 2% in dairy cattle cecal samples.
- Decreased susceptibility to azithromycin (DSA) was not detected in *E. coli* isolates from retail ground beef or dairy cattle cecal samples in 2019. Only one of 759 isolates collected from beef cattle ceca showed DSA in 2019.
- *E. coli* isolates from all cattle sources continue to show no carbapenem resistance in 2019 (meropenem testing became routine in 2016).
- The percentage of *E. coli* isolates from retail ground beef with decreased susceptibility to ciprofloxacin (DSC) was stable between 2018 and 2019, remaining below 1%. For beef and dairy cattle cecal samples, the percentage of *E. coli* isolates with DSC increased between 2018 and 2019 for beef (from 1.8% to 2.4%) and decreased for dairy (from 1.7% to 0.5%) cattle cecal samples, remaining below 3% for both.
- Ampicillin resistance in *E. coli* isolates from retail ground beef showed a statistically significant decrease comparing 2016 and 2019 (6.3% to 2.1%, p=0.02) and also showed decreases in cattle cecal samples over the same time period. Comparing 2018 and 2019, no significant differences were seen.
- Amoxicillin-clavulanic acid resistance decreased significantly in dairy cattle cecal samples (from 2.2% in 2018 to 0.9% in 2019; p<0.01).
- Chloramphenicol resistance in *E. coli* isolates from retail ground beef, beef cattle cecal and dairy cattle cecal samples showed variable decreases between 2018 and 2019, with the most decrease seen in beef cattle cecal samples (decreased from 8.1% to 6.7%).
- Compared to 2016, in 2019 there were significant decreases in tetracycline resistance in *E. coli* isolates from both beef (decreased from 38.8% to 33.2%, p=0.02) and dairy (decreased from 22% to 16.8%, p=0.05) cattle cecal samples. Tetracycline resistance comparing 2018 and 2019 was stable for all sample types.
- MDR in *E. coli* isolates showed no significant change in retail ground beef between 2018 and 2019, and showed decreases for both beef and dairy cattle cecal samples (from 14.4% to 12.1% for beef, and from 11.1% to 9.2% for dairy).

4.6.3.2 NONTYPHOIDAL *SALMONELLA* – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL GROUND BEEF AND CATTLE CECAL SAMPLES

Recovery of nontyphoidal serotypes of *Salmonella* from retail ground beef samples collected in the NARMS program remained very low, continuing to be less than 1%. **Tables 4-15 and 4-16** show the annual number of samples collected and number of *Salmonella* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 4-15: Number of retail ground beef samples collected by year (2015-2019), and percent positive for *Salmonella* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Ground Beef					
Number of samples	1649	1521	2094	2203	1647
Number of isolates	6	8	15	13	12
Prevalence (%)	0.4	0.5	0.7	0.6	0.7

Table 4-16: Number of beef and dairy cattle cecal samples collected by year (2015-2019), and percent positive for *Salmonella* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Beef Cattle Cecal					
Number of samples	1678	1744	2133	2392	2313
Number of isolates	126	150	183	214	225
Prevalence (%)	7.5	8.6	8.6	8.9	9.7
Dairy Cattle Cecal					
Number of samples	1055	1080	1197	1185	1241
Number of isolates	233	217	236	255	275
Prevalence (%)	22.1	20.1	19.7	21.5	22.2

Appendix 5 shows resistance trends (2015 to 2019) for *Salmonella* isolated from retail ground beef, beef cattle cecal, and dairy cattle cecal samples, for antimicrobials selected from the 10 antimicrobial drug classes tested. Cattle source *Salmonella* isolates are generally most resistant to tetracycline and streptomycin compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Salmonella* isolates from cattle samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- Between 2018 and 2019, ceftriaxone resistance in *Salmonella* isolates from retail ground beef decreased to zero and also showed decreases in cattle cecal samples. Newport and Typhimurium were the predominant ceftriaxone-resistant serotypes among *Salmonella* isolated from cattle sample types (beef cattle cecal and dairy cattle cecal) in 2019.

- The percentage of ***Salmonella*** isolates from cattle sources with DSC decreased between 2018 and 2019 for retail ground beef (from 14.3% to 8.3%, representing only 2 and 1 isolate(s), respectively) and beef cattle cecal samples (from 4.2% to 2.2%) and remained stable (less than 0.5%) for dairy cattle cecal samples. In beef cattle ceca, Newport was the predominant serotype.
- No DSA was detected in 2019 in ***Salmonella*** isolates from retail ground beef and dairy cattle cecal samples. For beef cattle cecal samples, only 2 of 225 ***Salmonella*** isolates showed DSA in 2019 (one each of serotype Newport and Tennessee). This represents a rare but important finding and will continue to be monitored closely. In human NARMS data, DSA appeared in only 0.7% of ***Salmonella*** isolates tested in 2018, with serotype Newport comprising the majority of isolates (CDC, 2021d). Some of these Newport isolates in were linked to a 2018-19 outbreak attributed to consumption of contaminated beef and dairy products (NARMS, 2020b; Plumb et al, 2019). Preliminary human NARMS data for 2019 indicates 1.2% of isolates showed DSA (CDC, 2021d).
- ***Salmonella*** isolates from all cattle sources continue to show no carbapenem resistance (meropenem testing became routine in 2016).
- Streptomycin resistance significantly decreased in ***Salmonella*** isolates from beef cattle cecal samples between 2018 and 2019 (from 25.8% to 8.9%; $p<0.01$). Streptomycin resistance also decreased in retail ground beef and dairy cattle cecal samples during the same time period.
- Tetracycline resistance significantly decreased in ***Salmonella*** isolates from beef cattle cecal samples between 2018 and 2019 (from 19.2% to 8.4%; $p<0.01$). Tetracycline resistance also decreased in retail ground beef and dairy cattle cecal samples during the same time period.
- Sulfisoxazole resistance significantly decreased in ***Salmonella*** isolates from beef cattle cecal samples between 2018 and 2019 (from 12.1% to 5.3%; $p=0.01$). Sulfisoxazole resistance also decreased in retail ground beef and remained stable in dairy cattle cecal samples during the same time period.
- The percentage of MDR ***Salmonella*** isolates decreased for retail ground beef and beef cattle cecal samples and remained stable for dairy cattle cecal samples between 2018 and 2019. The majority of beef and dairy cattle cecal MDR Salmonella isolates were serotypes Newport and Typhimurium.

4.6.3.3 *CAMPYLOBACTER* SPP. – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR CATTLE CECAL SAMPLES

Recovery of ***Campylobacter*** from beef and dairy cattle cecal samples collected in the NARMS program in 2019 was decreased compared to 2018. Retail ground beef has not been cultured for ***Campylobacter*** in the NARMS retail meat program since 2008, due to the low recovery of isolates. **Table 4-17** shows the annual number of samples collected and number of ***Campylobacter*** isolates (includes both ***Campylobacter jejuni*** and ***Campylobacter coli***) from the NARMS cecal sampling program for 2015 through 2019. The NARMS website should be consulted for information on sampling methodologies.

Table 4-17: Number of beef and dairy cattle cecal samples collected by year (2015-2019), and percent positive for *Campylobacter* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Beef Cattle Cecal					
Number of samples	1645	1713	2080	2392	2159
Number of isolates	682	657	934	983	975
Prevalence (%)	41.5	38.4	44.9	41.1	45.2
Dairy Cattle Cecal					
Number of samples	1045	1068	1166	1184	1220
Number of isolates	453	431	493	413	444
Prevalence (%)	43.3	40.4	42.3	34.9	36.4

Appendix 5 shows resistance trends (2015 to 2019) for *Campylobacter jejuni* (*C. jejuni*) and *Campylobacter coli* (*C. coli*) isolated from beef and dairy cattle cecal samples, for antimicrobials from five of the antimicrobial drug classes tested. Cattle source *Campylobacter* isolates are generally most resistant to tetracyclines compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Campylobacter* spp. isolates from cattle samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- In 2019, there was no macrolide resistance detected in *C. jejuni* isolates from beef cattle cecal samples, and macrolide resistance was below 0.5% for isolates from dairy cattle cecal samples. For *C. coli*, macrolide resistance was below 3% for beef cattle cecal isolates, and was around 4% for dairy cattle cecal isolates.
- Between 2018 and 2019, ciprofloxacin resistance increased for *C. jejuni* isolates from beef cattle cecal samples from 23.6%% to 27%, and also showed an increase in dairy cattle samples (from 19.3% to 21.3%). For *C. coli* in the same time period, ciprofloxacin resistance was stable for beef cattle cecal isolates, and increased for dairy cattle cecal isolates (from 42.7% to 45.2%). Among all animal (cecal) sources of *Campylobacter* spp. isolates tested in 2019, beef cattle cecal samples yielded the highest levels of ciprofloxacin resistance (about 38%).
- Between 2018 and 2019, *C. jejuni* isolates from beef cattle cecal samples had a statistically significant decrease in clindamycin (a lincosamide) resistance (from 3.6%% to 1.8%, p=0.04), and dairy cattle cecal isolates also showed a significant decrease in resistance (from 3% to 0.6%, p=0.02).
- Between 2018 and 2019, MDR in *C. jejuni* isolates from beef cattle cecal samples significantly decreased (from 2.6% to 0.8%, p<0.01), and also decreased for dairy cattle cecal isolates (from 2.1% to 0.3%). For *C. coli*, MDR in isolates from beef cattle cecal samples decreased from 9.6% to 7.7% and decreased for dairy cattle cecal samples from 10.7% to 5.5%.

4.6.3.4 *ENTEROCOCCUS* SPP. – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL GROUND BEEF AND CATTLE CECAL SAMPLES

Recovery of *Enterococcus* from retail ground beef samples collected in the NARMS program was stable, around 70% in 2019, and also decreased to below 80% and 90% for beef and dairy cattle cecal samples, respectively. *Enterococcus* spp. are a common commensal organism of the intestinal microbiota of humans and animals, so high prevalence levels are not unusual. **Tables 4-18 and 4-19** show the annual number of samples collected and number of *Enterococcus* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the cecal and retail sampling programs, as well as changes in sampling over the years.

Table 4-18: Number of retail ground beef samples collected by year (2015-2019), and percent positive for *Enterococcus* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Ground Beef					
Number of samples	480	427	591	847	681
Number of isolates	421	375	480	553	487
Prevalence (%)	87.7	87.8	81.2	65.3	71.5

Table 4-19: Number of beef and dairy cattle cecal samples collected by year (2015-2019), and percent positive for Enterococcus (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Beef Cattle Cecal					
Number of samples	608	819	967	1166	871
Number of isolates	566	695	877	980	668
Prevalence (%)	93.1	84.9	90.7	84.0	76.7
Dairy Cattle Cecal					
Number of samples	336	483	463	515	499
Number of isolates	336	430	430	441	409
Prevalence (%)	100.0	89.0	92.9	85.6	82.0

Appendix 5 shows resistance trends (2015 to 2019) for *Enterococcus faecalis* (*E. faecalis*) and *Enterococcus faecium* (*E. faecium*) isolated from retail ground beef and beef and dairy cattle cecal samples, for antimicrobials from eight or nine of the antimicrobial drug classes tested. Cattle source *Enterococcus* isolates are generally most resistant to tetracyclines compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *E. faecalis and E. faecium* isolates from cattle samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- For *E. faecalis*, macrolide (erythromycin) resistance increased in retail ground beef (from 0.8% to 1.6%) and beef cattle cecal samples (from 6.6% to 8.3%) between 2018 and 2019. In dairy cattle cecal samples, macrolide resistance decreased (from 5.1% to 1.3%) during the same time period. For *E. faecium*, erythromycin resistance in isolates from retail ground beef significantly decreased (from 11.4% to 3.5%, p=0.04), decreased for beef cattle cecal samples (from 7% to 5%) and stayed the same for dairy cattle cecal samples (1.5%).
- In 2019, no ciprofloxacin resistance was detected in *E. faecalis* isolates from cattle cecal samples, and it was detected in only 2 of 314 retail ground beef isolates (<1%). For *E. faecium* isolates, ciprofloxacin resistance was stable for retail ground beef and beef cattle cecal isolates, and increased for dairy cattle cecal isolates (from 17.6% to 19.7%).
- Between 2018 and 2019 there was a significant decrease in tetracycline resistance in *E. faecalis* isolates from dairy cecal samples (from 20.5% to 5.2%, p<0.01). Similarly, there was a significant decrease in tetracycline resistance in *E. faecium* isolates from beef cattle cecal samples (from 25.9% to 13.9%, p=0.02).
- With the exception of one retail ground beef *E. faecium* isolate, no decreased susceptibility to gentamicin was detected in retail ground beef or cattle cecal isolates of *E. faecalis* or *E. faecium* in 2019.
- *Enterococcus spp.* isolates from all cattle sources in 2019 showed no linezolid resistance and no vancomycin resistance.
- Between 2018 and 2019, MDR in E. faecalis isolates from retail ground beef was stable (around 1%), decreased to zero for beef cattle cecal samples, and decreased from about 5% to 1.3% for dairy cattle cecal samples. For *E. faecium* isolates during the same time period, MDR was stable (< 6%) for retail ground beef and beef cattle cecal samples, and decreased for dairy cattle cecal samples (from 4.4% to 3%).

4.7 Antimicrobial Stewardship in Cattle Production

4.7.1 Introduction

The FDA and other U.S. federal government agencies, as well as state government agencies and national and state veterinary medical associations, support the efforts of bovine veterinarians and producers in actions taken to preserve the effectiveness and availability of antimicrobials for animals and humans. As part of the USDA APHIS NAHMS antimicrobial use study conducted on U.S. feedlots in 2017, some data were collected about antimicrobial stewardship practices during 2016. This section provides a brief summary of some of those

results. The study report should be consulted for complete results (USDA-APHIS, 2019a). In 2021, USDA NAHMS launched the Health Management on U.S. Feedlots 2021 study, which is also intended to include information about antimicrobial use and stewardship on U.S. feedlots. In addition, veterinary and producer associations have actively been developing strategies and taking steps to provide information to veterinarians and producers working with these industries in the U.S. to reduce the need for antimicrobials and to use them judiciously when necessary. While information about all of these organizations' activities is beyond the scope of this report, we provide a few references later in this section.

4.7.2 USDA APHIS NAHMS Antimicrobial Use and Stewardship on U.S. Feedlots, 2017 – Stewardship Information

The NAHMS survey included questions about record-keeping for antimicrobial use, training for employees, periodic facility audits or assessments, using a veterinarian, having a valid veterinarian-client-patient relationship (VCPR), and taking steps to prevent disease. Some of these data are summarized here. Consult the published report for full details. The survey responses are referring to practices in 2016, prior to implementation of FDA GFI #213.

RECORD-KEEPING PRACTICES

Maintaining accurate, thorough, and current records of antimicrobial use and treatment outcomes is a core principle of judicious antimicrobial use (AVMA, 2020). Keeping records on antimicrobial use allows for the evaluation of therapeutic regimens and helps ensure adherence to appropriate withdrawal periods for drugs that have them. In the NAHMS Feedlot Antimicrobial Use Study, for 2016, of the 70.8% of feedlots that gave cattle any antimicrobials in feed, 50% of them 'most of the time' or 'always' recorded the antimicrobial used and over half (53.1%) 'most of the time' or 'always' recorded the date antimicrobial administration began. For the small percentage (8.5%) of feedlots (mostly small feedlots) that administered antimicrobials in water, about one-third of them 'most of the time' or 'always' recorded the antimicrobial used and date use began. For the 14.8% of feedlots that administered injectable antimicrobials to cattle as a group, over 50% of them 'always' recorded the antimicrobial given and date administered. Similarly, of the feedlots that administered injectable antimicrobials to individual sick cattle, over half of them 'always' recorded the antimicrobial given and the date administered.

BEEF QUALITY ASSURANCE

Beef Quality Assurance (BQA) is a national program that offers information about proper management techniques and a commitment to quality within the beef industry. BQA programs focus on education and training cattle producers, farm advisors, and veterinarians on issues related to food safety and quality. In the NAHMS 2017 Antimicrobial Use Survey, producers on 86.4% of all feedlots were familiar with or had heard of the BQA program. Overall, 29.5% of feedlots had a representative attend BQA training in the past 5 years.

USE OF VETERINARIAN SERVICES AND VCPR

Veterinarians help educate producers on appropriate and judicious use of antimicrobials and are vital to designing appropriate disease prevention programs and providing diagnoses. Nearly 80% of all feedlots used the services of a veterinarian in 2016 (100% of large feedlots and 78.1% of small feedlots). Overall, 84.8% of feedlots had a VCPR in place, with a higher percentage of large (98.6%) compared to small feedlots (83.6%).

ANTIMICROBIAL USE DECISIONS

In 2016, of the feedlots that gave any antimicrobials (both medically and non-medically important), about 84% of feedlots indicated that a non-veterinarian owner of the feedlot made decisions about antimicrobial use in feed and about 33% indicated a veterinarian made antimicrobial use decisions. Percentages were similar for other routes of administration.

4.7.3 Other Resources

In 2017, the American Association of Bovine Practitioners (AABP) published a document entitled "Key Elements for Implementing Antimicrobial Stewardship Plans in Bovine Veterinary Practices Working with Beef and Dairy Operations" to provide bovine veterinarians with best practices for designing, implementing, and monitoring antimicrobial stewardship programs with their clients. This supports the objectives of the AVMA's Steering Committee on Judicious Therapeutic Antimicrobial Use to help develop scientific knowledge that will provide the basis for judicious therapeutic antimicrobial use and support educational efforts that promote such use. These efforts will also help to both preserve therapeutic efficacy of antimicrobials and ensure current and future availability of antimicrobials (AVMA, 2020). In 2019, AABP also updated a joint guideline about judicious therapeutic use of antimicrobials in cattle, with the Academy of Veterinary Consultants.

A number of national and state trade and industry associations have also established resources to assist cattle producers and veterinarians with adopting the basic tenets of antimicrobial stewardship; for example, the National Cattlemen's Beef Association (NCBA), the Beef Quality Assurance program, and the National Milk Producers Federation. In addition, a number of organizations involved with the beef and dairy production industries have made public commitments as part of the U.S. government's AMR Challenge.

CHAPTER 5

Antimicrobial Use and Resistance in U.S. Swine Production

5.1 Introduction

5.2 Swine Production in the U.S.

5.3 Swine Health: Examples of Bacterial Diseases

5.4 Antimicrobial Sales and Biomass-Adjusted Antimicrobial Sales Estimates for Swine

5.5 Antimicrobial Use in Swine

5.6 Antimicrobial Resistance in Swine and Retail Pork

5.7 Antimicrobial Stewardship in Swine Production

5.1 Introduction

Swine play a significant role in the production of food for human consumption, due in part to their adaptability as a species to a wide range of environmental conditions. Globally, the swine industry is very dynamic and changes along with external forces that shape agricultural practices. The current trend is toward a fewer number of producers, responsible for larger numbers of pigs. Provision of optimal facilities, genetics, nutrition, and health programs for pigs helps maintain the ability to provide high quality protein for human consumption while also addressing issues such as environmental responsibility, food safety, and animal welfare. Worldwide, pork production is the second largest meat industry, behind poultry (FAO, 2021a).

Along with the global trend for fewer producers, the number of U.S. hog farms declined by more than 70% over the past two decades, while hog production rose by more than 30%. The result has been an industry with larger operations, increased specialization in a single phase of production, greater reliance on purchased feed (rather than feed grown on the farm), and an increased reliance on formal contracts that connect farmers and packers to coordinate production (USDA-ERS, 2020a). Technological innovation has also been a driving force behind the industry's structural shift and has contributed to substantial increases in hog farm productivity (USDA-ERS, 2013).

5.2 Swine Production in the U.S.

Detailed information about swine populations, production practices, and economic indicators are routinely or periodically published by USDA agencies, including the USDA Economic Research Service (ERS), the USDA National Agricultural Statistics Service (NASS), and the USDA Animal and Plant Health Inspection Service (APHIS), which conducts studies through the National Animal Health Monitoring System (NAHMS). Reports on these agency websites should be consulted for more information. In this section, we briefly summarize recent published information about U.S. swine production to provide some context for populations and antimicrobial use practices discussed later in the chapter.

The U.S. is the world's third-largest producer and consumer of pork and pork products (USDA-ERS, 2019). In recent years, the U.S. has been either the world's largest or second largest exporter of pork and pork products, with exports averaging over 20% of commercial pork production in most years (USDA-ERS, 2019). As of December 1, 2019 the U.S. inventory of all hogs and pigs was 77.3 million head, up 3% from the previous year (USDA-NASS, 2019). USDA defines 'hogs' as mature swine and 'pigs' as young hogs weighing less than 120 pounds (USDA-NASS, 2015). In 2019, Iowa was the state with the highest inventory of hogs and pigs, followed by North Carolina and Minnesota (USDA-NASS, 2020a). Pork meat production in the U.S. totaled 27.7 billion pounds in 2019, up 5% from the previous year (USDA-NASS, 2020c). According to the most recent food availability data published by USDA ERS, the availability (a proxy measure for consumption) of pork to consumers in the U.S. was 49 pounds (boneless) per capita in 2019 (USDA-ERS, 2021c).

Hog production can generally be divided into four phases: (1) breeding of sows and maintaining them during gestation; (2) farrowing (the process of birth to weaning at approximately 3 weeks of age); (3) the nursery phase, which includes the care of pigs immediately after weaning until about 60 pounds; and (4) finishing, which includes feeding pigs from about 60 pounds to a slaughter weight of 225-300 pounds. While most hog production once occurred on farrow-to-finish operations that raised animals from birth to market, many operations now specialize in specific phases of production; for example, 'farrow-to-finish' operations cover all phases, while 'grower-finisher' operations cover only phase 4. According to the USDA National Animal Health Monitoring System (NAHMS) Swine 2012 survey, over half (56%) of sites had a grower-finisher phase, and of those sites, about 43% of them specialized in that phase only (USDA-APHIS, 2015). Swine operations producing under contract are typically larger than independent operations and are more likely to specialize in one phase of production. The increased use of production contracts is largely related to improved efficiency and lower production costs (USDA-ERS, 2015).

5.3 Swine Health: Examples of Bacterial Diseases

Bacterial diseases in swine may affect any body system, but often affect the respiratory, enteric (intestinal), and reproductive systems. An extensive review of these is beyond the scope of this report; however, **Table 5-1** shows some examples of bacterial pathogens of swine and associated disease processes – it is not intended to be an exhaustive list of all potential bacterial diseases of swine. Veterinary and swine health references can be consulted for detailed information about bacterial diseases of swine including disease epidemiology, risk factors, diagnosis, prevention, and therapeutic management. Also shown in Table 5-1 are examples of antimicrobials which are currently approved for use in swine for therapy of these infections. Some of the drugs are approved only for certain production classes of swine (e.g., sows, grower-finisher, etc.). Table 5-1 is not intended to be an exhaustive list of all bacterial pathogens of swine and all approved antimicrobials for swine, but rather to provide examples. AnimalDrugs@FDA can be searched to find specific drug products with approved label information. Not all approved drugs are currently marketed in the U.S. Animal drug sponsors (i.e., pharmaceutical companies) decide what products they will manufacture and market at any given time. As discussed in Appendix 3, veterinarians may legally prescribe extralabel uses of approved animal drugs under specific conditions. Table 5-1 is not intended to capture legal extralabel use of approved antimicrobials.

Table 5-1: Examples of bacterial pathogens of swine and examples of FDA-approved antimicrobials for therapy of these infections

Bacterial Pathogen(s)	Disease Process(es)	Examples of FDA-Approved Therapeutic Antimicrobials[1,2]
Actinobacillus pleuropneumonia	Respiratory Disease/Pneumonia	Florfenicol; Ceftiofur; Enrofloxacin; Tilmicosin; Tulathromycin; Tiamulin[3]; Tetracycline; Chlortetracycline
Bordetella bronchiseptica	Respiratory Disease	Florfenicol; Enrofloxacin; Tulathromycin; Tylvalosin
Brachyspira hyodysenteriae	Swine Dysentery	Gentamicin; Lincomycin; Tylosin; Tiamulin[3]; Bacitracin Methylene Disalicylate (BMD)[3]; Virginiamycin
Clostridium perfringens	Enteritis	Bacitracin Methylene Disalicylate (BMD)[3]
Erysipelothrix rhusiopathiae	Erysipelas/Skin Lesions/Arthritis	Tylosin; Penicillin
Escherichia coli	Enteritis/Septicemia	Gentamicin; Neomycin; Spectinomycin; Streptomycin; Apramycin; Enrofloxacin; Avilamycin[3]; Amoxicillin; Ampicillin; Sulfachlorpyridazine; Sulfamethazine; Tetracycline; Chlortetracycline; Oxytetracycline
Haemophilus parasuis	Respiratory Disease/Pneumonia; Arthritis; Meningitis	Ceftiofur; Enrofloxacin; Tilmicosin; Tulathromycin; Tylvalosin; Chlortetracycline
***Klebsiella* spp.**	Respiratory Disease/Pneumonia	Tetracycline; Chlortetracycline
Lawsonia intracellularis	Porcine Proliferative Enteritis/Ileitis	Lincomycin; Tylvalosin; Tylosin; Tiamulin[3]; Chlortetracycline
***Leptospira* spp.**	Reproductive Disease/Abortions	Dihydrostreptomycin; Oxytetracycline; Chlortetracycline
Mycoplasma hyopneumoniae	Respiratory Disease/Pneumonia	Enrofloxacin; Lincomycin; Tilmicosin; Tulathromycin; Tylosin
Mycoplasma hyosynoviae	Infectious Arthritis	Lincomycin
***Pasteurella multocida*; *Pasteurella* spp.**	Respiratory Disease/Pneumonia	Florfenicol; Ceftiofur; Enrofloxacin; Tilmicosin; Tulathromycin; Tylvalosin; Tylosin; Ampicillin; Sulfamethazine; Tetracycline; Chlortetracycline; Oxytetracycline
***Salmonella* Choleraesuis; *Salmonella* spp.**	Enteritis; Respiratory Disease	Streptomycin; Florfenicol; Ceftiofur; Ampicillin; Sulfaethoxypyridazine; Chlortetracycline; Oxytetracycline
Streptococcus suis	Respiratory Disease/Pneumonia; Arthritis; Meningitis	Florfenicol; Ceftiofur; Enrofloxacin; Tylvalosin; Ampicillin
***Streptococcus* (Group E)**	Cervical Lymphadenitis (Jowl Abscesses)	Sulfamethazine; Chlortetracycline

1 See AnimalDrugs@FDA for information about approved antimicrobials, including specific indications, dose, duration, approved production classes, limitations, and approved combination products.
2 Not all antimicrobials are currently marketed.
3 Not currently considered a medically important antimicrobial according to Appendix A of GFI #152.

5.4 Antimicrobial Sales and Biomass-Adjusted Antimicrobial Sales Estimates for Swine

5.4.1 Introduction

In this section, information is presented about antimicrobial sales and distribution estimates for swine. These data are not necessarily indicative of how the antimicrobials were actually administered to or used in swine (e.g., for what indications, doses, or durations). Antimicrobial use information (i.e., record of on-farm administration) is helpful to determine what disease pressures exist and could help inform stewardship practices, as discussed later in this chapter. The overall amount of antimicrobials sold and used in swine is expected to change from year to year and will depend on multiple factors, including swine populations and disease pressures faced each year.

In order to further characterize the species-specific antimicrobial sales and distribution estimates, a biomass denominator adjustment is also included in this section. This allows for a representation of trends in annual antimicrobial sales and distribution relative to the estimated swine population in the U.S. in which the antimicrobials could be used.

5.4.2 Medically Important Antimicrobial Sales and Distribution Estimates for Swine

Table 5-2 shows the species-specific sales and distribution estimates, by medically important antimicrobial drug class, reported by antimicrobial drug sponsors for swine for 2016 through 2019, as well as the percent change in these estimates between time periods. Only the following drug classes can be shown for all four years because they had at least three drug sponsors and had species-specific estimates for swine: aminoglycosides, lincosamides, macrolides, sulfonamides, and tetracyclines. Fluoroquinolones are shown for 2019 only, because prior to that time, fluoroquinolone sales were not independently reportable for swine. Similarly, penicillin sales are shown only for 2016, because that is the last year sales were independently reportable for that drug class for swine. Other medically important drug classes that may have had drug sales for swine include amphenicols, cephalosporins, and streptogramins. However, these are not independently reported classes for swine (due to lack of three or more drug sponsors), so data cannot be shown in order to protect confidential business information of drug sponsors.

The majority of medically important antimicrobial sales estimated by drug sponsors for swine each year for 2016 through 2019 were for tetracyclines. **Figure 5-1** contains the same sales information as Table 5-2, but visually demonstrates the magnitude of the tetracycline class compared to the other medically important antimicrobial classes. As noted in Appendix 3, GFI #213 was completely implemented as of January 1, 2017. Between 2016 and 2017, total medically important antimicrobial sales estimated for swine decreased by about 35%. With the exception of lincosamides, there were overall decreases in all classes for which data can be shown, between 2016 and 2017. There were increases in most medically important antimicrobial classes (except lincosamides, which showed a decrease), between 2017 and 2018, with a small increase (about 17%) in the overall total. There were also increases in most medically important antimicrobial classes between 2018 and 2019, with a small increase (about 9%) in the overall total. The percent change in sales comparing 2016 and 2019 still indicates an

overall decrease of nearly 18% in total estimated sales for swine. Since the requirement for drug sponsors is only to provide estimated species-specific antimicrobial drug sales and distribution for the four major food-producing species, it is not possible to further break down the sales and distribution estimates into the various swine production classes (e.g., nursery pigs, grower-finishers, sows, etc.).

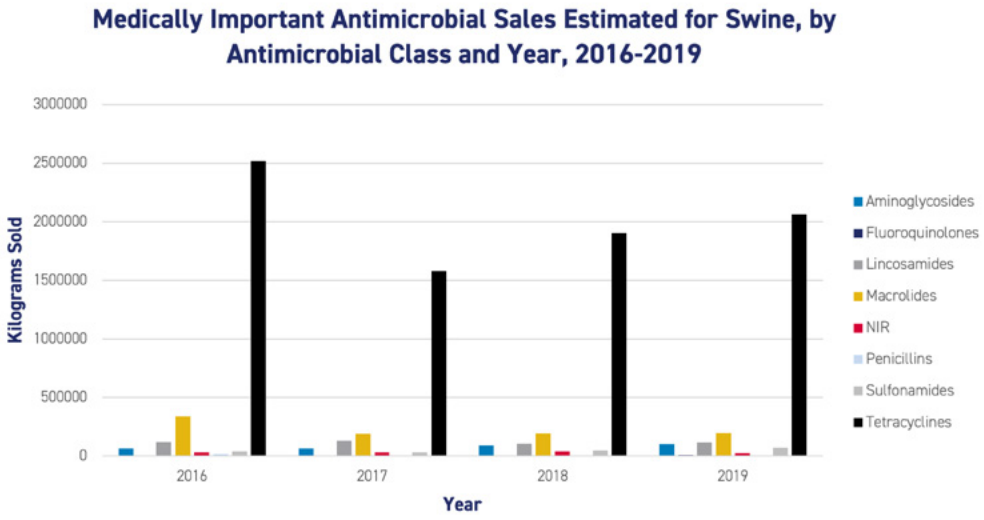
Table 5-2: Medically important antimicrobial sales and distribution estimates for swine by reportable drug class, 2016-2019

Medically Important Antimicrobial Drug Class	2016 Estimated Annual Sales Totals for Swine (kg)	2017 Estimated Annual Sales Totals for Swine (kg)	2018 Estimated Annual Sales Totals for Swine (kg)	2019 Estimated Annual Sales Totals for Swine (kg)	Overall Percent Change in Sales from 2016 to 2017	Overall Percent Change in Sales from 2017 to 2018	Overall Percent Change in Sales from 2018 to 2019	Overall Percent Change in Sales from 2016 to 2019
Aminoglycosides	65,850	63,602	90,708	101,270	-3.4%	42.6%	11.6%	53.8%
Fluoroquinolones	*	*	*	11,790	---	---	---	---
Lincosamides	118,916	128,642	104,527	114,398	8.2%	-18.7%	9.4%	-3.8%
Macrolides	337,295	189,503	192,175	195,441	-43.8%	1.4%	1.7%	-42.1%
Penicillins	17,958	*	*	*	---	---	---	----
Sulfonamides	40,215	31,024	45,581	72,126	-22.9%	46.9%	58.2%	79.4%
Tetracyclines	2,520,680	1,579,145	1,902,950	2,062,275	-37.4%	20.5%	8.4%	-18.2%
NIR[1]	32,348	31,016	38,336	25,099	-4.1%	23.6%	-34.5%	-22.4%
Total	3,133,262	2,022,932	2,374,277	2,582,399	-35.4%	17.4%	8.8%	-17.6%

1 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For swine, drug classes which cannot be shown in order to protect confidential business information are Amphenicols, Cephalosporins, Fluoroquinolones (for 2016-2018), Streptogramins, and Penicillins (for 2017-2019). The value of sales for this category was therefore calculated as the overall annual sales total for swine minus the sum of all reportable classes for that year. The individual drug classes within the NIR category may or may not have had actual sales in any given year. Penicillin sales may be included in the NIR category for 2017-2019 and Fluoroquinolone sales may be included in the NIR category for 2016-2018.

*Where drug class sales are not independently reportable for each comparison year, percent change in sales cannot be calculated.

Figure 5-1: Medically important antimicrobial sales and distribution estimates for swine, by antimicrobial class and year, 2016-2019



*NIR: Antimicrobial classes for swine which are not individually reportable in order to protect confidential business information – may include amphenicols, cephalosporins, fluoroquinolones (2016-2018 only), penicillins (2017-2019 only), and streptogramins.

5.4.3 Biomass-Adjusted Medically Important Antimicrobial Sales and Distribution Estimates for Swine

Appendix 4 shows the estimated annual population and weight in kilograms (kg) for each category of swine for 2016 through 2019. Using these data, the biomass total calculated for swine (including all categories) was approximately 16.2 billion kg in 2016, approximately 16.6 billion kg in 2017, approximately 17.1 billion kg in 2018, and approximately 17.9 billion kg in 2019, representing about a 10.9% increase in estimated U.S. swine biomass between 2016 and 2019.

Using the estimated annual total sales for medically important antimicrobials by drug class (in mg) for swine and estimated annual swine biomass (target animal biomass [TAB], in kg), **Table 5-3** shows the biomass-adjusted medically important antimicrobial sales and distribution data for swine, by drug class and year. Table 5-3 also indicates the percent change for each reportable drug class between time periods. Of the five antimicrobial classes which can be reported for all four years, three (lincosamides, macrolides, tetracyclines) showed a decreased mg/TAB value comparing 2016 to 2019, while two (aminoglycosides and sulfonamides) showed an increase. There was a nearly 26% decrease in the overall mg/TAB value between 2016 and 2019.

Table 5-3: Biomass-adjusted medically important antimicrobial sales and distribution estimates for swine, by reportable drug class, 2016-2019

Medically Important Antimicrobial Drug Class	2016 Estimated mg/TAB for Swine	2017 Estimated mg/TAB for Swine	2018 Estimated mg/TAB for Swine	2019 Estimated mg/TAB for Swine	Percent Change[1] in mg/TAB 2016 - 2017	Percent Change[1] in mg/TAB 2017 - 2018	Percent Change[1] in mg/TAB 2018 -2019	Percent Change[1] in mg/TAB 2016 - 2019
Aminoglycosides	4.06	3.83	5.30	5.64	-5.9%	38.5%	6.4%	38.6%
Fluoroquinolones	*	*	*	0.66	---	---	---	---
Lincosamides	7.34	7.74	6.11	6.37	5.5%	-21.1%	4.3%	-13.3%
Macrolides	20.82	11.40	11.23	10.88	-45.2%	-1.5%	-3.1%	-47.8%
Penicillins	1.11	*	*	*	---	---	---	---
Sulfonamides	2.48	1.87	2.66	4.01	-24.8%	42.6%	50.7%	61.7%
Tetracyclines	155.58	95.01	111.16	114.75	-38.9%	17.0%	3.2%	-26.2%
NIR[2]	2.0	1.87	2.24	1.40	-6.5%	20.0%	-37.6%	-30.0%
Total[1]	193.39	121.71	138.69	143.69	-37.1%	14.0%	3.6%	-25.7%

1 Calculations of the totals and the percent change were performed using the raw (unrounded) data for estimated mg/TAB. Calculations using the rounded numbers in this table will not yield exactly the same result.

* Penicillin class sales for 2017-2019 and Fluoroquinolone class sales for 2016-2018 are not reportable due to confidential business rule; therefore, percent change in sales cannot be calculated.

2 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For swine, drug classes which cannot be shown in order to protect confidential business information are Amphenicols, Cephalosporins, Fluoroquinolones (for 2016-2018), Streptogramins, as well as Penicillins (for 2017-2019). The value of sales for this category used in the mg/TAB calculation was therefore calculated as the overall annual sales total for swine minus the sum of all reportable classes. The individual drug classes within the NIR category may or may not have had actual sales in any given year. The swine biomass denominator is applied to the NIR category as a whole; therefore does not account for potential exclusions of swine categories for the denominator that may otherwise apply to individual NIR classes.

Table 5-4 shows the comparison of percent change in species-specific estimated sales volume (kg) and the percent change in biomass-adjusted species-specific estimated sales (mg/TAB) between 2016 and 2019 for swine. With the approximately 10.9% increase in estimated swine biomass between 2016 and 2019, the biomass denominator adjustment resulted in a variable degree of difference in the percent change in mg/TAB relative to the percent change in species-specific estimated sales volume (kg) for antimicrobial drug classes which can be reported.

Table 5-4: Percent change in estimated sales and distribution data for swine in sales volume (kg) and adjusted by a biomass denominator (mg/TAB), between 2016 and 2019

Medically Important Antimicrobial Drug Class	Percent Change in Species-Specific Estimated Sales Volume from 2016 to 2019	Percent Change in Biomass Adjusted Species-Specific Estimated Sales (mg/TAB) from 2016 to 2019
Aminoglycosides	53.8%	38.6%
Fluoroquinolones	*	*
Lincosamides	-3.8%	-13.3%
Macrolides	-42.1%	-47.8%
Penicillins	*	*
Sulfonamides	79.4%	61.7%
Tetracyclines	-18.2%	-26.2%
NIR[1]	-22.4%	-30.0%
Total	-17.6%	-25.7%

1 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For swine, drug classes which cannot be shown in order to protect confidential business information are Amphenicols, Cephalosporins, Fluoroquinolones (for 2016-2018), Streptogramins, and Penicillins (for 2017-2019). The individual drug classes within the NIR category may or may not have had actual sales in any given year. The swine biomass denominator is applied to the NIR category as a whole; therefore does not account for potential exclusions of swine categories for the denominator that may otherwise apply to individual NIR classes.

*Penicillin class sales for 2017-2019 and Fluoroquinolone class sales for 2016-2018 are not reportable due to confidential business rule; therefore, percent changes in sales and mg/TAB between 2016 and 2019 cannot be calculated for these classes.

5.5 Antimicrobial Use in Swine

5.5.1 Introduction

Nationally-representative and continuously collected data on antimicrobial use in swine in the U.S. are not currently publicly available. Some information about antimicrobial use in swine has been collected and published by USDA APHIS through periodic studies conducted by NAHMS. Swine studies were conducted by USDA NAHMS in 1990, 1995, 2000, 2006, 2007 (small enterprise study), and 2012. NAHMS is conducting a swine study in 2021 which will focus on both small and large swine enterprises in the U.S. Complete reports from these studies, including questionnaires, survey methodology and results are available on the USDA APHIS NAHMS website.

In this section, data are presented from two recent efforts that the U.S. government undertook to obtain antimicrobial use and stewardship information: the USDA NAHMS Antimicrobial Use and Stewardship on U.S. Swine Operations study conducted in 2017 (for collection of 2016 antimicrobial use information from swine operations), and part of an FDA cooperative agreement awarded in 2016 for collection of on-farm antimicrobial use information for swine.

5.5.2 USDA APHIS NAHMS Antimicrobial Use and Stewardship on U.S. Swine Operations, 2017

In 2017, USDA NAHMS, in collaboration with USDA NASS, conducted a national study focusing on how antimicrobials are used on swine operations in the U.S. (USDA-APHIS, 2020a). The study represented the first time that NAHMS conducted an in-depth look at antimicrobial use and stewardship practices on U.S. swine sites. As part of past national swine studies conducted in 1995, 2000, 2006, and 2012, NAHMS collected limited information on antimicrobials used on U.S. swine operations.

The 2017 study focused on how antimicrobials were used on U.S. swine sites from July 1 through December 31, 2016, before FDA completed implementation of GFI #213 on January 1, 2017. As such, some medically important antimicrobials were still used for swine production purposes (i.e., growth promotion and increased feed efficiency) in 2016. These data may be useful as part of a baseline for comparison in future studies of antimicrobial use on swine operations. The planned NAHMS Swine 2021 study on swine health and management practices is expected to incorporate some information about antimicrobial use and stewardship and may provide additional data to analyze trends in antimicrobial use and animal health in this sector.

The 2017 study's target population included all swine operations with nursery, wean-to-finish, and/or grower-finisher phases and with 1,000 or more market pigs. The study was conducted in 13 top swine-producing states, which represented 92.1% of the U.S. swine inventory and 93.8% of U.S. swine sites with 1,000 or more pigs in 2016. Swine sites were categorized for this study based on their capacity: small (1,000-1,999 pigs), medium (2,000-4,999 pigs), and large (5,000 or more pigs).

Antimicrobials used in feed and water were the main focus of the 2017 NAHMS study, although limited information about injectable antimicrobials was also reported. **Table 5-5** shows the percentage of sites in the study that administered market pigs any medically important or non-medically important antimicrobials in 2016, by route of administration and by site size. Some of the main findings from this study are provided below the table.

Table 5-5: Antimicrobial (medically and non-medically important) administration, by route and size of site, 2016

Route of Administration	Percent Sites, by Size							
	Small Sites (1,000-1,999 head)		Medium Sites (2,000-4,999 head)		Large Sites (5,000 head or more)		All Sites (1,000 head or more)	
	Percent	Standard Error	Percent	Standard Error	Percent	Standard Error	Percent	Standard Error
Feed – any antimicrobial (medically and not medically important)	94.1	(3.3)	91.6	(2.2)	97.9	(1.4)	93.5	(1.6)
Feed- medically important antimicrobials	87.6	(5.6)	87.0	87.0	94.0	(3.0)	88.6	(2.9)
Water – any antimicrobial (medically and not medically important)	71.3	(10.6)	84.8	(3.5)	71.7	(8.4)	78.4	(4.9)
Water- medically important antimicrobials	71.3	(10.6)	83.0	(4.2)	64.2	(7.6)	76.0	(5.5)
Injection	89.6	(4.8)	93.2	(2.3)	94.4	(3.1)	92.4	(2.0)
All antimicrobials (medically and not medically important), any route	100.0	(--)	95.4	(2.1)	100.0	(--)	97.6	(1.3)

Source: USDA NAHMS: Antimicrobial Use and Stewardship on U.S. Swine Operations, 2017 (Table B.1 and B.2.)

The 2017 NAHMS Swine Antimicrobial Use study collected information primarily for nursery-age pigs and grower-finisher pigs. The study defined nursery-age pigs as those that are weaned and weigh from 13 to 60 pounds. These pigs could be housed in a nursery unit or a wean-to-finish unit. Grower-finisher pigs were defined for the study as those that are about 9 weeks old and weigh approximately 60 pounds when they enter the grower-finisher phase. These pigs might be housed in a grower-finisher unit or a wean-to-finish unit until they reach market weight (usually about 280 pounds) and are shipped for slaughter at about 25 weeks of age. In this study, 68.1% of sites had nursery-age pigs, and 80.8% of sites had grower-finisher pigs.

Some key findings of the study (for antimicrobial use in 2016) included:

- 88.6% of all sites in the study administered medically important antimicrobials in feed and 76% of all sites administered medically important antimicrobials in water.
- Of sites that had nursery-age pigs, 83.9% gave medically important antimicrobials in feed and the most common reasons for use were for therapy of diarrhea (i.e., bacterial enteritis, ileitis, etc.) and therapy of bacterial pneumonia.
- Of sites that had grower-finisher pigs, 77.8% gave medically important antimicrobials in feed and the most common reason for use was for therapy of bacterial pneumonia.

- Chlortetracycline (for bacterial pneumonia) was the most commonly used medically important antimicrobial in feed for both nursery-age and grower-finisher pigs.
- Tiamulin and carbadox were the most commonly used non-medically important antimicrobials in feed for nursery-age pigs and were used primarily for therapy of diarrhea (carbadox) and respiratory disease (tiamulin). For grower-finisher pigs, bambermycins (for growth promotion) and tiamulin (in combination with chlortetracycline for respiratory disease and/or diarrhea) were the most commonly used non-medically important antimicrobials used.
- 45.5% of sites with nursery-age pigs gave medically important antimicrobials in water and the main reason for use was for therapy of bacterial pneumonia, therapy of diarrhea (i.e., bacterial enteritis, ileitis), and bacterial meningitis/polyserositis/arthritis.
- Of sites that had grower-finisher pigs, about 57% gave medically important antimicrobials in water and the most common reason for use was for therapy of bacterial pneumonia.
- Gentamicin (for diarrhea), penicillin (for meningitis), and oxytetracycline (for bacterial pneumonia) were the most commonly administered antimicrobials administered to nursery-age pigs in water.
- Oxytetracycline and lincomycin (both for bacterial pneumonia) were the most common antimicrobials administered to grower-finisher pigs in water.
- Approximately 92% of sites administered injectable medically important antimicrobials. No additional information about injectable antimicrobials was collected for this study.

Details of the conduct, methodology, and complete results (including standard errors, etc.) of the study can be found in the published report (USDA-APHIS, 2020a).

5.5.3 FDA Cooperative Agreement: Characterizing Antimicrobial Use in Swine

Chapter 3 described the Funding Opportunity Announcement that FDA issued in 2016, announcing the availability of grants in the form of cooperative agreements to develop and pilot methodologies for collecting and reporting antimicrobial use data in the four major food-producing species at the farm level. One of the grants (5U01FD005878) was awarded for the collection and reporting of antimicrobial use data in poultry and swine. This section describes the portion of the grant aimed at characterizing antimicrobial use in U.S. swine.

The primary goal of the overall project was to explore options for antimicrobial use monitoring in poultry and swine production systems, with a long-term goal of informing and supporting the continued advancement of antimicrobial stewardship within U.S. poultry and swine production systems. A specific aim of the project related to swine was to develop and pilot methodologies for implementation of an antimicrobial use data collection program in U.S. swine production. Components of this specific aim included the following activities:

1. Establishment of an expert committee to guide swine industry efforts on antimicrobial use and surveillance, including the development of methodologies to collect, summarize, and report antimicrobial use data and to protect confidential information;
2. Identification and description of existing swine industry data resources on antimicrobial use;
3. Assessment of biases inherent in existing industry data sources in relation to the national industry; identification of gaps in existing sources and evaluation of potential mechanisms to address data gaps; and
4. Collection and analysis of baseline data on antimicrobial use in a sample of swine production systems in the U.S.

With respect to the first three components above, the study investigators' initial activities in the first year of the project were focused on determining the extent of potentially existing antimicrobial use data in U.S. swine production systems, and communicating with the swine industry to determine the likely hurdles to establishment of a voluntary data collection system. The expert group discussed issues related to the feasibility of various data collection options, industry communication and collaboration, data confidentiality issues, and metrics for reporting. Differences in the breeding and growing phases of the industry, which are largely segregated, were considered and while both phases were considered important, growing pigs were determined to be a higher priority since it was thought that most use of antimicrobials is likely within this segment of production.

With regard to the most useful metrics for reporting of swine antimicrobial use data, it was determined that different levels of data granularity serve different purposes. For example, the lowest level of granularity would be collecting information at a swine production system level, by drug product, stratified by route of administration and production phase (e.g., nursery, grower-finisher). The primary metric would be weight of the drug product with a denominator of number of pigs marketed or weight of pigs marketed. The key purpose for collecting data at this level of granularity would be to report broad estimates of antimicrobial use by drug class and route in relation to overall production. This type of data was the focus of the first two years of data collection for the cooperative agreement project. A second level of granularity would be to obtain retrospective data from random samples of sites within swine production systems by production phase. The primary purpose for this type of data would be for benchmarking within and between production systems and to examine variability in antimicrobial use by production phase. Finally, a third level of granularity would likely provide the greatest value for understanding antimicrobial use practices and supporting antimicrobial stewardship initiatives. This level would be collection of actual antimicrobial use information (i.e., doses administered to pigs), in addition to data on age at administration, reasons for use, duration of use, and outcomes. These latter two levels of granularity may be explored through different mechanisms yet to be determined.

Specific records of antimicrobial administration on swine farms are often kept on paper and not readily accessible electronically, so the data collected in this project were derived from participating swine company accounting records of antimicrobial distribution to farms. This leads to lack of some details on dose, reasons for use, and duration, all of which are important elements to consider when assessing antimicrobial stewardship. Ongoing efforts are being directed at expanding participation in the project to increase representativeness and to collect additional information, including data on age at administration, dose, reason for use, and duration of use.

The next sections summarize some of the results for the swine antimicrobial use data collected during the first two years (2016-2017) of the cooperative agreement pilot project. Recently, investigators published detailed reports about the results for the first two years of data collection (Davies and Singer, 2020). Data collection is ongoing, and CVM expects to publish a more complete summary of the cooperative agreement results after the conclusion of the projects. In addition, CVM will use information gained from the cooperative agreement pilot projects to help inform development of a long-term strategy to support continued antimicrobial use data collection.

5.5.3.1 SWINE ANTIMICROBIAL USE DATA (2016-2017)

Seventeen large swine production companies (also called 'systems') were initially approached by the primary investigator, through direct personal contacts who were mostly swine veterinarians employed by the companies. All expressed interest in participating and 11 companies indicated willingness to participate in the first phase of the project. Ten systems eventually entered formalized non-disclosure agreements to ensure the confidentiality of the data, although one of these subsequently withdrew, leaving a total of nine large swine production companies which contributed data for 2016 and 2017. The combined production of these nine collaborating systems was over 20 million pigs each year, or approximately 20% of national production. As such, the antimicrobial use data described are not necessarily representative of the entire U.S. swine industry.

In addition to data collection from farms, a survey was administered to veterinarians with oversight of the participating systems to obtain some limited information about patterns of antimicrobial use, such as age at administration, distribution of use by production phase, and indications for use.

Methods – Data Collection from Records

The primary investigator met with relevant personnel of each participating system and provided a brief description of data needs with respect to antimicrobial use (active ingredient, weight of active ingredient, and route of administration), target population (growing pigs from wean to market, and live or carcass weight of pigs sold), and time frame (calendar year 2016 forward).

In order to minimize work burden on the companies providing the data, and recognizing the diversity of records systems utilized, companies were asked to provide the data in formats that fulfilled the data needs as much as possible with minimal disruption to staff. Therefore, the level of granularity in the data varied broadly across the nine systems. For example, antimicrobial use data may have been provided as aggregated annual use across an entire system, broken down by phase of pig growth (e.g., nursery, grower-finisher), broken down by individual lots (groups) of pigs, and/or with more detailed data such as date of treatment and numbers of pigs treated. In most instances, the amounts of antimicrobials were derived from cost accounting records and not from records of actual administration (with the exception of one participating system). Therefore, they generally represent maximal estimates of amounts administered in feed, water, or by injection.

None of the systems provided data in exactly the same format, so data from each system were standardized by the study investigators for aggregation and analysis. Standardized data fields included antimicrobial product, weight of active ingredient, route of administration, calendar year, and live weights of pigs marketed. Active ingredients were also classified by antimicrobial class and medical importance (as defined by Appendix A of FDA GFI #152). Data were screened for potential inconsistencies or outliers and confirmed with participants.

Methods – Data Collection from Surveys

Study investigators developed and administered an on-line survey to the veterinarians with oversight of

the nine participating swine companies. The survey was designed to capture some information about age at administration, indications for use, and distribution of antimicrobial use across different production phases. Since the survey responses were based on the swine veterinarians' expert opinions and general perceptions about antimicrobial use practices in these nine systems (i.e., not based on specific data), the results were described as 'perceived use.'

Measurements of Antimicrobial Use

The study investigators summarized aggregate data both qualitatively and quantitatively for 2016 and 2017. Patterns of use reported included the proportion of systems using, relative use by route, and means and medians of use in milligrams per pound (mg/lb) of live weight marketed. Analyses were structured on an active ingredient basis to report the patterns of use of individual drugs across the aggregate population, and not by the aggregate weight of all antimicrobials used at a system level.

Qualitative analysis described the relative use of antimicrobials at the levels of individual active ingredient, antimicrobial class, and FDA classification (i.e., GFI #152 Appendix A) of medical importance. Relative use by route of administration was also included. Quantitative analysis used the weight of active ingredients as the numerator (mg) and estimated live weight of pigs (pounds) as the denominator. In cases where use of combination products was reported as a single amount, use was separated into the weight of each ingredient based on the product label. Means and medians were calculated to summarize quantitative use at a system level. Overall means (i.e., total amount used across all systems divided by total live weight across all systems) were not calculated. This was because the small number of systems and the large range in size of the systems caused means to be overly influenced by use in the largest systems.

Results – Qualitative

Table 5-6 shows the relative use (i.e., percent of total use of antimicrobials) by drug class for each year, for the nine participating swine systems. Both medically important and non-medically important antimicrobial classes are included in the table. The number of systems using each class is also shown. Tetracyclines represented the largest relative use for both years, at 61.9% of total use in 2016 and decreasing to 57.6% in 2017. While it is tempting to compare the numbers in the table from year to year, the main point is that tetracyclines accounted for most antimicrobial use on the nine participating swine farms, for both 2016 and 2017. Small increases or decreases in most other antimicrobial classes may or may not be significant, since choice of antimicrobials used varies widely across the nine systems and may depend on a number of variables, such as types of disease pressures, changes in population, or shifts in production classes. Factors related to antimicrobial drug products are also important to choice of drug used, such as availability and cost of approved antimicrobials, specific indications approved, and spectrum of activity.

Table 5-6: Relative use of antimicrobials, by antimicrobial class and year, 2016 and 2017

Antimicrobial Class	2016		2017	
	Percent of Total Antimicrobial Use	# of Systems Using	Percent of Total Antimicrobial Use	# of Systems Using
Medically Important Antimicrobial Classes				
Aminocyclitols	0.13	2	0.003	1
Aminoglycosides	3.0	9	4.1	9
Beta-lactams	6.3	9	7.8	9
Cephalosporins	0.15	9	0.11	9
Lincosamides	8.2	9	9.0	9
Macrolides	3.3	9	3.2	9
Phenicols	0.002	5	0.014	4
Potentiated Sulfonamides	0.20	2	0.75	5
Quinolones	0.23	9	0.46	9
Streptogramins	1.2	3	0.0001	1
Sulfonamides	0.6	2	0.8	3
Tetracyclines	61.9	9	57.6	9
Not Medically Important Antimicrobials				
Bambermycins	0.001	1	N/A	0
Ionophores	2.8	2	3.4	1
Orthosomycins	0.06	3	0.9	4
Pleuromutilins	5.3	9	4.7	9
Polypeptides	5.6	5	6.0	2
Quinoxalines	1.0	6	1.1	7

Source: Davies PR and Singer RS. Antimicrobial use in wean to market pigs in the United States assessed via voluntary sharing of proprietary data. *Zoonoses and Public Health* 2020; 67 (Suppl. 1): 6-21.

With regard to route of administration, across all systems in 2016, 70.5% of antimicrobials by weight were administered in feed, 27.5% in water, and 1.9% by injection. Similar percentages were seen in 2017: 67.8% were administered in feed, 30.1% in water, and 2.1% by injection.

Table 5-7 shows the relative use at the active ingredient level for 2016 and 2017 for the top 10 medically important antimicrobials used. Chlortetracycline and oxytetracycline represented the most used antimicrobials. As noted for Table 5-6 above, the small increases or decreases between 2016 and 2017 are not the primary take-away here. Rather, it mainly indicates that four drugs (chlortetracycline, oxytetracycline, lincomycin, and penicillin) accounted for about 75% of medically important antimicrobial use on the participating swine farms, and the remaining drugs contributed very little to use during these two years.

Table 5-7: Relative medically important antimicrobial use, by active ingredient and year, 2016 and 2017

Antimicrobial	Percent of Total Antimicrobial Use	
	2016	2017
Chlortetracycline	49.3	40.9
Oxytetracycline	12.5	16.6
Lincomycin	8.2	9.0
Penicillin	5.8	7.5
Neomycin	2.9	4.0
Tylosin	1.6	0.2
Virginiamycin	1.2	0.0001
Tylvalosin	0.9	0.9
Tilmicosin	0.7	2.2
Sulfamethazine	0.6	0.7

Source: Davies PR and Singer RS. Antimicrobial use in wean to market pigs in the United States assessed via voluntary sharing of proprietary data. *Zoonoses and Public Health* 2020; 67 (Suppl. 1): 6-21.

Results – Quantitative

Quantitative analysis expressed the use of individual antimicrobials (active ingredients) in relation to a biomass denominator (live weight of pigs marketed, in kg) in each system for each year. **Table 5-8** shows the means and medians in mg/kg live weight for medically important antimicrobials. The number of systems using each antimicrobial is also shown.

Table 5-8: Means and medians in mg/kg live weight, for medically important antimicrobials, by active ingredient (in alphabetical order) and year, 2016 and 2017

Antimicrobial	Antimicrobial Class	2016			2017		
		Mean (mg/kg)	Median (mg/kg)	# of Systems Using	Mean (mg/kg)	Median (mg/kg)	# of Systems Using
Amoxicillin	Beta-lactams	4.0	1.9	4	2.2	0.73	5
Ampicillin	Beta-lactams	0.04	0.04	2	0.006	0.006	1
Ceftiofur	Cephalosporins	0.20	0.06	9	0.15	0.10	9
Chlortetracycline	Tetracyclines	139.4	73.4	9	70.4	55.1	9
Enrofloxacin	Quinolones	0.29	0.27	9	0.49	0.26	9
Florfenicol	Phenicols	0.013	0.007	5	0.07	0.05	4
Gentamicin	Aminoglycosides	0.21	0.20	6	0.12	0.11	7
Lincomycin	Lincosamides	42.5	3.8	9	10.1	2.3	9
Neomycin	Aminoglycosides	5.2	3.8	9	5.9	3.9	9
Oxytetracycline	Tetracyclines	15.0	4.8	7	21.9	3.8	6
Penicillin	Beta-lactams	6.6	1.7	9	8.4	2.6	9
Spectinomycin	Aminoglycosides	2.3	2.3	2	0.03	0.03	1
Sulfadimethoxine	Sulfonamides	0.05	0.05	1	0.86	0.86	1
Sulfamethazine	Sulfonamides	6.0	6.0	1	3.0	2.9	3
Sulfamethoxazole	Sulfonamides	0.004	0.004	1	N/A	N/A	0
Tetracycline	Tetracyclines	0.52	0.61	3	0.63	0.63	2
Tilmicosin	Macrolides	1.3	0.74	8	3.6	0.56	7
Trimethoprim/ Sulfadiazine	Potentiated Sulfonamides	0.76	0.76	2	1.3	0.59	5
Tulathromycin	Macrolides	0.87	0.01	7	0.02	0.002	7
Tylosin	Macrolides	1.9	0.22	9	0.45	0.13	8
Tylvalosin	Macrolides	1.6	1.1	6	1.9	1.8	5
Virginiamycin	Streptogramins	6.8	2.8	3	0.0004	0.0004	1

Source: Davies PR and Singer RS. Antimicrobial use in wean to market pigs in the United States assessed via voluntary sharing of proprietary data. ***Zoonoses and Public Health*** 2020; 67 (Suppl. 1): 6-21.

Results – Survey

Information regarding age of administration, age distributions of administration for various antimicrobials, and indications for use were collected from seven of the nine participating system swine veterinarians. This information was not derived through analysis of data in the study, but rather a survey based on expert opinion and practical experiences of veterinarians in the participating systems.

With respect to age of administration, across the nine participating systems, the majority of antimicrobial use occurred in the nursery phase (defined as 3 to 10 weeks for this project), particularly in the early nursery phase just after weaning. **Table 5-9** shows the mean of the participating veterinarians' perceived distribution (percent of use by production phase) of antimicrobial use (all active ingredients, both medically and non-medically important), by route of administration.

Table 5-9: Mean of perceived distribution of use (percent of use by production phase), by route of administration – survey of veterinarians for nine participating systems

Route of Administration	Overall Perceived Distribution (percent of use)	
	Production Phase	
	Nursery	Finishing
Feed	55	45
Water	60	40
Injection	59	41
Mean, all routes	58	42

Source: Davies PR and Singer RS. Antimicrobial use in wean to market pigs in the United States assessed via voluntary sharing of proprietary data. *Zoonoses and Public Health* 2020; 67 (Suppl. 1): 6-21.

With respect to reasons for use, the following indications were reported by the surveyed veterinarians to be most common for certain antimicrobials:

- Aminoglycosides (neomycin, gentamicin)- exclusively used for enteric (intestinal) diseases, particularly ***E. coli*** and ***Salmonella*** enteritis;
- Beta-lactams (penicillin, amoxicillin)- used predominantly for ***Streptococcus suis*** infections, with some stated indications for ***Haemophilus parasuis*** infections and wound infections;
- Lincomycin- primarily used to treat lameness/arthritis, and respiratory disease, with most respondents specifically stating mycoplasma infections (***Mycoplasma hyopneumoniae*** and ***Mycoplasma synoviae***); and
- Ceftiofur use was concentrated in the nursery phase for some systems, particularly for pneumonia and septicemia (***Streptococcus suis*** primarily), while other systems used ceftiofur for pleuropneumonia caused by ***Actinobacillus pleuropneumoniae***.

5.6 Antimicrobial Resistance in Swine and Pork

5.6.1 Introduction

In this section, some of the available information about antimicrobial resistance specific to swine pathogens is described. This is limited to information recently collected through the first two years of the USDA APHIS NAHLN Antimicrobial Resistance Pilot Project (2018-2019) and results from the first year of an FDA CVM Vet-LIRN collaborative antimicrobial resistance pilot project with veterinary diagnostic laboratories (2017). Some historical information has also been published as part of periodic USDA APHIS NAHMS swine studies, available on the NAHMS website.

In addition, this section highlights some of the 2019 antimicrobial resistance information for bacterial isolates collected from retail pork samples and cecal (intestinal) contents at the time of slaughter for market swine and sows, collected through the FDA (retail meat) and USDA FSIS (cecal) components of the NARMS program. Preliminary real-time genotypic data are available on the NARMS website, but not included here since the focus of this report is on 2016-2019.

5.6.2 Antimicrobial Resistance in Swine Pathogens

5.6.2.1 USDA APHIS NAHLN ANTIMICROBIAL RESISTANCE PILOT PROJECT – SWINE RESULTS (2018-2019)

As part of the USDA APHIS NAHLN Antimicrobial Resistance Pilot Project (see Chapter 3), pathogens tracked from swine included ***E. coli***, ***Salmonella enterica*** for 2018, and ***E. coli*** and ***Streptococcus suis*** in 2019 (***Salmonella enterica*** isolates were not included for 2019 since the goal of 100 isolates was not met in 2018 for swine). For the pilot project, information regarding swine production class and age was not collected. The full reports should be consulted for information on methodologies used and complete results for this project, including MIC data for the isolates (USDA-APHIS, 2019b and USDA-APHIS, 2019c).

E. coli

No antimicrobials have swine-specific clinical breakpoints established by the Clinical Laboratory Standards Institute (CLSI) for ***E. coli,*** so no percentage resistance was reported. In 2018, a total of 143 ***E. coli*** isolates from swine were submitted and 156 isolates were submitted in 2019. Overall, the most common clinical symptom or diagnoses associated with ***E. coli*** infections in swine were diarrhea (67.8% and 72.4% in 2018 and 2019, respectively) and pneumonia (16.1% and 10.9% in 2018 and 2019, respectively). Other less common clinical symptoms or diagnoses were septicemia, abortion, and wound infections.

Salmonella spp.

No antimicrobials have swine-specific CLSI clinical breakpoints for ***Salmonella*** spp., so no percentage resistance was reported. A total of 82 ***Salmonella*** spp. isolates were submitted for swine in 2018; 19 different serotypes were identified among these isolates. The three most common serotypes overall were 4,[5],12:i:- (34.1% of isolates), Typhimurium (18.3%), and Derby (12.2%). These three serotypes were the most frequent serotypes associated with diarrhea and pneumonia in swine. Typhimurium was also associated with septicemia in swine. Data for the other serotypes can be found in the published report.

Streptococcus suis

Twenty-one antimicrobials were tested, six of which have swine-specific CLSI clinical breakpoints established for ***S. suis***: ampicillin, penicillin, ceftiofur, enrofloxacin, florfenicol, and tetracycline (CLSI, 2018).

There were 167 isolates of ***S. suis***, a significant cause of pneumonia and meningitis in pigs, submitted in 2019. For the six antimicrobials with breakpoints established, 35.9% of the isolates were susceptible to all antimicrobials. Resistance to at least one of the antimicrobials was seen in 59.9% of the isolates, and another 10.7% were resistant to two antimicrobials. Four isolates exhibited multidrug resistance; one of these was resistant to 4 antimicrobials, and the other three of these isolates were resistant to 3 antimicrobials. **Table 5-10** shows the percentage resistance ***in S. suis*** isolates for the antimicrobials which have breakpoints.

Table 5-10: Percentage resistance – *Streptococcus suis* isolates from swine in 2019

Antimicrobial Class	Antimicrobial Drug	% Resistance (n=167 isolates)[1]
Amphenicols	Florfenicol	0.0
Cephalosporins	Ceftiofur	2.4
Fluoroquinolones	Enrofloxacin	2.4
Penicillins	Ampicillin	0.6
	Penicillin	15.6
Tetracyclines	Tetracycline	98.0

Source: USDA-APHIS National Animal Health Laboratory Network (NAHLN) Antimicrobial Resistance Pilot Project Year 2 Report: 2019 (Table 12).
1 For tetracyclines, the number of isolates tested was 102.

5.6.2.2 FDA CVM VET-LIRN COLLABORATIVE PROJECT WITH VETERINARY DIAGNOSTIC LABORATORIES, ANTIMICROBIAL RESISTANCE PILOT – SWINE RESULTS (*SALMONELLA* ONLY)

As part of the collaborative project with veterinary diagnostic laboratories in the U.S. and Canada, Vet-LIRN collected *Salmonella* isolates from veterinary diagnostic source labs from any host animal (see Chapter 3). In 2017, 586 *Salmonella enterica* isolates were collected, 69 of which were whole genome sequenced. Only 9 of these 69 isolates were of swine origin. The serovars for these were Typhimurium (2), 4,[5],12:i:- (2), Derby (2), and one each for serovars Infantis, Agona, and Worthington. For two of the isolates (Typhimurium and Infantis), no antimicrobial resistance genes (ARGs) were identified, while for the other seven isolates, multiple ARGs were present, ranging from two to thirteen. The one Agona isolate carried 13 ARGs, including ***strA*** and ***strB***, $bla_{CMY-17,}$ ***floR***, ***sul1, sul2***, and ***tet(A)***, conferring resistance to antimicrobials in the streptomycin, βlactamase, amphenicol, sulfonamide, and tetracycline classes, respectively. Both isolates of the serotype 4,[5],12:i:- carried 5 ARGs: ***StrA*** and ***StrB***, $bla_{TEM-105}$, ***sul1,*** and ***tet(B).*** None of the *Salmonella* isolates had fluoroquinolone resistance mutations in ***gyrA***. Only one of the isolates (serotype Worthington) carried the plasmid-mediated quinolone resistance gene ***qnrB5*** (Ceric et al, 2019).

5.6.3 Antimicrobial Resistance in Swine at Slaughter and Retail Pork

This section highlights antimicrobial resistance information for 2019, for generic ***E. coli, Salmonella***, ***Campylobacter***, and ***Enterococcus*** isolates collected from retail pork samples and cecal (intestinal) contents at the time of slaughter for market swine and sows. This information was collected through the FDA (retail meat) and USDA FSIS (cecal) components of the NARMS program. The CDC NARMS website should be consulted for information about bacteria isolated from humans that are monitored for antimicrobial resistance. For purposes of this report, antimicrobial susceptibility testing (i.e., phenotypic) data are described, including some information about multidrug resistance (MDR, defined by the NARMS program as resistance to three or more antimicrobial classes). The NARMS program websites and most recent integrated report (2018 NARMS Integrated Summary) can be consulted for more information, including whole genome sequencing data. **Appendix 6** provides line graphs depicting some of the resistance trends (from antimicrobial susceptibility testing) for a five-year period (2015-2019). Genotypic real-time data are published at NARMS Now and includes 2018-2021 data.

P-values, where reported in this section, were obtained using Fisher's exact test for comparing proportions (McDonald, 2014). P-values help assess statistical significance when comparing two or more sets of numerical data. In this case the proportions compared were the percentages of resistance (for a given bacteria and sample source) between 2018 and 2019, and the significance level was set at $p \leq 0.05$.

5.6.3.1 *E. COLI* – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL PORK AND SWINE CECAL SAMPLES

Recovery of *E. coli* from retail pork samples collected in the NARMS program was stable at about 32% in 2019. Recovery of *E. coli* from swine cecal samples has remained stable between 2018 and 2019. *E. coli* is a common commensal organism of the intestinal microbiota, so high prevalence levels are not unusual in animal cecal samples. **Tables 5-11 and 5-12** show the annual number of samples collected and number of *E. coli* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 5-11: Number of retail pork samples collected by year (2015-2019), and percent positive for *E. coli* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Pork Chops					
Number of samples	476	423	706	906	714
Number of isolates	161	137	226	234	229
Prevalence (%)	33.8	32.4	32.0	25.8	32.1

Table 5-12: Number of market swine and sow cecal samples collected by year (2015-2019), and percent positive for *E. coli* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Market Swine Cecal					
Number of samples	234	350	432	467	426
Number of isolates	224	341	414	444	404
Prevalence (%)	95.7	97.4	95.8	95.1	94.8
Sow Cecal					
Number of samples	224	287	151	127	150
Number of isolates	216	281	146	122	144
Prevalence (%)	96.4	97.9	96.7	96.1	96.0

Appendix 6 shows resistance trends (2015 to 2019) for *E. coli* isolated from retail pork and swine cecal samples (market swine and sows), for antimicrobials selected from the 10 antimicrobial drug classes tested. Swine source *E. coli* isolates are generally most resistant to tetracycline, ampicillin, and streptomycin compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *E.coli* isolates from swine samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- During 2019, ceftriaxone resistant *E. coli* from retail pork increased to about 7% from 4.3% in 2018. Ceftriaxone-resistant *E. coli* from sow cecal samples also increased to about 7% from 2.5% in 2018. Ceftriaxone-resistant *E. coli* in market swine cecal samples, decreased to 7.9% (from 8.6%).
- During 2019, decreased susceptibility to azithromycin (DSA) was detected in two *E. coli* isolates (less than 1%) from retail pork samples. DSA isolates from market swine decreased to below 2% and decreased to zero for sow cecal samples.
- *E. coli* isolates from all swine sources continued to show no carbapenem resistance (meropenem testing became routine in 2016).
- The percentage of *E. coli* isolates from retail pork with decreased susceptibility to ciprofloxacin (DSC) decreased between 2018 and 2019, from 6% to 5%. For market swine and sow cecal samples, the percentage of *E. coli* isolates with DSC decreased between 2018 and 2019 for market swine (from 7.2 to 5.9%) and increased for sow cecal (from 1.6 to 5.6%) samples.
- Chloramphenicol resistance in *E. coli* isolates from market swine cecal samples decreased between 2018 and 2019 (9.5% to 6.4%), but increased for retail pork (from 3 to 4.8%) and sow cecal (from 2.5 to 5.6%) samples during the same time frame.
- Ampicillin resistance in *E. coli* isolates from retail pork samples showed a statistically significant increase in 2019 (from 14.1% to 25.3%, $p<0.01$), but was stable in market swine and sow cecal samples.
- Tetracycline resistance in *E. coli* isolates from retail pork samples showed a statistically significant increase in 2019 (from 43.6% to 56.8%, $p<0.01$), but was stable in market swine and sow cecal samples.
- MDR in *E. coli* isolates showed no statistically significant changes in retail pork and swine cecal samples, comparing 2018 to 2019.

5.6.3.2 NONTYPHOIDAL *SALMONELLA* – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL PORK CHOPS AND SWINE CECAL SAMPLES

Recovery of nontyphoidal *Salmonella* from retail pork samples collected in the NARMS program increased between 2018 and 2019, but remained low, less than 5%. Recovery of *Salmonella* from swine cecal samples remained generally stable between 2018 and 2019. **Tables 5-13 and 5-14** show the annual number of samples collected and number of *Salmonella* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail and cecal sampling programs, as well as changes in sampling plans over the years.

Table 5-13: Number of retail pork samples collected by year (2015-2019), and percent positive for *Salmonella* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Pork Chops					
Number of samples	1641	1512	2085	2189	1631
Number of isolates	19	18	27	18	73
Prevalence (%)	1.2	1.2	1.3	0.8	4.5

Table 5-14: Number of market swine and sow cecal samples collected by year (2015-2019), and percent positive for *Salmonella* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Market Swine Cecal					
Number of samples	623	722	1006	1101	952
Number of isolates	216	305	500	513	433
Prevalence (%)	34.7	42.2	49.7	46.6	45.5
Sow Cecal					
Number of samples	556	577	331	297	282
Number of isolates	278	305	187	180	172
Prevalence (%)	50.0	52.9	56.5	60.6	61.0

Appendix 6 shows resistance trends (2015 to 2019) for *Salmonella* isolated from retail pork, market swine cecal, and sow cecal samples for antimicrobials selected from the 10 antimicrobial drug classes tested. Swine source *Salmonella* isolates are generally most resistant to tetracycline and streptomycin compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Salmonella* isolates from swine samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- In 2019, the percentage of ceftriaxone-resistant *Salmonella* for retail pork samples and market swine cecal samples remained stable, and there was a significant decrease in ceftriaxone resistance in *Salmonella* isolates from sow cecal samples (from 2.2% to zero, p=0.05). Derby was the predominant ceftriaxone-resistant serotype among *Salmonella* isolated from market swine cecal samples.
- The percentage of *Salmonella* isolates with DSC increased in 2019 for retail pork (from zero to 13.7% - representing 10 isolates; p=0.05). For swine cecal samples, the percentage of *Salmonella* isolates with DSC remained stable or decreased. I 4,[5],12:i:- and Derby were the predominant serotype with DSC

among *Salmonella* isolated from market swine cecal samples, while Johannesburg and Senftenberg were predominant for retail pork.

- In 2019, no decreased susceptibility to azithromycin (DSA) was detected in Salmonella isolates from retail pork or sow cecal samples, and six *Salmonella* isolates with DSA were detected in market swine cecal samples (<2%). Three of these six isolates were serotype I 4,[5],12:i:-.
- No carbapenem resistance was detected in *Salmonella* isolates from all swine sample types in 2019 (meropenem testing became routine in 2016).
- Tetracycline and streptomycin resistance in *Salmonella* isolates from market swine cecal samples significantly decreased between 2018 and 2019 (to 31% and 23%, respectively).
- The percentage of MDR *Salmonella* isolates remained stable for retail pork and market swine cecal samples between 2018 and 2019, but decreased in isolates from sow cecal samples (from 10 to 5.2%). The predominant serotypes were I 4,[5],12:i:- and Derby.

5.6.3.3 *CAMPYLOBACTER* SPP. – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR SWINE CECAL SAMPLES

Recovery of *Campylobacter* from swine cecal samples collected in the NARMS program in 2019 was mildly increased compared to 2018. Retail pork has not been cultured for *Campylobacter* in the NARMS retail meat program since 2008, due to the low recovery of isolates. **Table 5-15** shows the annual number of samples collected and number of *Campylobacter* isolates (includes both *Campylobacter jejuni* and *Campylobacter coli*) from the NARMS cecal sampling program for 2015 through 2019. The NARMS website should be consulted for information on sampling methodologies.

Table 5-15: Number of market swine and sow cecal samples collected by year (2015-2019), and percent positive for *Campylobacter* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Market Swine Cecal					
Number of samples	623	721	992	1100	984
Number of isolates	112	148	226	264	290
Prevalence (%)	18.0	20.5	22.8	24.0	29.5
Sow Cecal					
Number of samples	548	573	330	296	288
Number of isolates	144	142	83	69	81
Prevalence (%)	26.3	24.8	25.2	23.3	28.1

Appendix 6 shows resistance trends (2015 to 2019) for *Campylobacter jejuni* (*C. jejuni*) and *Campylobacter coli* (*C. coli*) isolated from market swine and sow cecal samples, for antimicrobials from six of the antimicrobial drug classes tested. Swine source *Campylobacter* isolates are generally most resistant to tetracyclines compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Campylobacter* spp. isolates from swine samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- Most of the *Campylobacter* spp. isolates from swine cecal samples have been *C. coli*. For *C. jejuni*, while there were some small increases or decreases in percentage resistance to antimicrobials tested between 2018 and 2019, most of these were not statistically significant, given the low number of isolates.
- In 2019, for *C. coli*, there were no significant changes in ciprofloxacin resistance in swine cecal samples. For *C. jejuni*, six of 27 market swine cecal isolates showed ciprofloxacin resistance in 2019.
- Macrolide resistance (erythromycin) for *C. coli* isolates showed a decrease for market swine cecal samples between 2018 and 2019 (from 28.6% to 26.4%), and a decrease for sow cecal samples (from 16.7% to 9.5%). In 2019, for *C. jejuni*, one market swine cecal isolate showed macrolide resistance (erythromycin).
- Lincosamide resistance in *C. coli* isolates from sow cecal samples decreased between 2018 and 2019 (from 27.3% to 17.6%), and remained stable for market swine cecal samples. For *C. jejuni*, lincosamide resistance decreased for market swine ceca (from 23.5% to 3.7%) and remained zero for sow cecal isolates.
- Telithromycin (a ketolide) resistance in *C. coli* isolates decreased significantly for both market swine ceca (from 28.2% to 4.3%, $p<0.01$) and sow ceca (from 12.1% to 2.7%, $p=0.03$).
- MDR *C. jejuni* from market swine cecal samples decreased between 2018 and 2019 (from 11.8% to 3.7%), and remained zero for sow cecal samples. MDR *C. coli* from market swine cecal samples also decreased between 2018 and 2019 (from 31.8% to 26.4%) and decreased for sow cecal samples, from 16.7% to 10.8%.

5.6.3.4 *ENTEROCOCCUS* SPP. – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL PORK CHOPS AND SWINE CECAL SAMPLES

Recovery of *Enterococcus* from retail pork samples collected in the NARMS program was below 70% in 2019, and also stable or decreased for swine cecal samples. *Enterococcus* spp. are a common commensal organism of the intestinal microbiota of humans and animals, so high prevalence levels are not unusual. **Tables 5-16 and 5-17** show the annual number of samples collected and number of *Enterococcus* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 5-16: Number of retail pork samples collected by year (2015-2019), and percent positive for *Enterococcus* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Pork Chops					
Number of samples	476	423	585	843	608
Number of isolates	389	340	429	490	408
Prevalence (%)	81.7	80.4	73.3	58.1	67.1

Table 5-17: Number of market swine and sow cecal samples collected by year (2015-2019), and percent positive for *Enterococcus* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Market Swine Cecal					
Number of samples	227	349	410	467	425
Number of isolates	217	313	384	406	373
Prevalence (%)	95.6	89.7	93.7	86.9	87.8
Sow Cecal					
Number of samples	223	278	141	127	150
Number of isolates	213	265	137	116	131
Prevalence (%)	95.5	95.3	97.2	91.3	87.3

Appendix 6 shows resistance trends (2015 to 2019) for *Enterococcus faecalis* (*E. faecalis*) and *Enterococcus faecium* (*E. faecium*) isolated from retail pork and swine cecal samples, for antimicrobials from nine of the antimicrobial drug classes tested. Swine source *Enterococcus* isolates are generally most resistant to tetracyclines compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Enterococcus* spp. isolates from swine samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- Between 2018 and 2019, macrolide (erythromycin) resistance in *E. faecalis* from retail pork and sow cecal samples increased, but decreased for market swine cecal samples, from 66.7% to 53.1% ($p<0.01$). For *E. faecium* isolates, erythromycin resistance decreased for retail pork, but increased (remaining less than 5%) for market swine cecal samples and remained zero for sow cecal samples.
- In 2019, ciprofloxacin resistance was not detected in retail pork or sow cecal *E. faecalis* isolates, and it decreased for *E. faecalis* from market swine cecal samples to below 1%. For *E. faecium*, ciprofloxacin resistance decreased for market swine cecal samples, but increased for retail pork (from 3.6% to 11.6%) and

sow cecal samples (from zero, to 4 out of 12 isolates).

- Chloramphenicol resistance, which had substantially risen among ***E. faecalis*** from market swine ceca and retail pork from 2013-2017, decreased in 2018 and remained stable in 2019. Chloramphenicol resistance in sow ceca deccreased from 11.8% to 10% in 2019. No chloramphenicol resistance was detected in ***E. faecium*** isolates in swine sources in 2019.
- Since cecal testing began in 2013, there had been a substantial decrease in gentamicin resistance in ***E. faecalis*** isolates from sow cecal samples (from 16.7% to 1.4% in 2017), although this rose to 5.9% in 2018 and increased further to 16.3% in 2019 (p=0.05). Gentamicin resistance in ***E. faecalis*** from market swine cecal samples decreased, from 14.3% to 9.5% and increased a small amount in retail pork (1% to 2.6%). No gentamicin resistance was detected in any swine source ***E. faecium*** isolates in 2019.
- Tetracycline and streptomycin resistance in ***E. faecalis*** isolates from market swine cecal samples significantly decreased between 2018 and 2019 (to 78% and 16.6%, respectively).
- ***Enterococcus spp.*** isolates from all swine sources in 2019 continued to show no linezolid resistance and no vancomycin resistance.
- Between 2018 and 2019, MDR ***E. faecalis*** significantly decreased in sow cecal samples, decreasing from 40.9% to 29.9% (p=0.01); however, increased in retail pork (from 3.6 to 6%) and market swine cecal samples (from 19.1 to 28.8%). For ***E. faecium***, MDR showed increases for all swine sample types, although none were statistically significant.

5.7 Antimicrobial Stewardship in Swine Production

5.7.1 Introduction

The FDA and other U.S. federal government agencies, as well as state government agencies and national and state veterinary medical associations, support the efforts of swine veterinarians and producers in actions taken to preserve the effectiveness and availability of antimicrobials for animals and humans. As part of the USDA APHIS NAHMS antimicrobial use study conducted on U.S. swine operations in 2017, some data were collected about antimicrobial stewardship practices during 2016. This section provides a brief summary of some of those results. The study report should be consulted for complete results (USDA-APHIS, 2020a). In 2021, USDA NAHMS launched the NAHMS Swine 2021 study, which is also intended to include information about antimicrobial use and stewardship on large and small swine enterprises. In addition, veterinary and producer associations have actively been developing strategies and taking steps to provide information to veterinarians and producers working with these industries in the U.S. to reduce the need for antimicrobials and to use them judiciously when necessary. While information about all of these organizations' activities is beyond the scope of this report, a few references are provided later in this section.

5.7.2 USDA APHIS NAHMS Antimicrobial Use and Stewardship on U.S. Swine Operations, 2017 - Stewardship

The NAHMS survey included questions about record-keeping for antimicrobial use, training for employees, periodic facility audits or assessments, using a veterinarian, having a valid VCPR, and taking steps to prevent disease. Some of these data are summarized here. Consult the published report for full details. The survey responses are referring to practices in 2016, prior to implementation of FDA GFI #213.

RECORD-KEEPING PRACTICES

Maintaining accurate records of antimicrobial use and treatment outcomes is an important principle of judicious antimicrobial use (AVMA, 2020). Keeping records on antimicrobial use allows for the evaluation of therapeutic regimens and also helps ensure adherence to appropriate withdrawal periods for drugs that have withdrawal periods established. In the NAHMS Swine Antimicrobial Use and Stewardship study, for 2016, of the 93.5% of sites that gave swine any antimicrobials in feed, about 97% of them always recorded the antimicrobial used, as well as the beginning date of administration. For the 78.4% of sites that gave market pigs any antimicrobials in water, 94% always recorded the antimicrobial used and nearly 90% recorded the date use began. For the 92.4% of sites that treated market pigs with injectable antimicrobials, 81.5% of them always recorded the antimicrobial given and about 79% of them always recorded the date of treatment (USDA-APHIS, 2020a).

PORK QUALITY ASSURANCE

Pork Quality Assurance® Plus (PQA® Plus) is a national program overseen by the National Pork Board that addresses issues such as food safety, animal welfare, environmental stewardship, and public health. Individuals can become certified and sites can receive PQA® Plus status through an on-farm site assessment. In the NAHMS 2017 Antimicrobial Use survey, almost all swine production sites (over 97%) had workers who were PQA® Plus certified.

USE OF VETERINARIAN SERVICES AND VCPR

Veterinarians help educate producers on appropriate and judicious use of antimicrobials and are vital to designing appropriate disease prevention programs and providing diagnoses. In the NAHMS 2017 Antimicrobial Use survey, of all sites surveyed, 69.4% used the services of a veterinarian in 2016. Overall, almost all sites (96.1%) had a VCPR.

ANTIMICROBIAL USE DECISIONS

In 2016, for swine production sites that gave any antimicrobials (both medically and non-medically important), about 84% of sites indicated that a veterinarian made decisions about when to use antimicrobials in feed, and nearly 87% of sites indicated a veterinarian made decisions about antimicrobials administered in water.

5.7.3 Other Resources

In 2014, the American Association of Swine Veterinarians (AASV) published a document entitled "Basic Guidelines of Judicious Therapeutic Use of Antimicrobials in Pork Production" and updated these guidelines in 2020, to provide swine veterinarians with best practices for antimicrobial stewardship. This supports the objectives of the AVMA's Steering Committee on Judicious Therapeutic Antimicrobial Use to help develop scientific knowledge that will provide the basis for judicious therapeutic antimicrobial use and support educational efforts that promote such use. These efforts will also help to both preserve therapeutic efficacy of antimicrobials and ensure current and future availability of antimicrobials (AVMA, 2020).

A number of national and state trade and industry associations have also established resources to assist swine producers and veterinarians with adopting the basic tenets of antimicrobial stewardship; for example, the National Pork Producers Council (NPPC), the National Pork Board (NPB), and the Pork Quality Assurance® Plus (PQA® Plus) program. In addition, a number of organizations involved with the swine production industry have made public commitments as part of the U.S. government's AMR Challenge.

CHAPTER 6
Antimicrobial Use and Resistance in U.S. Chicken Production

6.1 Introduction

6.2 Chicken Production in the U.S.

6.3 Chicken Health: Examples of Bacterial Diseases

6.4 Antimicrobial Sales and Biomass-Adjusted Antimicrobial Sales Estimates for Chickens

6.5 Antimicrobial Use in Chickens

6.6 Antimicrobial Resistance in Chickens and Chicken Meat

6.7 Antimicrobial Stewardship in Chicken Production

6.1 Introduction

Poultry are domesticated bird species that can be raised for eggs, meat, and/or feathers. The term 'poultry' generally covers a wide range of birds and may include chickens, turkeys, geese, ducks, quail, pheasants, pigeons, peafowls, and guineas (Taylor, 1998). Worldwide, poultry production is the largest meat industry (FAO, 2021a) and this sector continues to grow in many parts of the world largely due to increasing populations and urbanization. Chickens accounted for about 93% of the world's poultry population in 2019 (FAO, 2021c). Advances in poultry nutrition and processing technologies have led to improvements in efficiency and have resulted in concentration of large-scale poultry production close to input sources (such as feed) and vertical integration, as well as an increase in contract farming (FAO, 2021c). Traditional small-scale, rural, or family-based poultry systems still play a vital role in supporting livelihoods, especially in developing countries.

This chapter focuses on one part of the U.S. poultry industry: chickens - those raised for meat production (broilers) and egg production (layers). Poultry production requires a suitable physical environment, optimal nutrition, and protection from disease for the flock. This is often achieved through partial confinement, except in some free-range systems where birds spend more time foraging. While the popularity of raising urban or "backyard" chickens is increasing in some areas of the U.S., this chapter focuses on chickens raised in typical commercial production systems.

6.2 Chicken Production in the U.S.

Detailed information about poultry populations, production practices, and economic indicators are routinely or periodically published by USDA agencies, including the USDA Economic Research Service (ERS), the USDA National Agricultural Statistics Service (NASS), and the USDA Animal and Plant Health Inspection Service (APHIS), which conducts studies through the National Animal Health Monitoring System (NAHMS). Reports on these agency websites should be consulted for more information. In this section, we briefly summarize information about U.S. chicken production to provide context for populations and antimicrobial use practices discussed later in the chapter.

The U.S. is the world's largest producer and consumer of chickens and chicken meat, respectively, and in recent years, the U.S. has been the world's second largest exporter of chicken meat (USDA-FAS, 2021). The U.S. is also a major egg producer; the most recently available data show the U.S. ranks second among countries in terms of shell egg production (FAO, 2021d).

In 2019, approximately 9.2 billion broilers were produced in the U.S., with a total amount live weight produced of 58.3 billion pounds, up 3 percent from the prior year. Georgia was the state with the highest inventory of broilers, followed by Alabama and Arkansas (USDA-NASS, 2020f). Chicken meat production in the U.S. totaled about 44 billion pounds in 2019 (USDA-NASS, 2020g). In 2019, the average number of layers was about 400 million (USDA-NASS, 2020h) and egg production totaled 113 billion eggs. Iowa is the State that produced the most eggs in 2019, followed by Ohio and Indiana (USDA-NASS, 2020f). According to the most recent food availability data published

by USDA ERS, the availability (a proxy measure for consumption) of boneless chicken meat to consumers in the U.S. was 66.3 pounds per capita in 2019. The same data showed the availability of eggs (includes shell eggs and processed) to consumers in the U.S. was about 292 eggs per capita in 2019 (USDA-ERS, 2021c).

Chickens are typically bred specifically for either meat or egg production, each requiring specialized nutritional and health management. Commercial chicken production generally starts with primary breeders, the genetic stock for the industry. Primary breeder flocks consist of pedigree, great-grandparent, and grandparent birds. Grandparent flocks produce the final generation of breeding birds (also called multiplier or parent breeders). Parent breeders produce the fertile eggs which will become broiler chickens harvested for meat, or go on to become egg layers. Once hatched, broiler chicks intended for meat production are processed and delivered to grow-out farms. On grow-out farms, broiler chicks are grown to different sizes depending on the market they are destined for; typically reaching 5 pounds in 5 weeks. Once the birds reach the desired weight, they are transported to a processing plant. Market broiler chickens are generally processed before 8 weeks of age. In the case of chickens raised for egg production, once hatched, the layer chicks are processed and taken to pullet grow-out farms. Pullets are typically raised to the age of 18 weeks then sold to a layer farm or transferred to a poultry company's layer facility. There they begin laying eggs for human consumption around 20 weeks of age (USDA-ERS, 2021d).

For the past few decades, the broiler industry has been highly vertically integrated, with the majority of broilers being produced by large companies in the U.S. Integrators usually own hatcheries, feed mills, and processing plants. Farmers who have contracts with integrator companies typically handle the raising of birds from chick to market weight.

Organic agriculture is one of the fastest growing sectors within U.S. agriculture, particularly the poultry industry. Chicken products labeled as 'organic' must meet standards set by the National Organic Program (NOP) administered by the USDA's Agricultural Marketing Service (AMS). The USDA organic regulations specify production and processing requirements and specify which substances (such as animal drugs and feed additives) are allowed and prohibited (USDA-AMS, 2021). The USDA's Food Safety and Inspection Service (FSIS) is responsible for evaluation of poultry and other meat labeling claims, such as 'raised without antibiotics' and 'no antibiotics ever', among other animal-raising claims on meat labels (USDA-FSIS, 2019).

6.3 Chicken Health: Examples of Bacterial Diseases

Bacterial diseases in chickens may affect any body system, but often affect the respiratory and enteric (intestinal) systems. An extensive review of these is beyond the scope of this report; however, **Table 6-1** shows some examples of bacterial pathogens of chickens and associated disease processes – it is not intended to be an exhaustive list of all potential bacterial diseases of chickens. Veterinary and poultry health references can be consulted for detailed information about bacterial diseases of poultry including disease epidemiology, risk factors, diagnosis, prevention, and therapeutic management. Also shown in Table 6-1 are examples of antimicrobials

which are currently approved for use in chickens for therapy of these infections. Some of the drugs are approved only for certain chicken production types (e.g., broilers, layers, etc.). Table 6-1 is not intended to be an exhaustive list of all bacterial pathogens of chickens and all approved antimicrobials for chickens, but rather to provide examples. AnimalDrugs@FDA can be searched to find specific drug products with approved label information. Not all approved drugs are currently marketed in the U.S. Animal drug sponsors (i.e., pharmaceutical companies) decide what products they will manufacture and market at any given time. As discussed in Appendix 3, veterinarians may legally prescribe extralabel uses of approved animal drugs under specific conditions. Table 6-1 is not intended to capture legal extralabel use of approved antimicrobials.

Table 6-1: Examples of bacterial pathogens of chickens and examples of FDA-approved antimicrobials for therapy of these infections

Bacterial Pathogen(s)	Disease Process(es)	Examples of FDA-Approved Therapeutic Antimicrobials[1,2]
Avibacterium paragallinarum	Respiratory Disease/ Infectious Coryza	Erythromycin; Sulfadimethoxine; Sulfadimethoxine-ormetoprim; Sulfamerazine; Sulfamethazine; Sulfaquinoxaline
Clostridium perfringens	Necrotic Enteritis	Avilamycin[3]; Bacitracin methylene disalicylate (BMD)[3]; Bacitracin zinc[3]; Lincomycin; Tylosin; Virginiamycin
Clostridium species (e.g., C. septicum, C. perfringens Type A, C. novyi)	Gangrenous Dermatitis	Lincomycin
Escherichia coli	Multiple Systems (Intestinal; Respiratory; Septicemia; Other)	Ceftiofur; Gentamicin; Lincomycin-Spectinomycin; Streptomycin; Sulfadimethoxine-ormetoprim; Sulfamethazine; Sulfomyxin; Tetracycline; Chlortetracycline; Oxytetracycline
***Eimeria* species[4]**	Intestinal (Coccidiosis)	Bambermycins[3]; Lasalocid[3]; Monensin[3]; Narasin[3]; Salinomycin[3]; Sulfachloropyrazine; Sulfadimethoxine; Sulfadimethoxine-ormetoprim; Sulfamethazine; Sulfaquinoxaline; Sulfamerazine
Mycoplasma gallisepticum	Respiratory Disease/ Infectious Sinusitis/ Air Sacculitis	Erythromycin; Lincomycin-Spectinomycin; Neomycin; Tylosin; Chlortetracycline; Oxytetracycline; Tetracycline
Mycoplasma synoviae	Synovitis; Air Sacculitis	Neomycin; Lincomycin; Spectinomycin; Tylosin; Chlortetracycline; Oxytetracycline; Tetracycline
Pasteurella multocida	Fowl Cholera (Multiple Systems - Respiratory; Intestinal; Septicemia)	Sulfadimethoxine; Sulfadimethoxine-ormetoprim; Sulfamerazine; Sulfamethazine; Sulfaquinoxaline; Chlortetracycline; Oxytetracycline
Pseudomonas aeruginosa	Multiple Systems (Intestinal; Respiratory; Septicemia; Early Chick Mortality)	Gentamicin
***Salmonella* Gallinarum**	Fowl Typhoid (Multiple Systems - Intestinal; Respiratory; Septicemia; Early Mortality)	Sulfaquinoxaline
***Salmonella* Pullorum**	Pullorum disease (Multiple Systems - Intestinal; Respiratory; Septicemia; Early Mortality)	Sulfadimethoxine-ormetoprim; Sulfamerazine; Sulfamethazine; Sulfaquinoxaline
***Salmonella* Typhimurium; *Salmonella* spp.**	Enteritis; Respiratory Disease	Gentamicin; Spectinomycin; Streptomycin Oxytetracycline
***Staphylococcus* species**	Synovitis; Gangrenous Dermatitis; Breast Blisters	Novobiocin[3]

1 See AnimalDrugs@FDA for information about approved antimicrobials, including specific indications, dose, duration, approved production classes, limitations, and approved combination products.
2 Not all antimicrobials are currently marketed.
3 Not currently considered a medically important antimicrobial according to Appendix A of FDA GFI #152.
4 *Eimeria* spp. are protozoal organisms, not bacteria, but are a common infection in chickens for which antimicrobials may be used for therapy. Not all approved anticoccidial drugs or coccidiostats are shown in this table.

6.4 Antimicrobial Sales and Biomass-Adjusted Antimicrobial Sales Estimates for Chickens

6.4.1 Introduction

In this section, information is presented about antimicrobial sales and distribution estimates for chickens. These data are not necessarily indicative of how the antimicrobials were actually administered to or used in chickens (e.g., for what indications, doses, or durations). Antimicrobial use information (i.e., record of on-farm administration) is helpful to determine what disease pressures exist and could help inform stewardship practices, as discussed later in this chapter. The overall amount of antimicrobials sold and used in chickens is expected to change from year to year and will depend on multiple factors, including chicken populations and disease pressures faced each year.

In order to further characterize the species-specific antimicrobial sales and distribution estimates, a biomass denominator adjustment is also included in this section. This allows for a representation of trends in annual antimicrobial sales and distribution relative to the estimated chicken population in the U.S. in which the antimicrobials could be used.

6.4.2 Medically Important Antimicrobial Sales and Distribution Estimates for Chickens

Table 6-2 shows the species-specific sales and distribution estimates, by medically important antimicrobial drug class, reported by antimicrobial drug sponsors for chickens for 2016 through 2019, as well as the percent change in these estimates between time periods. Only the following drug classes can be shown for all four years because they had at least three drug sponsors and had species-specific estimates for chickens: aminoglycosides, lincosamides, macrolides, and tetracyclines. Sulfonamides are not shown for 2018 because sales of this drug class were not independently reportable for chickens that year. Other medically important drug classes that may have had drug sales for chickens include cephalosporins, diaminopyrimidines, polymyxins, and streptogramins. However, these are not independently reported classes for chickens (due to lack of three or more drug sponsors), so data cannot be shown in order to protect confidential business information of drug sponsors.

The majority of medically important antimicrobial sales estimated by drug sponsors for chickens for 2016 through 2019 were for tetracyclines. **Figure 6-1** contains the same sales information as Table 6-2, but visually demonstrates the magnitude of the tetracycline class compared to the other medically important antimicrobial classes. As noted in Appendix 3, GFI #213 was completely implemented as of January 1, 2017. Between 2016 and 2017, total medically important antimicrobial sales estimated for chickens decreased by about 47% and there were overall decreases in all classes for which data can be shown. There were small increases in macrolides and lincosamides between 2017 and 2018, but a decrease in other classes and a continued overall decrease in total estimated sales of medically important antimicrobials of about 17%. Between 2018 and 2019, there were increases in sales of aminoglycosides and tetracyclines, but decreases in other classes and an overall decrease in total estimated sales of medically important antimicrobials of 13%. The overall percent change in

sales comparing 2016 and 2019 indicates an overall decrease of approximately 62% in total estimated sales for chickens. Since the requirement for drug sponsors is only to provide estimated species-specific antimicrobial drug sales and distribution for the four major food-producing species, it is not possible to further break down the sales and distribution estimates into the various chicken production types (e.g., broilers, layers, etc.).

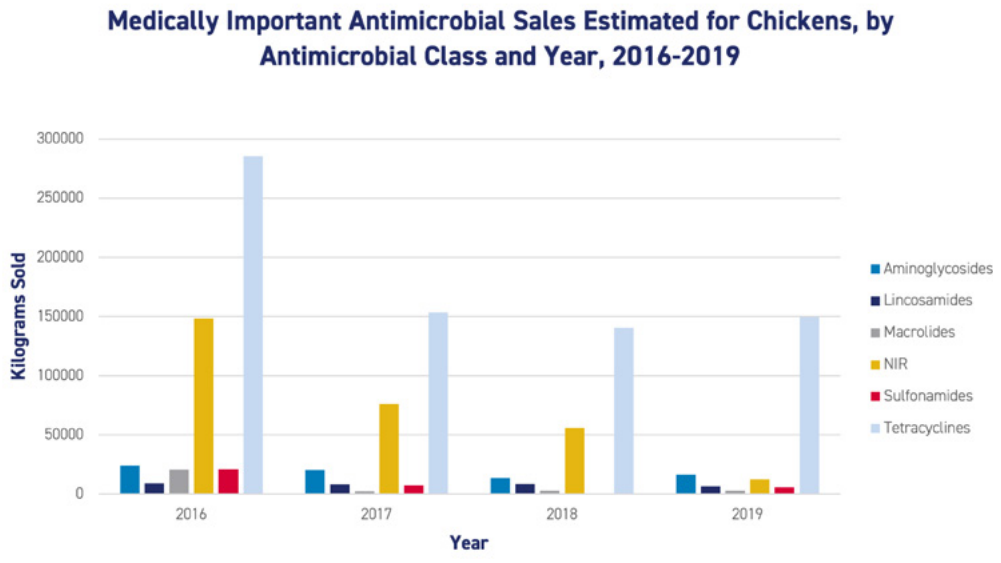
Table 6-2: Medically important antimicrobial sales and distribution estimates for chickens by reportable drug class, 2016-2019

Medically Important Antimicrobial Drug Class	2016 Estimated Annual Sales Totals for Chickens (kg)	2017 Estimated Annual Sales Totals for Chickens (kg)	2018 Estimated Annual Sales Totals for Chickens (kg)	2019 Estimated Annual Sales Totals for Chickens (kg)	Overall Percent Change in Sales from 2016 to 2017	Overall Percent Change in Sales from 2017 to 2018	Overall Percent Change in Sales from 2018 to 2019	Overall Percent Change in Sales from 2016 to 2019
Aminoglycosides	24,111	20,185	13,430	16,200	-16.3%	-33.5%	20.6%	-32.8%
Lincosamides	8,874	8,213	8,780	6,409	-7.4%	6.9%	-27.0%	-27.8%
Macrolides	20,718	2,614	2,971	2,760	-87.4%	13.7%	-7.1%	-86.7%
Sulfonamides	21,115	7,319	*	5,903	-65.3%	--	---	-72.0%
Tetracyclines	285,513	153,621	140,561	149,295	-46.2%	-8.5%	6.2%	-47.7%
NIR[1]	148,469	76,095	56,032	12,397	-48.7%	-26.4%	-77.9%	-91.7%
Total	508,800	268,047	221,774	192,964	-47.3%	-17.3%	-13.0%	-62.1%

1 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For chickens, drug classes which cannot be shown in order to protect confidential business information are Cephalosporins, Diaminopyrimidines, Polymyxins, and Streptogramins, as well as Sulfonamides for 2018. The value of sales for this category was therefore calculated as the overall annual sales total for chickens minus the sum of all reportable classes for that year. The individual drug classes within the NIR category may or may not have had actual sales in any given year.

* Sulfonamide class sales for 2018 are not independently reportable due to confidential business rule; therefore, percent change in sales cannot be calculated. Sulfonamide sales may be included in the NIR category for 2018.

Figure 6-1: Medically important antimicrobial sales and distribution estimates for chickens, by antimicrobial class and year, 2016-2019



*NIR: Antimicrobial classes for chickens which are not individually reportable in order to protect confidential business information – may include Cephalosporins, Diaminopyrimidines, Polymyxins, Streptogramins, and Sulfonamides for 2018.

6.4.3 Biomass-Adjusted Medically Important Antimicrobial Sales and Distribution Estimates for Chickens

Appendix 4 shows the population and weight in kilograms (kg) for each category of chickens for 2016 through 2019. Using these data, the biomass total calculated for chickens (except for up to 7 day old chicks) was approximately 24.9 billion kg in 2016, approximately 25.5 billion kg in 2017, approximately 26 billion kg in 2018, and approximately 26.8 billion kg in 2019, representing about a 7.5% increase in estimated U.S. chicken biomass between 2016 and 2019. The biomass total for young chickens is also calculated separately, because one drug class (lincosamides) is only approved for broiler chickens (and chicks up to 7 days old); therefore, this young chicken biomass denominator is applied to the lincosamide drug class only. Young chickens are defined in the USDA Poultry Slaughter Summary reports (see references, Appendix 4) as broilers and fryers, while mature chickens include breeding and market egg flocks.

Using the estimated annual total sales for medically important antimicrobials by drug class (in mg) for chickens and estimated annual chicken biomass (target animal biomass [TAB], in kg), **Table 6-3** shows the biomass-adjusted medically important antimicrobial sales and distribution data for chickens, by drug class and year. Table 6-3 also indicates the percent change for each reportable drug class between time periods. For all antimicrobial classes which can be shown, there was a decrease in the mg/TAB values comparing 2016 to 2019, and an overall decrease in mg/TAB of about 65%.

Table 6-3: Biomass-adjusted medically important antimicrobial sales and distribution estimates for chickens, by reportable drug class, 2016-2019

Medically Important Antimicrobial Drug Class	2016 Estimated mg/TAB for Chickens	2017 Estimated mg/TAB for Chickens	2018 Estimated mg/TAB for Chickens	2019 Estimated mg/TAB for Chickens	Percent Change1 in mg/TAB 2016 - 2017	Percent Change1 in mg/TAB 2017 - 2018	Percent Change1 in mg/TAB 2018 - 2019	Percent Change1 in mg/TAB 2016 - 2019
Aminoglycosides	0.97	0.79	0.52	0.60	-18.1%	-34.9%	17.2%	-37.5%
Macrolides	0.83	0.10	0.11	0.10	-87.7%	11.2%	-9.7%	-87.6%
Sulfonamides	0.85	0.29	*	0.22	-66.1%	--	--	-74.0%
Tetracyclines	11.46	6.03	5.40	5.57	-47.4%	-10.5%	3.2%	-51.4%
NIR[2]	5.96	2.99	2.15	0.46	-49.9%	-27.9%	-78.5%	-92.2%
Total (not including lincosamides)[1]	20.07	10.20	8.18	6.97	-49.2%	-19.8%	-14.9%	-65.3%
Lincosamides[3]	0.36	0.33	0.34	0.24	-9.6%	4.5%	-29.2%	-33.1%

1 Calculations of percent change and totals were performed using the raw (unrounded) data for estimated mg/TAB. Calculations using the rounded numbers in this table will not yield exactly the same result.

2 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For chickens, drug classes which cannot be shown in order to protect confidential business information are Cephalosporins, Diaminopyrimidines, Polymyxins, and Streptogramins, and Sulfonamides for 2018. The value of sales for this category used in the mg/TAB calculation was therefore calculated as the overall annual sales total for chickens minus the sum of all reportable classes. The individual drug classes within the NIR category may or may not have had actual sales in any given year. The chicken biomass denominator is applied to the NIR category as a whole; therefore does not account for potential exclusions of chicken categories for the denominator that may otherwise apply to individual NIR classes.

3 Mg/TAB values for the lincosamide drug class were calculated using the estimated biomass for young chickens only.

*Sulfonamide class sales for 2018 are not reportable due to confidential business rule; therefore, percent change in mg/TAB cannot be calculated.

Table 6-4 shows the comparison of percent change in species-specific estimated sales volume (kg) and the percent change in biomass-adjusted species-specific estimated sales (mg/TAB) between 2016 and 2019 for chickens. With the approximately 7.5% increase in estimated chicken biomass between 2016 and 2019, the biomass denominator adjustment resulted in a variable degree of difference in the percent change in mg/TAB relative to the percent change in species-specific estimated sales volume (kg) for antimicrobial drug classes which can be reported.

Table 6-4: Percent change in estimated sales and distribution data for chickens in sales volume (kg) and adjusted by a biomass denominator (mg/TAB), between 2016 and 2019

Medically Important Antimicrobial Drug Class	Percent Change in Species-Specific Estimated Sales Volume from 2016 to 2019	Percent Change in Biomass Adjusted Species-Specific Estimated Sales (mg/TAB) from 2016 to 2019
Aminoglycosides	-32.8%	-37.5%
Lincosamides[1]	-27.8%	-33.1%
Macrolides	-86.7%	-87.6%
Sulfonamides	-72.0%	-74.0%
Tetracyclines	-47.7%	-51.4%
NIR[2]	-91.7%	-92.2%
Total[3]	-62.1%	-65.3%

1 Mg/TAB values for the lincosamide drug class was calculated using the estimated biomass for young chickens only.
2 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For chickens, drug classes which cannot be shown in order to protect confidential business information are Cephalosporins, Diaminopyrimidines, Polymyxins, Streptogramins, and Sulfonamides for 2018. The individual drug classes within the NIR category may or may not have had actual sales in any given year. The chicken biomass denominator is applied to the NIR category as a whole; therefore does not account for potential exclusions of chicken categories for the denominator that may otherwise apply to individual NIR classes.
3 Calculation of total percent change for antimicrobial sales includes all drug classes. Calculation of total percent change for mg/TAB does not include the lincosamide class since it was calculated using the estimated biomass for young chickens only.

6.5 Antimicrobial Use in Chickens

6.5.1 Introduction

Nationally-representative and continuously collected data on antimicrobial use in chickens in the U.S. are not currently publicly available. Some information about antimicrobial use in poultry has been collected and published by USDA APHIS through periodic studies conducted by NAHMS. Poultry studies were conducted by USDA NAHMS in 1999, 2004, 2007, 2010, and 2013. The most recent NAHMS poultry study which contained antimicrobial use information was the NAHMS Layer 2013 study. Complete reports from this and other poultry studies are available on the NAHMS website. This section presents data from part of an FDA cooperative agreement awarded in 2016 intended to pilot methodologies for collection of on-farm antimicrobial use information for food-producing animals, including poultry.

6.5.2 FDA Cooperative Agreement: Antimicrobial Use Data Collection in U.S. Poultry

Chapter 3 described the Funding Opportunity Announcement that FDA issued in 2016, announcing the availability of grants in the form of cooperative agreements to develop and pilot methodologies for collecting and reporting antimicrobial use data in the four major food-producing species at the farm level. One of the grants (5U01FD005878) was awarded for the collection and reporting of antimicrobial use data in poultry and swine. This section describes the portion of the grant aimed at characterizing antimicrobial use in U.S. poultry and presents some of the results obtained for broiler chickens.

The primary goal of the overall project was to explore options for antimicrobial use monitoring in poultry and swine production systems, with a long-term goal of informing and supporting the continued advancement of antimicrobial stewardship within U.S. poultry and swine production systems. A specific aim of the project related to poultry was to expand and optimize an ongoing pilot of an on-farm antimicrobial use data collection program in U.S. poultry production. Components of this specific aim included the following activities:

1. Collection of antimicrobial use data from broiler, turkey, and table egg production in the U.S.;
2. Development of an auditing and reporting system; and
3. Identification of optimal platforms for long-term data collection efforts.

The next sections summarize results for the broiler chicken antimicrobial use data collected during the first two years (2016-2017) of the cooperative agreement, as well as some data that were collected by the study investigator prior to the cooperative agreement being awarded. The primary investigator had begun a pilot program for data collection in the U.S. poultry system in 2014 with assistance from the poultry industry (U.S. Poultry & Egg Association). Beginning with the FDA cooperative agreement in 2016, that program was expanded to include more of the U.S. broiler and turkey industries. Recently, investigators published detailed reports about the results for 2016 and 2017 (Singer et al, 2020a). Data collection is ongoing, and CVM expects to publish a more complete summary of the cooperative agreement results after the conclusion of the projects. In addition, CVM will use information gained from the cooperative agreement pilot projects to help inform development of a long-term strategy to support continued antimicrobial use data collection.

6.5.2.1 BROILER ANTIMICROBIAL USE DATA (2013-2017)

The broiler industry data collection effort targeted all major companies that raise broilers commercially in the U.S. Companies that agreed to participate tracked production parameters, antimicrobial use for the hatchery, and antimicrobial use in broiler feed and water. Companies also provided some information on reasons for use and captured all of this information retrospectively as best possible. This was difficult for many companies since prior to January of 2017, all antimicrobials were not necessarily under veterinary oversight, especially those administered in feed. While the use of antimicrobials would have been overseen by someone within the poultry company, the records were often not kept centrally, so antimicrobial administration data were not easy to access in many instances. Surveys to capture quantitative on-farm antimicrobial use estimates were also administered. Information captured included antimicrobial compound, indication, route, dose, duration, age at administration, and number of birds receiving the drug. After experience with the initial survey design, the investigator determined that the data collection approach needed to be customized for each company due to differences in

data format and availability. This made a single, standardized approach to data collection difficult for the first round of data collection.

The primary investigator's published report should be consulted for full details and results. For purposes of this report, the approach and methodology are briefly described and a summary of some of the results for broiler chickens are provided. Antimicrobial use data for layer chickens in table egg production are not yet available at the time of this report.

Methods – Data Collection

Data were submitted by participating companies in a variety of ways and at differing levels of granularity, for example:

- **Flock-level records:** These data were primarily submitted for antimicrobials administered in water and may have included number of birds, disease indication, age, estimated weight, antimicrobial drug, total amount of antimicrobial administered, and duration of administration.
- **Calendar year basis:** Especially for earlier years of data, the total amount of antimicrobial drug used in a calendar year was reported, sometimes stratified by disease indication.
- **Feed mill data:** Most integrated poultry companies have dedicated feed mills. Some participating poultry companies submitted data regarding the total amount of feed produced during each year, including amounts of feed for each ration formulation and estimates of the total amounts of antimicrobials administered in feed for each ration time period (based on company protocols).
- **Antimicrobial purchases in a calendar year:** Some companies submitted purchase records. Amounts obtained in this way represented the maximum amount of antimicrobial that a company could have used during the year.
- **Number of birds receiving treatment with each antimicrobial for different diseases:** This was primarily for the injectable (hatchery) antimicrobials and antimicrobials administered in water. The total amount of antimicrobial administered was not provided in these cases, but in some cases could be estimated using the age of the birds, dose, and duration of treatment.

Methods – Data Aggregation and Analysis

Data from each company were validated and aggregated using spreadsheet formats. Errors detected during this step were discussed with submitting companies and corrected. Records were then imported into a relational database for additional error checks and validation. Once all of the data were in a standardized format and validated, all of the companies were then aggregated. As part of the cooperative agreement conditions to protect the privacy of data contributors, participating poultry companies were not identified, and data were kept strictly confidential. The USDA APHIS Center for Epidemiology and Animal Health (CEAH) played a role in auditing the procedures used for data collection, aggregation, and analysis. CEAH also reviewed survey design, procedures for estimating representativeness of the data, and provided input on metrics for reporting.

To estimate the industry representativeness of the data collected, the investigators used a list published by WATT PoultryUSA which reports the annual production data for the major broiler chicken and turkey companies

in the U.S. (WATT, 2020). It includes the size of each company based on the total number of birds slaughtered and the total pounds liveweight produced per week for each company. The annual totals for each year of data collection were used as the denominator for the calculation of national representativeness. The sum of production totals for companies enrolled in the project and that submitted data served as the numerator in this calculation. Representativeness estimates were presented as a range in order to protect the confidentiality of the participating companies. In addition, representativeness in this context means the percentage of U.S. broiler production that is likely covered in this data collection effort; it does not mean that the use practices described completely characterize the entirety of national broiler production.

Measurements of Antimicrobial Use

The study investigators used the following measurements to summarize antimicrobial use data:

- Hatchery antimicrobials:
  - Total kilograms of each antimicrobial used per year;
  - Total grams of each antimicrobial class used per year per 100,000 birds placed during that year
- Antimicrobials used in feed or water:
  - Total kilograms of each antimicrobial used per year;
  - Total grams of each antimicrobial class used per year per 1,000,000 pounds liveweight slaughtered during that year

Due to differences in drug potencies and pharmacokinetic/pharmacodynamic properties, the weights of antimicrobials were not summed across antimicrobial classes or across different routes of administration.

Results – Broiler Hatchery Antimicrobial Use

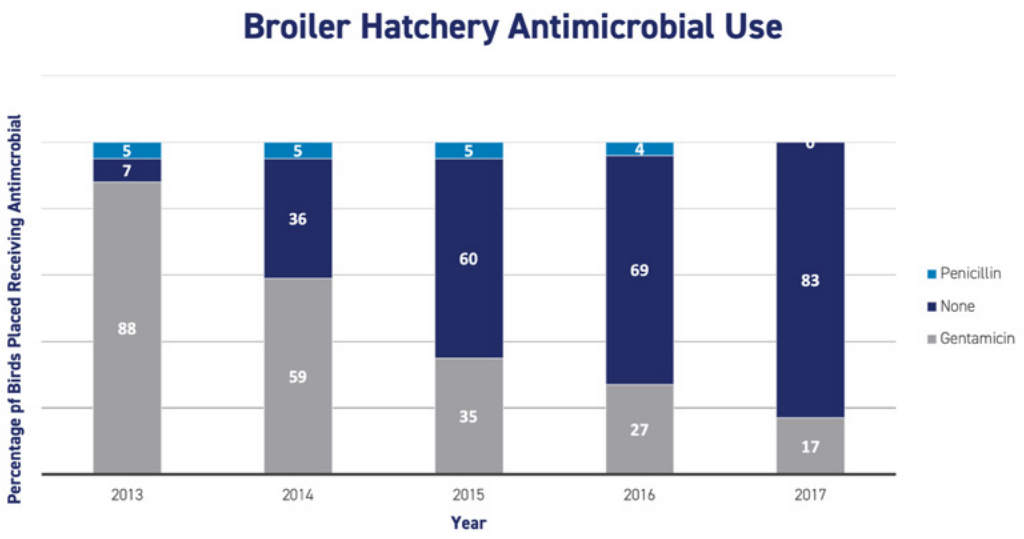
The broiler hatchery data representativeness ranged from 80 to 93% of U.S. broiler production, depending on the year (2013-2017). **Table 6-5** shows the total estimates of antimicrobials used in participating broiler hatcheries each year. Note that the upper part of the table shows total kilograms of drug, while the lower part of the table shows the drug amounts in grams of antimicrobial used per 100,000 birds placed. **Figure 6-2** shows the broiler hatchery antimicrobial use as a percentage of total birds placed each year. The main antimicrobial used in hatcheries was gentamicin given *in ovo* (injected into the egg). This is an extralabel use, as the drug is approved as a subcutaneous injection in day-old chicks for prevention of early mortality associated with *E. coli*, *Salmonella* Typhimurium, and *Pseudomonas aeruginosa* susceptible to gentamicin. There was also some penicillin use in the hatchery; no ceftiofur use was reported. As shown in Table 6-5, gentamicin use decreased by about 74% (in grams per 100,000 birds placed) between 2013 and 2017, and penicillin use dropped to zero. Overall, the percentage of broiler chicks placed that received antimicrobials in the hatchery decreased from 93 to 17% between 2013 and 2017 (Figure 6-2).

Table 6-5: Broiler hatchery antimicrobial use, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
		Kilograms of Drug				
Aminoglycosides	Gentamicin	926.0	825.8	537.2	417.3	270.5
Penicillins	Penicillin G	518.0	615.3	607.0	469.8	0
		Grams of Drug per 100,000 Birds Placed				
Aminoglycosides	Gentamicin	13.0	11.8	7.0	5.4	3.4
Penicillins	Penicillin G	7.3	8.8	7.9	6.0	0

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in broiler chicken production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 22-35.

Figure 6-2: Broiler hatchery antimicrobial use as a percentage of birds placed, 2013-2017



Source: Singer RS et al. Estimates of on-farm antimicrobial usage in broiler chicken production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 22-35.

Results – Broiler Antimicrobial Use in Feed

The broiler antimicrobial use in feed data representativeness ranged from 80 to 93% of U.S. broiler production, depending on the year (2013-2017). **Tables 6-6 and 6-7** show the amounts of antimicrobials used in broiler feed each year, by drug class and year, for both medically important and non-medically important antimicrobials (as defined by GFI #152). Table 6-6 shows total kilograms of drug, while Table 6-7 shows the amount in grams of antimicrobial used per 1 million pounds liveweight produced. The main medically important antimicrobial classes used in broiler feed were streptogramins (virginiamycin) and tetracyclines (chlortetracycline and oxytetracycline). All of the medically important antimicrobial classes used showed a decline between 2013 and 2017. Lincosamides had no use between 2014 and 2017, and macrolides dropped to zero in 2017. In terms of grams per 1 million pounds liveweight, virginiamycin showed a decrease of about 60% between 2013 and 2017, and tetracyclines showed a decrease of 95%. Non-medically important antimicrobials also showed overall decreases, except for avilamycin and bacitracin, which increased.

Table 6-6: Antimicrobial use (in kilograms) in broiler feed, by drug class, ingredient, and year, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
Medically Important Antimicrobials[1]		**Kilograms of Drug**				
Diaminopyrimidines	Ormetoprim	47.5	818.1	175.4	188.6	22.6
Lincosamides	Lincomycin	816.8	0	0	0	0
Macrolides	Tylosin	6,378.7	4,923.7	6,075.6	8,190.7	0
Streptogramins	Virginiamycin	148,266.3	139,755.6	160,976.8	125,669.7	70,082.0
Sulfonamides	Sulfadimethoxine	79.1	1,363.6	292.4	314.4	37.7
Tetracyclines	Tetracyclines[2]	93,150.4	45,130.0	5,151.2	3,616.3	5,325.3
Not Medically Important Antimicrobials[1]		**Kilograms of Drug**				
Glycolipids	Bambermycins	159.9	145.8	718.7	1,786.0	1,603.1
Ionophores	Lasalocid	132,705.9	163,339.5	115,276.6	104,376.2	90,251.2
	Monensin	254,867.4	287,022.1	232,578.8	368,534.8	279,104.1
	Narasin	494,224.7	333,361.0	423,374.9	375,668.0	311,035.5
	Salinomycin	260,762.6	369,700.1	330,092.7	311,380.7	212,249.0
Orthosomycins	Avilamycin[3]	-	-	-	519.8	13,372.4
Polypeptides	Bacitracin	441,210.7	434,205.3	479,788.3	396,882.2	451,077.3

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in broiler chicken production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 22-35.

1 Refers to medical importance in human medicine, as defined by Appendix A of FDA GFI #152.
2 Includes chlortetracycline and oxytetracycline.
3 Avilamycin was FDA-approved in 2016.

Table 6-7: Antimicrobial use (in grams per 1 million pounds liveweight produced) in broiler feed, by drug class, ingredient, and year, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
Medically Important Antimicrobials[1]		**Grams of Drug per 1 Million Pounds Liveweight Produced**				
Diaminopyrimidines	Ormetoprim	1.2	19.9	3.8	4.0	0.5
Lincosamides	Lincomycin	19.9	0	0	0	0
Macrolides	Tylosin	155.1	119.6	132.6	172.0	0
Streptogramins	Virginiamycin	3,604.5	3,395.3	3,513.7	2,639.4	1,453.2
Sulfonamides	Sulfadimethoxine	1.9	33.1	6.4	6.6	0.8
Tetracyclines	Tetracyclines[2]	2,264.6	1,096.4	112.4	76.0	110.4
Not Medically Important Antimicrobials[1]		**Grams of Drug per 1 Million Pounds Liveweight Produced**				
Glycolipids	Bambermycins	3.9	3.5	15.7	37.5	33.2
Ionophores	Lasalocid	3,226.2	3,968.2	2,516.2	2,192.2	1,871.5
	Monensin	6,196.1	6,973.0	5,076.6	7,740.3	5,787.5
	Narasin	12,015.1	8,098.8	9,241.1	7,890.1	6,449.7
	Salinomycin	6,339.4	8,981.6	7,205.0	6,539.9	4,401.2
Orthosomycins	Avilamycin[3]	-	-	-	10.9	277.3
Polypeptides	Bacitracin	10,726.3	10,548.7	10,472.5	8,335.6	9,353.6

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in broiler chicken production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 22-35.

1 Refers to medical importance in human medicine, as defined by Appendix A of FDA GFI #152.
2 Includes chlortetracycline and oxytetracycline.
3 Avilamycin was FDA-approved in 2016.

Results – Broiler Antimicrobial Use in Water

The broiler antimicrobial use in water data representativeness ranged from 72 to 93% of U.S. broiler production, depending on the year (2013-2017). **Tables 6-8 and 6-9** show the amounts of antimicrobials used in broiler water each year, by drug class and year, for both medically important and non-medically important antimicrobials (as defined by GFI #152). Table 6-8 shows total kilograms of drug, while Table 6-9 shows the amount in grams of antimicrobial used per 1 million pounds liveweight produced. The main medically important antimicrobial classes used in broiler water were penicillins (penicillin G) and tetracyclines (chlortetracycline, oxytetracycline, and tetracycline). Most of the medically important antimicrobial classes used showed a decline between 2013 and 2017. Erythromycin had no use in 2016 or 2017 and spectinomycin had no use in 2017. In terms of grams per 1 million pounds liveweight, the largest percentage decreases between 2013 and 2017 were for neomycin (about 75% decreased) and sulfonamides (about 70% decreased). Tylosin also showed about a 60% decrease between 2013 and 2017. Bacitracin, the only non-medically important antimicrobial used in water, showed an increase between 2013 and 2017.

Table 6-8: Antimicrobial use (in kilograms) in broiler water, by drug class, ingredient, and year, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
Medically Important Antimicrobials[1]		**Kilograms of Drug**				
Aminoglycosides	Neomycin	725.2	1,764.8	892.3	406.4	237.8
	Spectinomycin	0	0	40.8	13.6	0
Lincosamides	Lincomycin	2,767.5	4,293.6	6,226.3	4,360.1	2,603.8
Macrolides	Erythromycin	6.9	3.5	5.2	0	0
	Tylosin	1,669.5	2,556.1	2,124.1	2,399.9	899.9
Penicillins	Penicillin G	16,791.0	25,057.0	29,996.8	27,485.2	17,398.3
Sulfonamides	Sulfonamides[2]	5,142.0	4,731.5	5,598.1	1,601.1	1,854.0
Tetracyclines	Tetracyclines[3]	14,482.6	12,142.1	16,156.5	18,486.4	10,040.5
Not Medically Important Antimicrobials[1]		**Kilograms of Drug**				
Polypeptides	Bacitracin	1,035.5	2,340.6	1,376.6	1,269.4	4,847.2

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in broiler chicken production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 22-35.

1 Refers to medical importance in human medicine, as defined by Appendix A of FDA GFI #152.

2 Includes sulfadimethoxine, sulfamerazine, sulfamethazine, and sulfaquinoxaline.

3 Includes chlortetracycline, oxytetracycline, and tetracycline.

Table 6-9: Antimicrobial use (in grams per 1 million pounds liveweight produced) in broiler water, by drug class, ingredient, and year, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
Medically Important Antimicrobials[1]		**Grams of Drug per 1 Million Pounds Liveweight Produced**				
Aminoglycosides	Neomycin	19.9	48.6	19.8	8.7	5.0
	Spectinomycin	0	0	0.9	0.3	0
Lincosamides	Lincomycin	76.1	118.2	138.3	93.1	54.9
Macrolides	Erythromycin	0.2	0.1	0.1	0	0
	Tylosin	45.9	70.4	47.2	51.3	19.0
Penicillins	Penicillin G	461.8	689.7	666.2	587.0	366.6
Sulfonamides	Sulfonamides[2]	141.4	130.2	124.3	34.2	39.1
Tetracyclines	Tetracyclines[3]	398.3	334.2	358.8	394.8	211.6
Not Medically Important Antimicrobials[1]		**Grams of Drug per 1 Million Pounds Liveweight Produced**				
Polypeptides	Bacitracin	28.5	64.4	30.6	27.1	102.1

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in broiler chicken production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 22-35.

1 Refers to medical importance in human medicine, as defined by Appendix A of FDA GFI #152.

2 Includes sulfadimethoxine, sulfamerazine, sulfamethazine, and sulfaquinoxaline.

3 Includes chlortetracycline, oxytetracycline, and tetracycline.

Results – Disease Indications for Broiler Antimicrobial Use in Water

The study investigators also collected some preliminary data on reasons for use of antimicrobials in the water of broilers, for 2017. Listed below are the antimicrobials used in water and the main reasons for use. Complete details about reasons for use and age at time of disease onset can be found in the primary investigator's published report (Singer et al, 2020a).

- Lincomycin – gangrenous dermatitis and necrotic enteritis
- Neomycin – *E. coli* infections
- Penicillin G – gangrenous dermatitis, necrotic enteritis, and vertebral osteomyelitis
- Sulfonamides – *E. coli* infections and air sacculitis
- Tetracycline – primarily for air sacculitis and *E. coli*; also, for gangrenous dermatitis, vertebral osteomyelitis, staphylococcal infections, and synovitis
- Tylosin – necrotic enteritis
- Bacitracin – necrotic enteritis

6.6 Antimicrobial Resistance in Chickens and Retail Chicken Meat

6.6.1 Introduction

In this section, some of the available information about antimicrobial resistance specific to chicken pathogens is described. This is limited to information recently collected through the first two years of the USDA APHIS NAHLN Antimicrobial Resistance Pilot Project and results from the first year of an FDA CVM Vet-LIRN collaborative antimicrobial resistance pilot project with veterinary diagnostic laboratories.

In addition, this section highlights some of the 2019 antimicrobial resistance information for bacterial isolates collected from retail chicken samples and chicken cecal (intestinal) contents at the time of slaughter, collected through the FDA (retail meat) and USDA FSIS (cecal) components of the NARMS program. Preliminary real-time genotypic data are available on the NARMS website, but not included here since the focus of this report is on 2016-2019.

6.6.2 Antimicrobial Resistance in Chicken Pathogens

6.6.2.1 USDA APHIS NAHLN ANTIMICROBIAL RESISTANCE PILOT PROJECT – CHICKEN RESULTS (2018-2019)

As part of the USDA APHIS NAHLN Antimicrobial Resistance Pilot Project (see Chapter 3), bacterial isolates were submitted for domestic chickens, turkeys, and ducks. Pathogens tracked included ***E. coli*** and ***Salmonella enterica*** for 2018, and ***E. coli*** and ***Pasteurella multocida*** for 2019 (***Salmonella enterica*** isolates were not included for 2019 since the goal of 100 isolates was not met in 2018 for poultry). For the pilot project, information regarding production class and age was not collected. The full reports should be consulted for information on methodologies used and complete results for this project, including MIC distribution data for the isolates (USDA-APHIS, 2019b and USDA-APHIS, 2019c).

E. coli

No poultry-specific clinical breakpoints have been established by the Clinical Laboratory Standards Institute (CLSI) for ***E. coli***, with the exception of enrofloxacin, which is not approved for use in poultry, so no percentage resistance was reported.

In 2018, a total of 272 ***E. coli*** isolates from poultry were submitted in 2018 for the pilot project, and 374 isolates were submitted in 2019. In 2018, of the 272 poultry isolates, 204 (75%) were from chickens. In 2019, of the 374 poultry ***E. coli*** isolates, 253 (68%) were from chickens. Overall, the most common clinical diagnoses associated with ***E. coli*** infections in chickens for both years were septicemia/colibacillosis (31.7% and 29.6% in 2018 and 2019, respectively) and reproductive tract disease/yolk sac infections (26.3% and 20.2% in 2018 and 2019, respectively). Other less common diagnoses were peritonitis/hepatitis, pneumonia/bronchitis, air sacculitis, and enteritis.

Salmonella spp.

Poultry-specific CLSI-defined breakpoints for *Salmonella* have not been established, so no percentage resistance was reported. A total of 63 *Salmonella* spp. isolates were submitted for poultry in 2018. Of these 63 poultry isolates, 52 (82.5%) were from chickens. Twelve different serotypes were identified among these isolates. The three most common serotypes were Enteriditis (34.6% of isolates), Typhimurium (23.1%), and Kentucky (13.5%). Diagnoses associated with *Salmonella* isolates submitted for chickens included yolk sac infections, air sacculitis, colibacillosis, arthritis/synovitis, and hepatitis, among others. Twenty-six of the isolates were submitted only for *Salmonella* serotyping. Data for other serotypes can be found in the published report.

Pasteurella multocida

No antimicrobials have poultry-specific CLSI clinical breakpoints established for *P. multocida*, so no percentage resistance was reported. Of the 51 *P. multocida* isolates submitted for poultry in 2019, 39 were from chickens. Fowl cholera/septicemia was the most common diagnosis associated with *P. multocida* infections in chickens; joint infections and pneumonia were reported with less frequency.

6.6.2.2 FDA CVM VET-LIRN COLLABORATIVE PROJECT WITH VETERINARY DIAGNOSTIC LABORATORIES, ANTIMICROBIAL RESISTANCE PILOT – CHICKEN RESULTS (*SALMONELLA* ONLY)

As part of the collaborative project with veterinary diagnostic laboratories in the U.S. and Canada, Vet-LIRN collected *Salmonella* isolates from veterinary diagnostic source labs from any host animal (see Chapter 3). In 2017, 586 *Salmonella enterica* isolates were collected, 69 of which were whole genome sequenced. Only six of these isolates were of chicken origin. The serovars for these were Typhimurium (2), and one each for Cerro, Mbandaka, Kentucky, and Schwarzengrund. Five of the six isolates had no antimicrobial resistance genes (ARGs) identified. The Kentucky isolate carried 3 ARGs, including *strA* and *strB*, and *tet(B)*, conferring resistance to antimicrobials in the streptomycin and tetracycline classes, respectively (Ceric et al, 2019).

6.6.3 Antimicrobial Resistance in Chickens at Slaughter and Retail Chicken Meat

This section highlights antimicrobial resistance information for 2019, for generic *E. coli, Salmonella*, *Campylobacter*, and *Enterococcus* isolates collected from retail chicken samples and chicken cecal (intestinal) contents at the time of slaughter. This information was collected through the FDA (retail meat) and USDA FSIS (cecal) components of the NARMS program. The CDC NARMS website should be consulted for information about bacteria isolated from humans that are monitored for antimicrobial resistance. For purposes of this report, antimicrobial susceptibility testing (i.e., phenotypic) data are described, including some information about multidrug resistance (MDR, defined by the NARMS program as resistance to three or more antimicrobial classes). The NARMS program websites and most recent report (2018 NARMS Integrated Summary) can be consulted for more information, including whole genome sequencing data. **Appendix 7** provides line graphs depicting some of the resistance trends (from antimicrobial susceptibility testing) for a five-year period (2015-2019). Genotypic real-time data are published at NARMS Now and includes 2018-2021 data.

P-values, where reported in this section, were obtained using Fisher's exact test for comparing proportions (McDonald, 2014). P-values help assess statistical significance when comparing two or more sets of numerical data. In this case the proportions compared were the percentages of resistance (for a given bacteria and sample source) between 2018 and 2019, and the significance level was set at $p \leq 0.05$.

6.6.3.1 *E. COLI* – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL CHICKEN AND CHICKEN CECAL SAMPLES

Recovery of ***E. coli*** from retail chicken samples collected in the NARMS program was about 24% in 2019, down from around 63% in 2015. Recovery of ***E. coli*** from chicken cecal samples has remained stable, with a small decrease between 2018 and 2019. ***E. coli*** is a common commensal organism of the intestinal microbiota, so high prevalence levels are not unusual in animal cecal samples. **Tables 6-10 and 6-11** show the annual number of samples collected and number of ***E. coli*** isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 6-10: Number of retail chicken samples collected by year (2015-2019), and percent positive for *E. coli* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Chicken					
Number of samples	481	442	856	1556	1259
Number of isolates	305	211	352	299	304
Prevalence (%)	63.4	47.7	41.1	19.2	24.1

Table 6-11: Number of chicken cecal samples collected by year (2015-2019), and percent positive for *E. coli* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Chicken Cecal					
Number of samples	152	216	298	342	328
Number of isolates	150	212	295	335	310
Prevalence (%)	98.7	98.1	99.0	97.9	94.5

Appendix 7 shows resistance trends (2015 to 2019) for *E. coli* isolated from retail chicken and chicken cecal samples, for antimicrobials selected from the 10 antimicrobial drug classes tested. Chicken source *E. coli* isolates are generally most resistant to tetracycline and streptomycin compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *E. coli* isolates from chicken samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- During 2019, ceftriaxone-resistant *E. coli* isolates from retail chicken samples decreased by a small amount to 3.6% (from 5.7%) and also decreased to 2.9% (from 3.6%) for chicken cecal samples.
- In 2019, no decreased susceptibility to azithromycin (DSA) was detected in chicken cecal samples, and one out of 304 isolates from retail chicken showed DSA.
- *E. coli* isolates from chicken sources continue to show no carbapenem resistance (meropenem testing became routine in 2016).
- The percentage of *E. coli* isolates from retail chicken with decreased susceptibility to ciprofloxacin (DSC) increased to 3.6% in 2019 (from 1.7% in 2018). For chicken cecal samples, the percentage of *E. coli* isolates with DSC was stable compared to 2018, around 7.5%.
- Gentamicin (an aminoglycoside) resistance in *E. coli* isolates from retail chicken samples showed a statistically significant decrease between 2018 and 2019 (21.1% to 14.8%, p=0.04), and for chicken cecal samples also decreased (from 25.7% to 20.3%).
- Trimethoprim-sulfamethoxazole (a folate pathway inhibitor) resistance in *E. coli* isolates from retail chicken samples continued a downward trend (decreased to 2.3% in 2019) and was stable for chicken cecal samples, also at 2.3% in 2019.
- MDR in *E. coli* isolates decreased a small amount (to around 17-18%) in retail chicken and chicken cecal samples, comparing 2018 to 2019.

6.6.3.2 NONTYPHOIDAL *SALMONELLA* – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL CHICKEN AND CHICKEN CECAL SAMPLES

Recovery of nontyphoidal serotypes of *Salmonella* from retail chicken samples collected in the NARMS program increased in 2019, to about 16%. Between 2018 and 2019, recovery of *Salmonella* from chicken cecal samples also increased, from about 46% to 50%. **Tables 6-12 and 6-13** show the annual number of samples collected and number of *Salmonella* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 6-12: Number of retail chicken samples collected by year (2015-2019), and percent positive for *Salmonella* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Chicken					
Number of samples	3847	5528	8302	8777	8713
Number of isolates	237	241	270	325	1400
Prevalence (%)	6.2	4.4	3.3	3.7	16.1

Table 6-13: Number of chicken cecal samples collected by year (2015-2019), and percent positive for *Salmonella* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Chicken Cecal					
Number of samples	553	569	835	869	811
Number of isolates	130	134	314	399	407
Prevalence (%)	23.5	23.6	37.6	45.9	50.2

Appendix 7 shows resistance trends (2015 to 2019) for *Salmonella* isolated from retail chicken and chicken cecal samples for antimicrobials selected from the 10 antimicrobial drug classes tested. Chicken source *Salmonella* isolates are generally most resistant to streptomycin and tetracycline compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Salmonella* isolates from chicken source samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- In 2019, there was an increase in the percentage of ceftriaxone-resistant *Salmonella* isolates from retail chickens, from 10.4% in 2018 to 15.3% in 2019 (p=0.02). In contrast, ceftriaxone resistance in *Salmonella* isolates from chicken ceca decreased from 15.3% in 2018 to 12.5% in 2019. Infantis was the predominant ceftriaxone-resistant serotype among *Salmonella* isolated from retail chicken and chicken cecal samples.
- The percentage of *Salmonella* isolates with DSC increased in 2019 for chicken source samples. For retail chicken, DSC in *Salmonella* isolates significantly increased (from 17.6% in 2018 to 31.4% in 2019, p<0.01). For *Salmonella* isolates from chicken ceca, DSC also increased (from 26.3% to 31.7%) in the same time period. Infantis was the predominant serotype with DSC among *Salmonella* isolated from retail chicken and chicken ceca. Increases in DSC among poultry isolates has primarily been due to the increase in MDR Infantis that

exhibited DSC caused by mutations in the *gyrA* gene (NARMS, 2020b).

- No DSA in *Salmonella* isolates from chicken sources was detected in 2019.
- No carbapenem resistance was detected in *Salmonella* isolates from chicken sources in 2019 (meropenem testing became routine in 2016).
- For *Salmonella* isolated from chicken ceca in 2019, there was a significant decrease in gentamicin resistance (from 7% to 2%, $p<0.01$) and also a significant decrease for retail chicken isolates (from 9.5% to 4.8%, $p<0.01$).
- For *Salmonella* isolated from retail chicken in 2019, there were significant increases in resistance to other drugs (e.g., ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline) and for chicken cecal samples, a significant decrease in streptomycin resistance was seen.
- The percentage of MDR *Salmonella* isolates increased for retail chicken between 2018 and 2019 and remained stable for chicken cecal samples. For retail chickens, it increased from 20.2% to 31.6% ($p<0.01$); and for chicken cecal samples it was stable, around 32%. The predominant MDR serotype was Infantis. As noted in the NARMS 2018 Integrated Report, the MDR Infantis strain has become the leading poultry serotype since its first identification in 2014. This strain shows decreased susceptibility to fluoroquinolones and contains an MDR plasmid that carries up to 10 resistance genes. It has been identified in retail poultry, cecal samples, and human patients. While the initial human cases of illness were associated with international travel, the later cases were mainly domestically acquired. NARMS researchers believe that this represents international spread of a clone that emerged in one region and spread to other countries. While it carries resistance to antimicrobial drugs not used in domestic poultry production systems, this strain has gained a foothold in U.S. poultry production and can even be found in animals and food products raised without antimicrobials (NARMS, 2020b).

6.6.3.3 *CAMPYLOBACTER* SPP. – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL CHICKEN AND CHICKEN CECAL SAMPLES

Recovery of *Campylobacter* from retail chicken samples collected in the NARMS program increased to around 14% in 2019, from about 11% in 2018. Recovery of *Campylobacter* from chicken cecal samples collected in the NARMS program increased to about 66% in 2019. **Tables 6-14 and 6-15** show the annual number of samples collected and number of *Campylobacter* spp. isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 6-14: Number of retail chicken samples collected by year (2015-2019), and percent positive for *Campylobacter* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Chicken					
Number of samples	2402	3081	4284	4860	4664
Number of isolates	577	538	773	546	665
Prevalence (%)	24.0	17.5	18.0	11.2	14.3

Table 6-15: Number of chicken cecal samples collected by year (2015-2019), and percent positive for *Campylobacter* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Chicken Cecal					
Number of samples	553	574	827	867	808
Number of isolates	53	59	235	410	536
Prevalence (%)	9.6	10.3	28.4	47.3	66.3

Appendix 7 shows resistance trends (2015 to 2019) for *Campylobacter jejuni* (*C. jejuni*) and *Campylobacter coli* (*C. coli*) isolated from retail chicken and chicken cecal samples, for antimicrobials from six of the antimicrobial drug classes tested. Chicken source *Campylobacter* isolates are generally most resistant to tetracyclines compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Campylobacter* spp. isolates from chicken samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- In 2019, there were small but not statistically significant changes in ciprofloxacin resistance among *Campylobacter* spp. isolated from chickens as compared to the previous year. For *C. coli*, there was a decrease in ciprofloxacin resistance in retail chicken (from 17.5% in 2018 to 15.7% in 2019); cecal samples also showed a decrease, from 19% to 16.7%. For *C. jejuni*, there was a small increase in ciprofloxacin resistance for retail chickens (from 19.8% to 22.4%) and a small increase for chicken ceca (from 20.5% to 25.6%).
- No macrolide (azithromycin or erythromycin) resistance was detected on antimicrobial susceptibility testing for *C. jejuni* isolates from chicken ceca in 2019. For retail chicken, macrolide resistance in *C. jejuni* isolates remained below 1% in 2019, with only one of 428 isolates showing resistance. Between 2018 and 2019, macrolide resistance increased a small amount in *C. coli* isolates from retail chickens (from 2.6% to 3.8%) and remained stable for chicken ceca (below 5%).
- Tetracycline resistance in *C. coli* and *C. jejuni* isolates from retail chicken significantly increased between 2018 and 2019 (from 35% to 50% and from 37% to 49%, respectively; $p<0.01$), but was stable for chicken cecal isolates.
- Clindamycin (a lincosamide) resistance in *C. jejuni* isolates from chicken ceca significantly decreased between 2018 and 2019 (from 3.4% to zero, $p<0.01$).
- MDR *C. jejuni* isolates from chicken ceca decreased to below 1% in 2019 and remained zero in retail chicken isolates. For *C. coli* isolates, MDR increased a small amount for retail chicken (from 1.6% to 3.4%, representing eight isolates) and decreased to below 5% for chicken cecal isolates.

6.6.3.4 *ENTEROCOCCUS* SPP. – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL CHICKEN AND CHICKEN CECAL SAMPLES

Recovery of *Enterococcus* from retail chicken samples collected in the NARMS program was around 26% in 2019, and stable for chicken cecal samples. *Enterococcus* spp. are a common commensal organism of the intestinal microbiota of humans and animals, so high prevalence levels are not unusual. **Tables 6-16 and 6-17** show the annual number of samples collected and number of *Enterococcus* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 6-16: Number of retail chicken samples collected by year (2015-2019), and percent positive for *Enterococcus* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Chicken					
Number of samples	489	442	708	1459	1126
Number of isolates	365	275	342	281	291
Prevalence (%)	74.6	62.2	48.3	19.2	25.8

Table 6-17: Number of chicken cecal samples collected by year (2015-2019), and percent positive for *Enterococcus* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Chicken Cecal					
Number of samples	152	216	300	342	328
Number of isolates	151	210	293	323	310
Prevalence (%)	99.3	97.2	97.7	94.4	94.5

Appendix 7 shows resistance trends (2015 to 2019) for *Enterococcus faecalis* (*E. faecalis*) and *Enterococcus faecium* (*E. faecium*) isolated from retail chicken and chicken cecal samples, for antimicrobials from nine of the antimicrobial drug classes tested. Chicken source *Enterococcus* isolates are generally most resistant to tetracyclines and/or streptogramins compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Enterococcus* spp. isolates from chicken source samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- Between 2018 and 2019, macrolide (erythromycin) resistance in ***E. faecalis*** and ***E. faecium*** isolates from retail chicken and chicken cecal samples decreased by variable amounts (except ***E. faecalis*** from retail chicken, which increased from 22.4% to 27.5%).
- In 2019, ciprofloxacin resistance was not detected in chicken cecal ***E. faecalis*** isolates and was detected in only two of 160 retail chicken isolates. For ***E. faecium***, ciprofloxacin resistance decreased in retail chicken (from 28.2% to 19%) and increased for chicken ceca (from 7.1% to 14.6%, representing six isolates).
- Since cecal testing began in 2013, there has been a substantial decrease in gentamicin resistance in ***E. faecalis*** isolates from chicken cecal samples (from 45.7% in 2013 to 11.4% in 2019). Gentamicin resistance in ***E. faecalis*** from retail chicken also decreased, from 24.3% in 2013 to 5% in 2019. For ***E. faecium***, gentamicin decreased to below 1% for retail chicken in 2019, and decreased to below 3% for chicken ceca.
- ***Enterococcus spp.*** isolates from retail chicken and chicken ceca continue to show no linezolid resistance and no vancomycin resistance.
- Streptomycin resistance in ***E. faecalis*** isolates from chicken ceca significantly decreased between 2018 and 2019 (from 12.2% to 5.9%, p=0.02).
- Between 2018 and 2019, MDR ***E. faecalis*** was stable for retail chicken (aaround 10%) and decreased below 10% for cecal samples. For ***E. faecium***, MDR was stable for retail chicken and chicken cecal samples, around 17-18%.

6.7 Antimicrobial Stewardship in Chicken Production

6.7.1 Introduction

The FDA and other U.S. federal government agencies, as well as state government agencies and national and state veterinary medical associations, support the efforts of poultry veterinarians and producers in actions taken to preserve the effectiveness and availability of antimicrobials for animals and humans. In addition, veterinary and producer associations have developed strategies and taken steps to provide information to veterinarians and producers working within these industries in the U.S. to reduce the need for antimicrobials and to use them judiciously when necessary.

Poultry integrators have changed production practices to meet the demands of the marketplace in the U.S. Poultry growers, nutritionists, and veterinarians have been developing ways to raise birds using fewer antimicrobials while still maintaining good performance and welfare without increasing food safety concerns. In addition, the USDA's Agricultural Research Service National Poultry Research Center and others conduct research in several areas important to poultry health, including development of new strategies and non-antimicrobial alternatives for disease prevention and treatment that do not result in creation of selection pressures favoring the development of antimicrobial resistance.

Programs such as the National Poultry Improvement Plan (NPIP) administered by USDA APHIS work to improve poultry health by establishing standards for testing of poultry breeding stock, chicks, poults, and hatching eggs with respect to freedom from certain diseases, including avian influenza, *Salmonella* Pullorum, *Salmonella* Gallinarum, *Salmonella* Enteriditis, *Mycoplasma gallisepticum*, *Mycoplasma synoviae*, and *Mycoplasma meleagridis*. The NPIP was established in the 1930s and is a voluntary State-Federal cooperative testing and certification program for poultry. In addition to disease monitoring, NPIP has established programs such as 'U.S. *Salmonella* Monitored' and 'U.S. Sanitation Monitored' that are intended to reduce the incidence of *Salmonella* in hatching eggs, chicks, and poults (USDA-APHIS, 2020b). Programs such as NPIP that work to improve poultry health also help to provide information that could be useful for informing disease prevention programs for poultry, including strategies that could help reduce the need for antimicrobials.

6.7.2 Resources

The American Association of Avian Pathologists (AAAP) has published information about poultry health and judicious use of antimicrobials in poultry production on their website. This organization has also developed guidelines for judicious therapeutic use of antimicrobials in poultry following the AVMA framework. These guidelines are available on AVMA's website (AVMA, 2020).

A number of national and state trade and industry associations have also established resources to assist poultry producers and veterinarians with adopting the basic tenets of antimicrobial stewardship; for example, the National Chicken Council and the U.S. Poultry & Egg Association. In addition, a number of organizations involved with poultry production have made public commitments as part of the U.S. government's AMR Challenge.

CHAPTER 7

Antimicrobial Use and Resistance in U.S. Turkey Production

7.1 Introduction

7.2 Turkey Production in the U.S.

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7.6 Antimicrobial Resistance in Turkeys and Retail Turkey Meat

7.7 Antimicrobial Stewardship in Turkey Production

7.1 Introduction

Poultry are domesticated bird species that can be raised for eggs, meat, and/or feathers. The term 'poultry' covers a wide range of birds and may include chickens, turkeys, geese, ducks, quail, pheasants, pigeons, peafowls, and guineas (Taylor, 1998). Worldwide, poultry production is the largest meat industry (FAO, 2021a) and this sector continues to grow in many parts of the world largely due to increasing populations and urbanization. Turkeys accounted for about 2% of the world's poultry population in 2019 (FAO, 2021c). Advances in poultry nutrition and processing technologies have led to improvements in efficiency and have resulted in concentration of large-scale poultry production close to input sources (such as feed) and vertical integration, as well as an increase in contract farming (FAO, 2021c). Traditional small-scale, rural, or family-based poultry systems still play a vital role in supporting livelihoods, especially in developing countries.

This chapter focuses on one part of the U.S. poultry industry: turkeys raised for meat production. Poultry production requires a suitable physical environment, optimal nutrition, and protection from disease for the flock. This is often achieved through partial confinement, except in some free-range systems where birds spend more time foraging. This chapter focuses on turkeys raised in typical commercial production systems.

7.2 Turkey Production in the U.S.

Detailed information about poultry populations, production practices, and economic indicators are routinely or periodically published by USDA agencies, including the USDA Economic Research Service (ERS), the USDA National Agricultural Statistics Service (NASS), and the USDA Animal and Plant Health Inspection Service (APHIS), which conducts studies through the National Animal Health Monitoring System (NAHMS). Reports on these agency websites should be consulted for more information. In this section, we briefly summarize information about U.S. turkey production to provide context for populations and antimicrobial use practices discussed later in the chapter.

The U.S. is the world's largest producer of turkeys and turkey meat according to the most recently available data from FAOSTAT (FAO, 2021d). U.S. exports of turkey meat have averaged around 8% of commercial turkey meat production for the last 3 years (USDA-ERS, 2020b) and according to 2019 FAOSTAT data, the U.S. was the largest exporter of turkey meat (FAO, 2021d). In 2019, approximately 229 million turkeys were raised in the U.S., with a total amount live weight produced of 7.4 billion pounds, similar to the prior year. Minnesota was the State with the highest inventory of turkeys followed by North Carolina and Arkansas (USDA-NASS, 2020f). Turkey meat production in the U.S. totaled about 5.8 billion pounds (chilled and frozen) in 2019 (USDA-NASS, 2020g). According to the most recent food availability data published by USDA ERS, the availability (a proxy measure for consumption) of boneless turkey meat to consumers in the U.S. was 12.6 pounds per capita in 2019 (USDA-ERS, 2021c).

In commercial turkey production, reproduction occurs primarily through the use of artificial insemination programs. Turkey breeder females begin laying around 28 weeks of age and eggs are incubated in the hatchery.

Similar to broiler production companies, much of the turkey industry is also vertically integrated. Most integrated turkey growing companies own their own hatcheries, feed mills, and processing plants. Poults hatch after 28 days and are transported to a grow-out farm. Farmers who have contracts with integrator companies typically handle the raising of birds from poult to market weight. Birds are grown to different weights depending on the market for which they are intended. Female birds typically reach 14-20 pounds in 12-14 weeks, while tom turkeys reach about 35-42 pounds body weight in 16-19 weeks. Once the birds reach the desired weight, they are transported to a processing plant (Clauer, 2016).

Turkeys may also be pasture-raised for organic markets. As for organic chicken production, the USDA National Organic Program sets organic turkey production and processing requirements and specifies which substances (such as animal drugs and feed additives) are allowed and prohibited (USDA-AMS, 2021). The USDA's Food Safety and Inspection Service (FSIS) is responsible for evaluation of poultry and other meat labeling claims, such as 'raised without antibiotics' and 'no antibiotics ever', among other animal-raising claims on meat labels (USDA-FSIS, 2019).

7.3 Turkey Health: Examples of Bacterial Diseases

Bacterial diseases in turkeys may affect any body system, but often affect the respiratory and enteric (intestinal) systems. An extensive review of these is beyond the scope of this report; however, **Table 7-1** shows some examples of bacterial pathogens of turkeys and associated disease processes - it is not intended to be an exhaustive list of all potential bacterial diseases of turkeys. Veterinary and poultry health references can be consulted for detailed information about bacterial diseases of poultry including disease epidemiology, risk factors, diagnosis, prevention, and therapeutic management. Also shown in Table 7-1 are examples of antimicrobials which are currently approved for use in turkeys for therapy of these infections. Some of the drugs are approved only for certain turkey production types (e.g., poults, growing turkeys, etc.). Table 7-1 is not intended to be an exhaustive list of all bacterial pathogens of turkeys and all approved antimicrobials for turkeys, but rather to provide examples. AnimalDrugs@FDA can be searched to find specific drug products with approved label information. Not all approved drugs are currently marketed in the U.S. Animal drug sponsors (i.e., pharmaceutical companies) decide what products they will manufacture and market at any given time. As discussed in Appendix 3, veterinarians may legally prescribe extralabel uses of approved animal drugs under specific conditions. Table 7-1 is not intended to capture legal extralabel use of approved antimicrobials.

Table 7-1: Examples of bacterial pathogens affecting turkeys and examples of FDA-approved antimicrobials for therapy of these infections

Bacterial Pathogen(s)	Disease Process(es)	Examples of FDA-Approved Therapeutic Antimicrobials[1,2]
Arizona paracolon	Early poult mortality	Gentamicin; Spectinomycin
***Eimeria* species**[3]	Intestinal (Coccidiosis)	Lasalocid[4]; Monensin[4]; Sulfadimethoxine; Sulfadimethoxine-ormetoprim; Sulfamerazine; Sulfamethazine; Sulfaquinoxaline
Escherichia coli	Multiple Systems – Respiratory; Intestinal; Septicemia	Ceftiofur; Neomycin; Oxytetracycline; Spectinomycin; Sulfomyxin
Erysipelothrix rhusiopathiae	Erysipelas	Penicillin
Mycoplasma meleagridis	Air sacculitis	Gentamicin; Spectinomycin
Mycoplasma gallisepticum	Respiratory Disease/ Infectious Sinusitis/Air Sacculitis	Oxytetracycline; Tylosin
Mycoplasma synoviae	Synovitis; Air Sacculitis	Chlortetracycline; Neomycin-oxytetracycline; Oxytetracycline; Tetracycline
Pasteurella multocida	Fowl Cholera (Multiple Systems – Respiratory; Intestinal; Septicemia)	Novobiocin[4]; Oxytetracycline; Sulfadimethoxine; Sulfadimethoxine-ormetoprim; Sulfamerazine; Sulfamethazine; Sulfaquinoxaline
***Salmonella* Gallinarum**	Fowl Typhoid (Multiple Systems – Intestinal; Respiratory; Septicemia; Early Mortality)	Sulfaquinoxaline
Salmonella Typhimurium	Fowl Paratyphoid (Enteritis)	Chlortetracycline
Spironucleus* (formerly *Hexamita*) *meleagridis	Hexamitiasis	Chlortetracycline; Neomycin-oxytetracycline; Oxytetracycline
***Staphylococcus* species**	Synovitis; Gangrenous dermatitis; Breast blisters	Novobiocin[4]

1 See AnimalDrugs@FDA for information about approved antimicrobials, including specific indications, dose, duration, approved production classes, limitations, and approved combination products.
2 Not all antimicrobials are currently marketed.
3 *Eimeria* spp. are protozoal organisms, not bacteria, but are a common infection in chickens for which antimicrobials may be used for therapy. Not all approved anticoccidial drugs or coccidiostats are shown in this table.
4 Not currently considered a medically important antimicrobial according to Appendix A of FDA GFI #152.

7.4 Antimicrobial Sales and Biomass-Adjusted Antimicrobial Sales Estimates for Turkeys

7.4.1 Introduction

In this section, information is presented about antimicrobial sales and distribution estimates for turkeys. These data are not necessarily indicative of how the antimicrobials were actually administered to or used in turkeys (e.g., for what indications, doses, or durations). Antimicrobial use information (i.e., record of on-farm administration) is helpful to determine what disease pressures exist and could help inform stewardship practices, as discussed later in this chapter. The overall amount of antimicrobials sold and used in turkeys is expected to change from year to year and will depend on multiple factors, including turkey populations and disease pressures faced each year.

In order to further characterize the species-specific antimicrobial sales and distribution estimates, a biomass denominator adjustment is also included in this section. This allows for a representation of trends in annual antimicrobial sales and distribution relative to the estimated turkey population in the U.S. in which the antimicrobials could be used.

7.4.2 Medically Important Antimicrobial Sales and Distribution Estimates for Turkeys

Table 7-2 shows the species-specific sales and distribution estimates, by medically important antimicrobial drug class, reported by antimicrobial drug sponsors for turkeys for 2016 through 2019, as well as the percent change in these estimates between time periods. Only the following drug classes can be shown for all four years because they had at least three drug sponsors and had species-specific estimates for turkeys: aminoglycosides, macrolides, penicillins, sulfonamides, and tetracyclines. Other medically important drug classes that may have had drug sales for turkeys include cephalosporins and streptogramins. However, these are not independently reported classes for turkeys (due to lack of three or more drug sponsors), so data cannot be shown in order to protect confidential business information of drug sponsors.

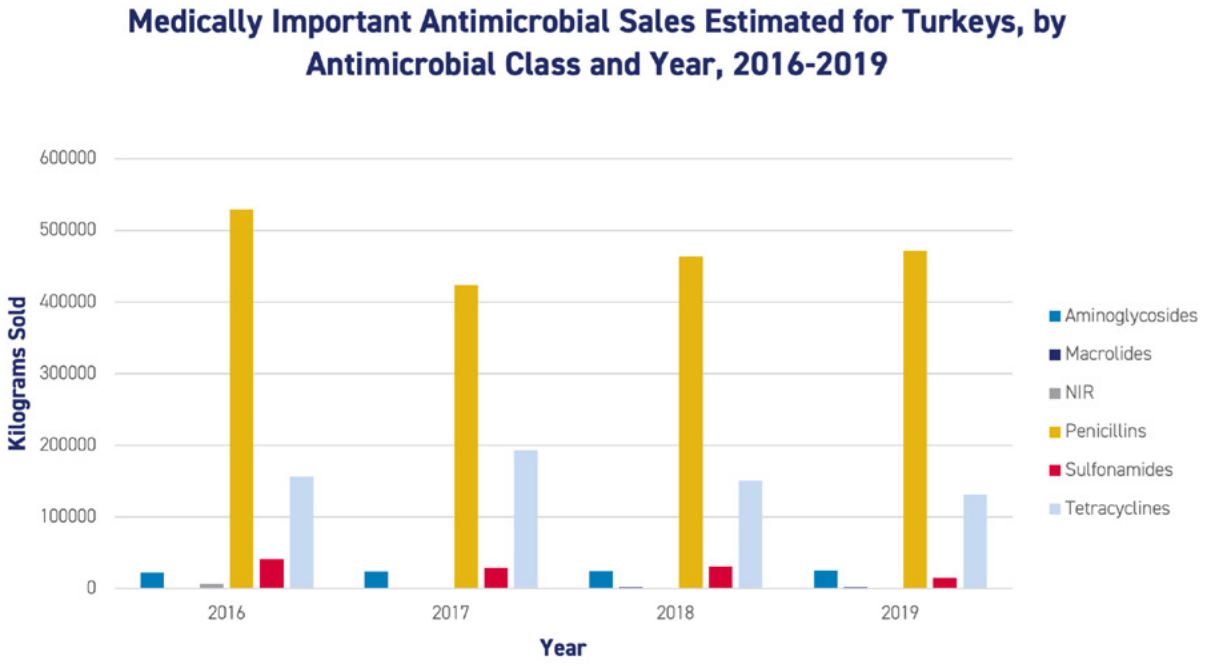
The majority of medically important antimicrobial sales estimated by drug sponsors for turkeys each year for 2016 through 2019 were for penicillins. **Figure 7-1** contains the same sales information as Table 7-2, but visually demonstrates the magnitude of the penicillin class compared to the other medically important antimicrobial classes. As noted in Appendix 3, GFI #213 was completely implemented as of January 1, 2017. Between 2016 and 2017, total medically important antimicrobial sales estimated for turkeys decreased by about 11%, particularly for penicillins and sulfonamides. Between 2017 and 2018, there were variable increases for most classes (with the exception of tetracyclines, which decreased), although the increase in overall sales was very small (0.04%). Between 2018 and 2019, sulfonamides and tetracyclines decreased, there were small increases in other drug classes, and there was an overall decrease in sales of about 4%. The overall percent change in sales comparing 2016 and 2019 indicates a decrease of approximately 15% in total estimated sales for turkeys. While macrolides and aminoglycosides did increase during that time period, these two classes made up less than 4% of total sales, with macrolides representing only about 0.2% of total sales. Since the requirement for drug sponsors is only to provide estimated species-specific antimicrobial drug sales and distribution for the four major food-producing species, it is not possible to further break down the sales and distribution estimates into the various turkey production types (e.g., breeders, growing, etc.).

Table 7-2: Medically important antimicrobial sales and distribution estimates for turkeys by reportable drug class, 2016-2019

Medically Important Antimicrobial Drug Class	2016 Estimated Annual Sales Totals for Turkeys (kg)	2017 Estimated Annual Sales Totals for Turkeys (kg)	2018 Estimated Annual Sales Totals for Turkeys (kg)	2019 Estimated Annual Sales Totals for Turkeys (kg)	Overall Percent Change in Sales from 2016 to 2017	Overall Percent Change in Sales from 2017 to 2018	Overall Percent Change in Sales from 2018 to 2019	Overall Percent Change in Sales from 2016 to 2019
Aminoglycosides	22,198	24,042	24,321	25,125	8.3%	1.2%	3.3%	13.2%
Macrolides	1,176	1,307	1,653	1,944	11.1%	26.5%	17.6%	65.3%
Penicillins	529,083	423,689	463,939	471,660	-19.9%	9.5%	1.7%	-10.9%
Sulfonamides	41,127	28,817	30,446	14,908	-29.9%	5.7%	-51.0%	-63.8%
Tetracyclines	156,617	192,976	150,749	131,034	23.2%	-21.9%	-13.1%	-16.3%
NIR[1]	6,419	0	0	250	-100%	--	--	-96.1%
Total	756,620	670,831	671,108	644,921	-11.3%	0.04%	-3.9%	-14.8%

1 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For turkeys, drug classes which cannot be shown in order to protect confidential business information are Cephalosporins, Diaminopyrimidines, Lincosamides, Polymyxins, and Streptogramins. The value of sales for this category was therefore calculated as the overall annual sales total for turkeys minus the sum of all reportable classes for that year. The individual drug classes within the NIR category may or may not have had actual sales in any given year.

Figure 7-1: Medically important antimicrobial sales and distribution estimates for turkeys, by antimicrobial class and year, 2016-2019



*NIR: Antimicrobial classes for turkeys which are not individually reportable in order to protect confidential business information – may include Cephalosporins, Diaminopyrimidines, Lincosamides, Polymyxins, and Streptogramins.

7.4.3 Biomass-Adjusted Medically Important Antimicrobial Sales and Distribution Estimates for Turkeys

Appendix 4 shows the population and weight in kilograms (kg) for each category of turkeys for 2016 through 2019. Using these data, the biomass total calculated for turkeys (including all categories) was approximately 3.4 billion kg in 2016, approximately 3.4 billion kg in 2017, and approximately 3.3 billion kg in 2018 and 2019, representing about a 1.4% decrease in estimated U.S. turkey biomass between 2016 and 2019.

Using the estimated annual total sales for medically important antimicrobials by drug class (in mg) for turkeys and estimated annual turkey biomass (target animal biomass [TAB], in kg), **Table 7-3** shows the biomass-adjusted medically important antimicrobial sales and distribution data for turkeys, by drug class and year. Table 7-3 also indicates the percent change in mg/TAB for each reportable drug class between time periods. With the exception of aminoglycosides and macrolides, for antimicrobial drug classes that can be shown, there was a decrease in the mg/TAB values comparing 2016 to 2019, and an overall decrease in mg/TAB of about 13%.

Table 7-3: Biomass-adjusted medically important antimicrobial sales and distribution estimates for turkeys, by reportable drug class, 2016-2019

Medically Important Antimicrobial Drug Class	2016 Estimated mg/ TAB for Turkeys	2017 Estimated mg/ TAB for Turkeys	2018 Estimated mg/ TAB for Turkeys	2019 Estimated mg/ TAB for Turkeys	Percent Change[1] in mg/TAB 2016 - 2017	Percent Change[1] in mg/TAB 2017 - 2018	Percent Change[1] in mg/TAB 2018 - 2019	Percent Change[1] in mg/TAB 2016 - 2019
Aminoglycosides	6.56	7.10	7.29	7.60	8.2%	2.7%	4.3%	15.9%
Macrolides	0.35	0.39	0.50	0.59	11.1%	28.3%	18.8%	69.3%
Penicillins	156.29	125.08	138.98	142.69	-20.0%	11.1%	2.7%	-8.7%
Sulfonamides	12.15	8.51	9.12	4.51	-30.0%	7.2%	-50.6%	-62.9%
Tetracyclines	46.27	56.97	45.16	39.64	23.1%	-20.7%	-12.2%	-14.3%
NIR[2]	1.90	0	0	0.08	-100%	--	--	-96.0%
Total[1]	223.51	198.04	201.05	195.11	-11.4%	1.5%	-3.0%	-12.7%

1 Calculations of percent change and totals were performed using the raw (unrounded) data for estimated mg/TAB. Calculations using the rounded numbers in this table will not yield exactly the same result.

2 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For turkeys, drug classes which cannot be shown in order to protect confidential business information are Cephalosporins, Diaminopyrimidines, Lincosamides, Polymyxins, and Streptogramins. The value of sales for this category used in the mg/TAB calculation was therefore calculated as the overall annual sales total for turkeys minus the sum of all reportable classes. The individual drug classes within the NIR category may or may not have had actual sales in any given year.The turkey biomass denominator is applied to the NIR category as a whole; therefore does not account for potential exclusions of turkey categories for the denominator that may otherwise apply to individual NIR classes.

Table 7-4 shows the comparison of percent change in species-specific estimated sales volume (kg) and the percent change in biomass-adjusted species-specific estimated sales (mg/TAB) between 2016 and 2019 for turkeys. With the approximately 1.4% decrease in estimated turkey biomass between 2016 and 2019, the biomass denominator adjustment resulted in a variable degree of difference in the percent change in mg/TAB relative to the percent change in species-specific estimated sales volume (kg) for antimicrobial drug classes which can be reported.

Table 7-4: Percent change in estimated sales and distribution data for turkeys in sales volume (kg) and adjusted by a biomass denominator (mg/TAB), between 2016 and 2019

Medically Important Antimicrobial Drug Class	Percent Change in Species-Specific Estimated Sales Volume from 2016 to 2019	Percent Change in Biomass Adjusted Species-Specific Estimated Sales (mg/TAB) from 2016 to 2019
Aminoglycosides	13.2%	15.9%
Macrolides	65.3%	69.3%
Penicillins	-10.9%	-8.7%
Sulfonamides	-63.8%	-62.9%
Tetracyclines	-16.3%	-14.3%
NIR[1]	-96.1%	-96.0%
Total	-14.8%	-12.7%

1 NIR (Not Independently Reported). Certain drug classes are not reported independently at the species level in the summary reports on antimicrobials sold or distributed for use in food-producing animals, but rather values for all species have been combined to protect confidential information. In addition, some antimicrobial classes for which there are fewer than three distinct sponsors actively marketing products domestically are not independently reported. For turkeys, drug classes which cannot be shown in order to protect confidential business information are Cephalosporins, Diaminopyrimidines, Lincosamides, Polymyxins, and Streptogramins. The individual drug classes within the NIR category may or may not have had actual sales in any given year.The turkey biomass denominator is applied to the NIR category as a whole; therefore does not account for potential exclusions of turkey categories for the denominator that may otherwise apply to individual NIR classes.

7.5 Antimicrobial Use in Turkeys

7.5.1 Introduction

Nationally-representative and continuously collected data on antimicrobial use in turkeys in the U.S. are not currently publicly available. Some information about antimicrobial use in poultry has been collected and published by USDA APHIS through periodic studies conducted by NAHMS; however, no studies specifically for turkeys. The NAHMS Poultry 2010 study did report on the prevalence and risk factors for clostridial dermatitis in U.S. turkey-grower farms, but no information about antimicrobial use was included beyond mention that ionophores were used. Complete reports from this and other poultry studies are available on the NAHMS website. This section presents turkey-specific data from part of an FDA cooperative agreement awarded in 2016 intended to pilot methodologies for collection of on-farm antimicrobial use information for food-producing animals, including poultry.

7.5.2 FDA Cooperative Agreement: Antimicrobial Use Data Collection in U.S. Poultry

Chapter 3 described the Funding Opportunity Announcement that FDA issued in 2016, announcing the availability of grants in the form of cooperative agreements to develop and pilot methodologies for collecting and reporting antimicrobial use data in the four major food-producing species at the farm level. One of the grants

(5U01FD005878) was awarded for the collection and reporting of antimicrobial use data in poultry and swine. This section describes the portion of the grant aimed at characterizing antimicrobial use in U.S. poultry and presents some of the results obtained for turkeys. Chapter 6 described the overall goals and specific aims and activities of the cooperative agreement related to chickens and turkeys.

The next sections summarize results for the turkey antimicrobial use data collected during the first two years (2016-2017) of the cooperative agreement, as well as some data that were collected by the study investigator prior to the cooperative agreement being awarded. The primary investigator had begun a pilot program for data collection in the U.S. poultry system in 2014 with assistance from the poultry industry (U.S. Poultry & Egg Association). Beginning with the FDA cooperative agreement in 2016, that program was expanded to include more of the U.S. broiler and turkey industries. Recently, the study investigators published detailed reports about the results for 2016 and 2017 (Singer et al, 2020b). Data collection is ongoing, and CVM expects to publish a more complete summary of the cooperative agreement results after the conclusion of the projects. In addition, CVM will use information gained from the cooperative agreement pilot projects to help inform development of a long-term strategy to support continued antimicrobial use data collection.

7.5.2.1 TURKEY ANTIMICROBIAL USE DATA (2013-2017)

Similar to the broiler data collection, the turkey industry data collection effort targeted all major companies that raise turkeys commercially in the U.S. Companies that agreed to participate tracked production parameters, antimicrobial use for the hatchery, and antimicrobial use in turkey feed and water. Companies also provided some information on reasons for use and captured all of this information retrospectively as best possible. Surveys to capture quantitative on-farm antimicrobial use estimates were also administered. Information captured included antimicrobial compound, indication, route, dose, duration, age at administration, and number of birds receiving the drug. After experience with the initial survey design, the investigator determined that the data collection approach needed to be customized for each company due to differences in data format and availability. This made a single, standardized approach to data collection difficult for the first round of data collection.

The primary investigator's published report should be consulted for full details and results. For purposes of this report, the approach and methodology are briefly described and a summary of some of the results for turkeys are provided.

Methods – Data Collection, Aggregation, and Analysis

Data were submitted by participating companies in a variety of ways and at differing levels of granularity, for example: flock-level records, calendar year basis, feed mill data, antimicrobial purchase records, and the number of birds receiving antimicrobials for different diseases (see Chapter 6 for description of methods). Data from turkey companies were aggregated and analyzed as described for broiler chickens in Chapter 6. Representativeness (percent of U.S. turkey production that is likely covered by this data collection effort) was calculated as described in Chapter 6.

Measurements of Antimicrobial Use

The study investigators used the following measurements to summarize antimicrobial use data:

- Hatchery antimicrobials:
  - Total kilograms of each antimicrobial used per year;
  - Total grams of each antimicrobial class used per year per 100,000 birds placed during that year
- Antimicrobials used in feed or water:
  - Total kilograms of each antimicrobial used per year;
  - Total grams of each antimicrobial class used per year per 1,000,000 pounds liveweight slaughtered during that year

Due to differences in drug potencies and pharmacokinetic/pharmacodynamic properties, the weights of antimicrobials were not summed across antimicrobial classes or across different routes of administration.

Results – Turkey Hatchery Antimicrobial Use

The turkey hatchery data representativeness ranged from 77 to 82% of U.S. turkey production, depending on the year (2013-2017). **Table 7-5** shows the total amounts of antimicrobials used in participating turkey hatcheries each year. Note that the upper part of the table shows total kilograms of drug, while the lower part of the table shows the drug amounts in grams of antimicrobial used per 100,000 birds placed. **Figure 7-2** shows the turkey hatchery antimicrobial use as a percentage of total birds placed each year.

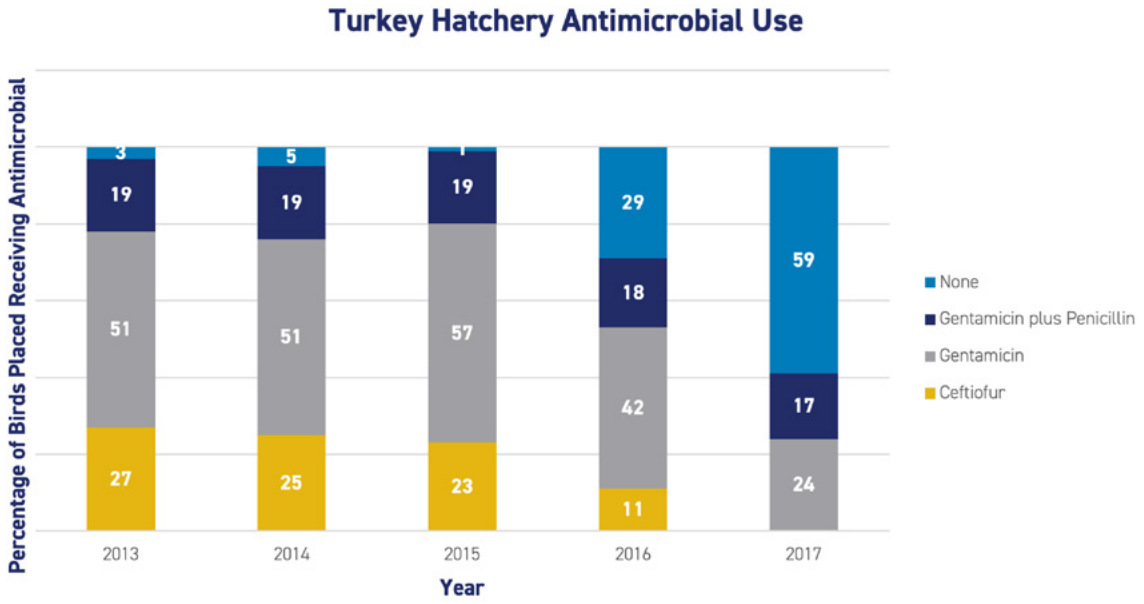
The main antimicrobial used in turkey hatcheries was gentamicin given as a subcutaneous injection in day-old poults, although some of the administration was *in ovo* (injected into the egg). Gentamicin is approved for use in turkeys as an aid in prevention of early mortality of 1 to 3-day old turkeys associated with *Arizona paracolon* infections susceptible to gentamicin. There was also some ceftiofur use in the hatchery; ceftiofur is approved for control of early mortality associated with *E. coli* infections susceptible to ceftiofur, in day-old turkey poults. Some penicillin use was also reported; when it was used it was used in combination with gentamicin. As shown in Table 7-5, gentamicin use decreased by about 42% (in grams per 100,000 birds placed) between 2013 and 2017, penicillin use dropped by 9%, and ceftiofur use dropped to zero. Overall, the percentage of turkey poults placed that received antimicrobials in the hatchery decreased from 96% to 41% between 2013 and 2017 (Figure 7-2).

Table 7-5: Turkey hatchery antimicrobial use, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
		Kilograms of Drug				
Aminoglycosides	Gentamicin	126.4	128.6	139.7	114.8	76.0
Cephalosporins	Ceftiofur	19.4	18.2	16.8	8.3	-
Penicillins	Penicillin G	271.5	280.3	283.5	280.7	254.5
		Grams of Drug per 100,000 Birds Placed				
Aminoglycosides	Gentamicin	69.5	70.2	76.8	60.1	40.6
Cephalosporins	Ceftiofur	10.7	9.9	9.2	4.4	-
Penicillins	Penicillin G	149.3	152.9	155.7	146.9	136.1

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 36-50.

Figure 7-2: Turkey hatchery antimicrobial use, 2013-2017, as a percentage of birds placed



Source: Singer RS et al. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013-2017. ***Zoonoses Public Health*** 2020; 67(Suppl.1): 36-50.

Results – Turkey Antimicrobial Use in Feed

The turkey antimicrobial use in feed data representativeness ranged from 77 to 82% of U.S. turkey production, depending on the year (2013-2017). **Tables 7-6 and 7-7** show the amounts of antimicrobials used in turkey feed each year, by drug class and year, for both medically important and non-medically important antimicrobials (as defined by GFI #152). Table 7-6 shows total kilograms of drug, while Table 7-7 shows the amount in grams of antimicrobial used per 1 million pounds liveweight produced.

The main medically important antimicrobial classes used in turkey feed were tetracyclines (chlortetracycline and oxytetracycline) and streptogramins (virginiamycin). All of the medically important antimicrobial classes used showed a decline between 2013 and 2017. Diaminopyrimidines and sulfonamides had no use in 2016 and 2017, and streptogramins dropped to zero in 2017. In terms of grams per 1 million pounds liveweight, tetracyclines showed a decrease of about 67% between 2013 and 2017. Along with these decreases, between 2013 and 2017 there were some shifts to more use of non-medically important antimicrobials, such as bambercycins. Between 2016 and 2017 there were overall decreases in lasalocid, monensin, and bacitracin.

Table 7-6: Antimicrobial use (in kilograms) in turkey feed, by drug class, ingredient, and year, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
Medically Important Antimicrobials[1]		**Kilograms of Drug**				
Diaminopyrimidines	Ormetoprim	927.5	467.2	486.8	0	0
Streptogramins	Virginiamycin	29,544.0	43,710.7	25,057.4	7,239.3	0
Sulfonamides	Sulfadimethoxine	1,545.9	778.7	811.3	0	0
Tetracyclines	Tetracyclines[2]	95,818.0	52,215.4	50,327.6	70,994.0	33,316.3
Not Medically Important Antimicrobials[1]		**Kilograms of Drug**				
Glycolipids	Bambermycins	222.0	619.1	0	310.4	1,163.5
Ionophores	Lasalocid	86,846.4	75,876.4	100,913.9	110,550.3	60,268.6
	Monensin	39,933.3	73,930.4	57,248.0	75,271.0	58,837.8
Polypeptides	Bacitracin	65,268.4	38,212.2	54,458.4	64,941.9	54,245.3

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 36-50.
1 Refers to medical importance in human medicine; as defined by Appendix A of FDA GFI #152
2 Includes chlortetracycline and oxytetracycline.

Table 7-7: Antimicrobial use (in grams per 1 million pounds liveweight produced) in turkey feed, by drug class, ingredient, and year, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
Medically Important Antimicrobials[1]		**Grams of Drug per 1 Million Pounds Liveweight Produced**				
Diaminopyrimidines	Ormetoprim	190.9	93.7	101.8	0	0
Streptogramins	Virginiamycin	6,082.2	8,764.5	5,238.6	1,378.8	0
Sulfonamides	Sulfadimethoxine	318.2	156.1	169.6	0	0
Tetracyclines	Tetracyclines[2]	19,725.8	10,469.8	10,521.8	13,521.2	6,433.7
Not Medically Important Antimicrobials[1]		**Grams of Drug per 1 Million Pounds Liveweight Produced**				
Glycolipids	Bambermycins	45.7	124.1	0	59.1	224.7
Ionophores	Lasalocid	17,878.9	15,214.1	21,097.6	21,054.9	11,638.4
	Monensin	8,221.0	14,824.0	11,968.6	14,335.8	11,362.1
Polypeptides	Bacitracin	13,436.7	7,662.0	11,385.4	12,368.6	10,475.2

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 36-50.
1 Refers to medical importance in human medicine; as defined by Appendix A of FDA GFI #152.
2 Includes chlortetracycline and oxytetracycline.

Results – Turkey Antimicrobial Use in Water

The turkey antimicrobial use in water data representativeness ranged from 70 to 93% of U.S. turkey production, depending on the year (2013-2017). **Tables 7-8 and 7-9** show the amounts of antimicrobials used in turkey water each year, by drug class and year, for both medically important and non-medically important antimicrobials (as defined by FDA GFI #152). Table 7-8 shows total kilograms of drug, while Table 7-9 shows the amount in grams of antimicrobial used per 1 million pounds liveweight produced.

The main medically important antimicrobial classes used in water for turkeys were penicillins (penicillin G) and tetracyclines (chlortetracycline, oxytetracycline, and tetracycline). Most of the medically important antimicrobial classes used showed a decline between 2013 and 2017. However, use of a few of the medically important antimicrobials increased, for example, tylosin and some sulfonamides. In terms of grams per 1 million pounds liveweight, the largest percentage decreases between 2013 and 2017 were for gentamicin (about 83% decreased) and erythromycin (about 65% decreased). Penicillins and tetracyclines also showed a decrease between 2013 and 2017 of about 42% and 28%, respectively. Bacitracin, a non-medically important antimicrobial used in water, showed an increase between 2013 and 2017.

Table 7-8: Antimicrobial use (in kilograms) in turkey water, by drug class, ingredient, and year, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
Medically Important Antimicrobials[1]		**Kilograms of Drug**				
Aminoglycosides	Gentamicin	1,178.2	909.9	641.9	467.9	241.2
	Neomycin	10,062.5	10,287.6	10,900.5	8,596.4	6,165.4
	Spectinomycin	14.4	4.3	0	99.2	96.6
Amphenicols	Florfenicol	27.4	46.6	111.3	87.1	153.5
Diaminopyrimidines	Trimethoprim[2]	39.9	69.4	182.1	236.5	383.9
Lincosamides	Lincomycin	4,363.5	4,004.2	4,512.8	5,424.0	2,847.2
Macrolides	Erythromycin	101.9	337.6	220.2	87.5	43.5
	Tylosin	143.9	100.2	87.9	232.3	649.5
Penicillins	Penicillin G	398,731.3	441,101.9	433,039.8	384,652.2	280,647.0
Sulfonamides	Sulfonamides[3]	21,782.1	19,253.1	17,985.5	15,888.3	20,851.2
Tetracyclines	Tetracyclines[4]	90,806.3	94,081.0	105,098.4	93,667.9	78,519.7
Not Medically Important Antimicrobials[1]		**Kilograms of Drug**				
Pleuromutilins	Tiamulin	193.7	62.0	121.2	106.4	109.6
Polypeptides	Bacitracin	17.4	5.1	3.6	556.0	224.5

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013-2017. ***Zoonoses Public Health*** 2020; 67(Suppl.1): 36-50.

1 Refers to medical importance in human medicine; as defined by Appendix A of FDA GFI #152.
2 Trimethoprim use occurred in combination with a potentiated sulfonamide (sulfadiazine).
3 Includes sulfadiazine, sulfadimethoxine, sulfamerazine, sulfamethazine, and sulfaquinoxaline.
4 Includes chlortetracycline, oxytetracycline, and tetracycline.

Table 7-9: Antimicrobial use (in grams per 1 million pounds liveweight produced) in turkey water, by drug class, ingredient, and year, 2013-2017

Drug Class	Active Ingredient	2013	2014	2015	2016	2017
Medically Important Antimicrobials[1]		**Grams of Drug per Million Pounds Liveweight**				
Aminoglycosides	Gentamicin	274.0	192.2	134.2	89.1	46.6
	Neomycin	2,339.9	2,173.6	2,278.9	1,637.2	1,190.6
	Spectinomycin	3.3	0.9	0	18.9	18.7
Amphenicols	Florfenicol	6.4	9.8	23.3	16.6	29.6
Diaminopyrimidines	Trimethoprim[2]	9.3	14.7	38.1	45.0	74.1
Lincosamides	Lincomycin	1,014.7	846.0	943.5	1,033.0	549.8
Macrolides	Erythromycin	23.7	71.3	46.0	16.7	8.4
	Tylosin	33.5	21.2	18.4	44.2	125.4
Penicillins	Penicillin G	92,719.0	93,196.6	90,533.8	73,259.2	54,195.4
Sulfonamides	Sulfonamides[3]	5,065.1	4,067.8	3,760.2	3,026.0	4,026.5
Tetracyclines	Tetracyclines[4]	21,115.7	19,877.6	21,972.5	17,839.6	15,162.8
Not Medically Important Antimicrobials[1]		**Grams of Drug per Million Pounds Liveweight**				
Pleuromutilins	Tiamulin	45.0	13.1	25.3	20.3	21.2
Polypeptides	Bacitracin	4.0	1.1	0.7	105.9	43.3

Source: Singer RS et al. Estimates of on-farm antimicrobial usage in turkey production in the United States, 2013-2017. *Zoonoses Public Health* 2020; 67(Suppl.1): 36-50.

1 Refers to medical importance in human medicine; as defined by Appendix A of FDA GFI #152.
2 Trimethoprim use occurred in combination with a potentiated sulfonamide (sulfadiazine).
3 Includes sulfadiazine, sulfadimethoxine, sulfamerazine, sulfamethazine, and sulfaquinoxaline.
4 Includes chlortetracycline, oxytetracycline, and tetracycline.

Results – Disease Indications for Antimicrobial Use in Water

The study investigators also collected some preliminary data on reasons for use of antimicrobials in the water of turkeys, for 2017. Listed below are the antimicrobials used in water and the main reasons for use. Complete details about reasons for use and age at time of disease onset can be found in the primary investigator's published report (Singer et al, 2020b).

- Gentamicin – bacterial enteritis
- Lincomycin – gangrenous dermatitis; bacterial enteritis; *Ornithobacterium rhinotracheale* (ORT); *E. coli* infections
- Neomycin – bacterial enteritis; *E. coli* infections; *Salmonella* infections
- Penicillin G – gangrenous dermatitis; bacterial enteritis; ORT
- Sulfonamides – *E. coli* infections; coccidiosis; septicemia; ORT
- Tetracycline – *E. coli* infections; septicemia; *Salmonella* infections; *Pasteurella multocida* infections; ORT
- Tylosin – *Mycoplasma* spp. infections
- Erythromycin – *E. coli* infections; ORT
- Florfenicol – *Pasteurella multocida* infections; septicemia
- Bacitracin – gangrenous dermatitis; bacterial enteritis; spirochetosis
- Tiamulin – spirochetosis

7.6 Antimicrobial Resistance in Turkeys and Retail Ground Turkey

7.6.1 Introduction

In this section, some of the available information about antimicrobial resistance specific to turkey pathogens is described. This is limited to information recently collected through the first two years of the USDA APHIS NAHLN Antimicrobial Resistance Pilot Project and results from the first year of an FDA CVM Vet-LIRN collaborative antimicrobial resistance pilot project with veterinary diagnostic laboratories.

In addition, this section highlights some 2019 antimicrobial resistance information for bacterial isolates collected from retail ground turkey meat samples and turkey cecal (intestinal) contents at the time of slaughter, collected through the FDA (retail meat) and USDA FSIS (cecal) components of the NARMS program. Preliminary real-time genotypic data are available on the NARMS website, but not included here since the focus of this report is on 2016-2019.

7.6.2 Antimicrobial Resistance in Turkey Pathogens

7.6.2.1 USDA APHIS NAHLN ANTIMICROBIAL RESISTANCE PILOT PROJECT – TURKEY RESULTS (2018-2019)

As part of the USDA APHIS NAHLN Antimicrobial Resistance Pilot Project (see Chapter 3), bacterial isolates were submitted for domestic chickens, turkeys, and ducks. Pathogens tracked included *E. coli* and *Salmonella enterica* for 2018, and *E. coli* and *Pasteurella multocida* for 2019 (*Salmonella enterica* isolates were not included for 2019 since the goal of 100 isolates was not met in 2018 for poultry). For the pilot project, information regarding turkey production class and age was not collected. The full reports should be consulted for information on methodologies used and complete results for this project, including MIC distribution data for the isolates (USDA-APHIS, 2019b and USDA-APHIS, 2019c).

E. coli

No poultry-specific clinical breakpoints have been established by the Clinical Laboratory Standards Institute (CLSI) for *E. coli*, with the exception of enrofloxacin, which is not approved for use in poultry, so no percentage resistance was reported.

A total of 272 *E. coli* isolates from poultry were submitted in 2018 for the pilot project, and 374 isolates were submitted in 2019. In 2018, of the 272 poultry isolates, 67 (24.6%) were from turkeys. In 2019, of the 374 poultry *E. coli* isolates, 117 (31.2%) were from turkeys. Overall, the most common clinical diagnoses associated with *E. coli* infections in turkeys for both years were septicemia/colibacillosis (31.3% and 23.1% in 2018 and 2019, respectively) and pneumonia (25.4% and 21.3% in 2018 and 2019, respectively). Other less common diagnoses were peritonitis/hepatitis, enteritis, and joint infections, among others.

Salmonella spp.

Poultry-specific CLSI-defined breakpoints for *Salmonella* have not been established, so no percentage resistance was reported. A total of 63 *Salmonella* spp. isolates were submitted for poultry in 2018. Of these 63 poultry isolates, only 11 (17.5%) were from turkeys. Six different serotypes were identified among these isolates. The most common serotypes were Typhimurium (27.3% of isolates), Bredeney (18.2%), and Uganda (18.2%). Diagnoses associated with *Salmonella* isolates submitted for turkeys included enteritis, yolk sac infections/ septicemia, and non-specific infections. Data for other serotypes can be found in the published report.

Pasteurella multocida

No antimicrobials have poultry-specific CLSI clinical breakpoints established for *P. multocida*, so no percentage resistance was reported. Of the 51 *P. multocida* poultry isolates submitted in 2019, only 9 were from turkeys. Fowl cholera/septicemia was the primary diagnosis associated with *P. multocida* infections in turkeys.

7.6.2.2 FDA CVM VET-LIRN COLLABORATIVE PROJECT WITH VETERINARY DIAGNOSTIC LABORATORIES, ANTIMICROBIAL RESISTANCE PILOT – TURKEY RESULTS (*SALMONELLA* ONLY)

As part of the collaborative project with veterinary diagnostic laboratories in the U.S. and Canada, Vet-LIRN collected *Salmonella* isolates from veterinary diagnostic source labs from any host animal (see Chapter 3). In 2017, 586 *Salmonella enterica* isolates were collected, 69 of which were whole genome sequenced. Only one of these isolates was of turkey origin; the bird was a wild turkey, not from commercial production. The serovar for this isolate was Reading, and it carried 6 antimicrobial resistance genes (Ceric et al, 2019).

7.6.3 Antimicrobial Resistance in Turkeys at Slaughter and Retail Ground Turkey

This section highlights antimicrobial resistance information for 2019, for generic *E. coli, Salmonella*, *Campylobacter*, and *Enterococcus* isolates collected from retail ground turkey samples and turkey cecal (intestinal) contents at the time of slaughter. This information was collected through the FDA (retail meat) and USDA FSIS (cecal) components of the NARMS program. The CDC NARMS website should be consulted for information about bacteria isolated from humans that are monitored for antimicrobial resistance. For purposes of this report, antimicrobial susceptibility testing (i.e., phenotypic) data are described, including some information about multidrug resistance (MDR, defined by the NARMS program as resistance to three or more antimicrobial classes). The NARMS program websites and most recent report (2018 NARMS Integrated Summary) can be consulted for more information, including whole genome sequencing data. **Appendix 8** provides line graphs depicting some of the resistance trends (from antimicrobial susceptibility testing) for a five-year period (2015-2019). Genotypic real-time data are published at NARMS Now and includes 2018-2021 data.

P-values, where reported in this section, were obtained using Fisher's exact test for comparing proportions (McDonald, 2014). P-values help assess statistical significance when comparing two or more sets of numerical data. In this case the proportions compared were the percentages of resistance (for a given bacteria and sample source) between 2018 and 2019, and the significance level was set at $p \leq 0.05$.

7.6.3.1 *E. COLI* – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL GROUND TURKEY AND TURKEY CECAL SAMPLES

Recovery of *E. coli* from retail ground turkey samples collected in the NARMS program was about 59% in 2019. Recovery of *E. coli* from turkey cecal samples has remained stable between 2018 and 2019. *E. coli* is a common commensal organism of the intestinal microbiota, so high prevalence levels are not unusual in animal cecal samples. **Tables 7-10 and 7-11** show the annual number of samples collected and number of *E. coli* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 7-10: Number of retail ground turkey samples collected by year (2015-2019), and percent positive for *E. coli* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Ground Turkey					
Number of samples	489	445	663	1041	843
Number of isolates	375	331	481	473	496
Prevalence (%)	76.7	74.4	72.5	45.4	58.8

Table 7-11: Number of turkey cecal samples collected by year (2015-2019), and percent positive for *E. coli* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Turkey Cecal					
Number of samples	89	103	143	207	216
Number of isolates	87	96	137	200	210
Prevalence (%)	97.8	93.2	95.8	96.6	97.2

Appendix 8 shows resistance trends (2015 to 2019) for *E. coli* isolated from retail ground turkey and turkey cecal samples, for antimicrobials selected from the 10 antimicrobial drug classes tested. Turkey source *E. coli* isolates are generally most resistant to tetracycline, streptomycin, and ampicillin compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *E. coli* isolates from turkey samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- During 2019, ceftriaxone-resistant *E. coli* isolates from retail ground turkey samples fell below 1% and decreased to 1.9% for turkey cecal samples.
- During 2019, no decreased susceptibility to azithromycin (DSA) was detected in turkey cecal samples. For retail ground turkey, one of 496 isolates showed DSA.
- *E. coli* isolates from turkey sources continue to show no carbapenem resistance (meropenem testing became routine in 2016).
- The percentage of *E. coli* isolates from retail ground turkey with decreased susceptibility to ciprofloxacin (DSC) was stable at about 2% in 2019. For turkey cecal samples, the percentage of *E. coli* isolates with DSC increased from 2.5% in 2018 to 4.8% in 2019.
- Gentamicin resistance in *E. coli* isolates from turkey cecal samples significantly decreased (from 27.5% to 16.2%, $p<0.01$) and also decreased for retail ground turkey isolates between 2018 and 2019.
- MDR in *E. coli* isolates significantly decreased (from 38.8% to 32.7%, $p=0.05$) in retail ground turkey and was stable for turkey cecal samples, comparing 2018 to 2019.

7.6.3.2 NONTYPHOIDAL *SALMONELLA* – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL GROUND TURKEY AND TURKEY CECAL SAMPLES

Recovery of nontyphoidal *Salmonella* from retail ground turkey samples collected in the NARMS program increased to 11.7% in 2019. Between 2018 and 2019, recovery of *Salmonella* from turkey cecal samples was stable, around 15%. **Tables 7-12 and 7-13** show the annual number of samples collected and number of *Salmonella* isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 7-12: Number of retail ground turkey samples collected by year (2015-2019), and percent positive for *Salmonella* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Ground Turkey					
Number of samples	2373	2907	4199	4386	4320
Number of isolates	145	152	260	305	507
Prevalence (%)	6.1	5.2	6.2	7.0	11.7

Table 7-13: Number of turkey cecal samples collected by year (2015-2019), and percent positive for *Salmonella* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Turkey Cecal					
Number of samples	266	266	307	437	428
Number of isolates	25	49	42	66	64
Prevalence (%)	9.4	18.4	13.7	15.1	15.0

Appendix 8 shows resistance trends (2015 to 2019) for *Salmonella* isolated from retail ground turkey and turkey cecal samples for antimicrobials selected from the 10 antimicrobial drug classes tested. Turkey source *Salmonella* isolates are generally most resistant to tetracycline, streptomycin, and sulfisoxazole compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing results) in *Salmonella* isolates from turkey source samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- In 2019, there was a small decrease in the percentage of ceftriaxone-resistant *Salmonella* isolates from retail ground turkey, from 6.2% in 2018 to 5.7% in 2019. Ceftriaxone resistance in *Salmonella* isolates from turkey ceca was stable between 2018 and 2019, around 3% (representing only 2 isolates). Infantis was the predominant ceftriaxone-resistant serotype among *Salmonella* isolated from retail ground turkey.
- The percentage of *Salmonella* isolates with DSC decreased between 2018 and 2019 for retail ground turkey (from 9.2% to 7.3%), and was stable (below 2%) for turkey ceca (only one isolate) in the same time period. Infantis was the predominant serotype with DSC among *Salmonella* isolated from retail ground turkey. As noted in the NARMS data for chickens, the increase in DSC among poultry isolates in prior years was primarily due to the increase in MDR Infantis that exhibited DSC caused by mutations in the *gyrA* gene (NARMS, 2020b).
- No DSA in *Salmonella* isolates from turkey sources was detected in 2019.
- No carbapenem resistance was detected in *Salmonella* isolates from turkey sources in 2019 (meropenem testing became routine in 2016).
- For *Salmonella* isolated from retail ground turkey in 2019, there was a significant decrease in ampicillin resistance (from 35.5% to 29.2%, p=0.05) compared to 2018.
- For *Salmonella* isolated from turkey cecal samples in 2019, there was a significant increase in sulfisoxazole resistance (from 15.2% to 34.4%, p=0.01) compared to 2018.
- The percentage of MDR *Salmonella* isolates was essentially stable for retail ground turkey between 2018 and 2019, decreasing a small amount (from 25.1% to 21.1%). In contrast, MDR in *Salmonella* isolates from turkey ceca increased during the same time period, from 22.7% to 31.3%. The predominant MDR serotypes for turkey sources were Reading and Infantis.

7.6.3.3 *CAMPYLOBACTER* SPP. – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL GROUND TURKEY AND TURKEY CECAL SAMPLES

Recovery of *Campylobacter* from retail ground turkey samples collected in the NARMS program remained very low, less than 1%. Recovery of *Campylobacter* from turkey cecal samples collected in the NARMS program increased to about 57% in 2019. **Tables 7-14 and 7-15** show the annual number of samples collected and number of *Campylobacter* spp. isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 7-14: Number of retail ground turkey samples collected by year (2015-2019), and percent positive for *Campylobacter* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Ground Turkey					
Number of samples	2372	2907	4174	4271	4272
Number of isolates	5	16	18	12	12
Prevalence (%)	0.2	0.6	0.4	0.3	0.3

Table 7-15: Number of turkey cecal samples collected by year (2015-2019), and percent positive for *Campylobacter* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Turkey Cecal					
Number of samples	265	269	303	437	431
Number of isolates	11	15	58	144	244
Prevalence (%)	4.2	5.6	19.1	32.9	56.6

Appendix 8 shows resistance trends (2015 to 2019) for *Campylobacter coli* (*C. coli*) isolated from turkey cecal samples, for antimicrobials from five of the antimicrobial drug classes tested. Turkey source *Campylobacter* isolates are generally most resistant to tetracyclines compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Campylobacter* spp. isolates from turkey samples include the following (**unless noted otherwise, increases or**

decreases were not statistically significant):

- In 2019, there were small but not statistically significant changes in ciprofloxacin resistance among *Campylobacter* spp. isolated from turkey sources as compared to the previous year. For ***C. coli***, there were small increases in ciprofloxacin resistance in retail ground turkey (from 50% in 2018 to 71% in 2019 - representing only 5 isolates); cecal samples also showed a numerical but not significant increase, from 40.3% to 42.2%. For ***C. jejuni***, no ciprofloxacin resistance was detected in retail ground turkey samples, and there was an increase in ciprofloxacin resistance for ***C. jejuni*** isolates from turkey ceca (from 15% to 25%, representing 11 isolates).
- No macrolide (azithromycin or erythromycin) resistance was detected on antimicrobial susceptibility testing for ***C. jejuni*** isolates from retail ground turkey or turkey ceca in 2019. For ***C. coli***, there were small but statistically insignificant changes: for retail ground turkey, 3 of 7 isolates showed macrolide resistance in 2019, and for turkey cecal samples, macrolide resistance increased to about 13% (from about 8% in 2018 for erythromycin).
- MDR ***C. coli*** from turkey cecal samples increased between 2018 and 2019, from 13.7% to 19.1%. Only one MDR ***C. jejuni*** turkey isolate was detected in 2019, from a turkey cecal sample.

7.6.3.4 *ENTEROCOCCUS* SPP. – PREVALENCE AND RESISTANCE HIGHLIGHTS FOR RETAIL GROUND TURKEY AND TURKEY CECAL SAMPLES

Recovery of ***Enterococcus*** from retail ground turkey samples collected in the NARMS program was about 63% in 2019, and was also stable for turkey cecal samples. ***Enterococcus*** spp. are a common commensal organism of the intestinal microbiota of humans and animals, so high prevalence levels are not unusual. **Tables 7-16 and 7-17** show the annual number of samples collected and number of ***Enterococcus*** isolates from the NARMS retail meat and cecal sampling programs for 2015 through 2019. The NARMS website should be consulted for information on differences in sampling methodologies between the retail meat and cecal sampling programs, as well as changes in sampling plans over the years.

Table 7-16: Number of retail ground turkey samples collected by year (2015-2019), and percent positive for *Enterococcus* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Retail Ground Turkey					
Number of samples	490	440	558	940	739
Number of isolates	436	401	489	448	467
Prevalence (%)	89.0	91.1	87.6	47.7	63.2

Table 7-17: Number of turkey cecal samples collected by year (2015-2019), and percent positive for *Enterococcus* (prevalence)

Sample Type	Year				
	2015	2016	2017	2018	2019
Turkey Cecal					
Number of samples	90	103	141	207	215
Number of isolates	88	93	138	196	204
Prevalence (%)	97.8	90.3	97.9	94.7	94.9

Appendix 8 shows resistance trends (2015 to 2019) for *Enterococcus faecalis* (*E. faecalis*) and *Enterococcus faecium* (*E. faecium*) isolated from retail ground turkey and turkey cecal samples, for antimicrobials from nine of the antimicrobial drug classes tested. Turkey source *Enterococcus* isolates are generally most resistant to tetracyclines and streptogramins compared to other antimicrobials tested.

Notable findings from 2019 with regard to resistance (based on antimicrobial susceptibility testing) in *Enterococcus* spp. isolates from turkey source samples include the following (**unless noted otherwise, increases or decreases were not statistically significant**):

- Between 2018 and 2019, macrolide (erythromycin) resistance in *E. faecalis* isolates from retail ground turkey remained stable, around 26%, and was also stable for turkey cecal isolates, around 34%. For *E. faecium*, macrolide resistance decreased for turkey ceca (from 19% to 15%) and remained stable for retail ground turkey.
- In 2019, ciprofloxacin resistance remained under 1% for *E. faecalis* isolates from retail ground turkey and decreased to zero for turkey ceca. Ciprofloxacin resistance in *E. faecium* isolates from retail ground turkey increased (from 28.3% to 37.6%) and for turkey ceca decreased to around 15% in 2019, from about 29% in 2018.
- Since 2014, there has been a substantial decrease in gentamicin resistance in *E. faecalis* isolates from turkey cecal samples (from 41.7% in 2014 to 14.5% in 2019). Gentamicin resistance in *E. faecalis* from retail ground turkey remained stable between 2018 and 2019, at about 16%. For *E. faecium*, gentamicin resistance also decreased to zero in isolates from turkey ceca, and remained stable for retail ground turkey.
- *Enterococcus spp.* isolates from retail ground turkey and turkey ceca continue to show no linezolid resistance and no vancomycin resistance.
- Between 2018 and 2019, MDR *E. faecalis* remained stable (around 12%) in retail ground turkey and increased for turkey cecal samples (from 23.8% to 57.5%, $p<0.01$). For *E. faecium*, MDR showed some statisticially insignificant changes, increasing to 51.4% for retail ground turkey and decreasing to 27% for turkey cecal samples.

7.7 Antimicrobial Stewardship in Turkey Production

7.7.1 Introduction

The FDA and other U.S. federal government agencies, as well as state government agencies and national and state veterinary medical associations, support the efforts of poultry veterinarians and producers in actions taken to preserve the effectiveness and availability of antimicrobials for animals and humans. In addition, veterinary and producer associations have developed strategies and taken steps to provide information to veterinarians and producers working within these industries in the U.S. to reduce the need for antimicrobials and to use them judiciously when necessary.

Poultry integrators have changed production practices to meet the demands of the marketplace in the U.S. Poultry growers, nutritionists, and veterinarians have been developing ways to raise birds using fewer antimicrobials while still maintaining good performance and welfare without increasing food safety concerns. In addition, the USDA's Agricultural Research Service National Poultry Research Center and others conduct research in several areas important to poultry health, including development of new strategies and non-antimicrobial alternatives for disease prevention and treatment that do not result in creation of selection pressures favoring the development of antimicrobial resistance.

As mentioned in Chapter 6, programs such as the National Poultry Improvement Plan (NPIP), administered by USDA APHIS, work to improve poultry health by establishing standards for testing of poultry breeding stock, chicks, poults, and hatching eggs with respect to freedom from certain diseases, including avian influenza, ***Salmonella*** Pullorum, ***Salmonella*** Gallinarum, ***Salmonella*** Enteriditis, and certain ***Mycoplasma*** spp. In addition to disease monitoring, NPIP has established programs such as 'U.S. ***Salmonella*** Monitored' and 'U.S. Sanitation Monitored' that are intended to reduce the incidence of ***Salmonella*** in hatching eggs, chicks, and poults (USDA-APHIS, 2020b). Programs such as NPIP that work to improve poultry health also help to provide information that could be useful for informing disease prevention programs for poultry, including strategies that could help reduce the need for antimicrobials.

7.7.2 Resources

The American Association of Avian Pathologists (AAAP) has published information about poultry health issues and judicious use of antimicrobials in poultry production on their website. This organization has also developed guidelines for judicious therapeutic use of antimicrobials in poultry following the AVMA framework. These guidelines are available on AVMA's website (AVMA, 2020).

A number of national and state trade and industry associations have also established resources to assist poultry producers and veterinarians with adopting the basic tenets of antimicrobial stewardship; for example, the National Turkey Federation and the U.S. Poultry & Egg Association. In addition, a number of organizations involved with poultry production have made public commitments as part of the U.S. government's AMR Challenge.

CHAPTER 8
Conclusion

Within the One Health paradigm where human, animal, and environmental health concerns intersect, many of the same antimicrobial classes are used and can contribute to the emergence and spread of antimicrobial resistance. Many activities are ongoing across the One Health spectrum aimed at promoting judicious antimicrobial use and slowing development of antimicrobial resistance. Important progress has been made in each sector, but more work remains to be done. Cooperation and collaboration between U.S. government agencies (local, state, and federal), multinational organizations, animal drug manufacturers, animal industry organizations, veterinary organizations, veterinarians, and producers are essential to continue building upon the progress already made in animal agriculture.

This report was intended to provide a description and summary of some of the data that FDA and partner organizations have been collecting and reporting regarding antimicrobial sales, use, and resistance in animal agriculture and the related food chain. Knowledge of antimicrobial selection pressures, among other factors, helps improve understanding of potential risk factors for development of antimicrobial resistance and helps inform the development of strategies and policies related to antimicrobial stewardship. Continued and enhanced data collection on antimicrobial use and resistance are essential components to inform U.S. government policies and strategies for the containment of antimicrobial resistance.

8.1 Knowledge and Data Gaps

While much progress has been made, there remain some important gaps in data needed to inform risk assessments and to reduce the threat of antimicrobial resistance. Some of these data and knowledge gaps are described in this section.

8.1.1 Routine animal health monitoring or surveillance programs

Animal health surveillance programs are an important component of maintaining health and productivity of livestock. Currently, national livestock health surveillance systems in the U.S. focus on reportable and/or high-consequence foreign animal diseases. For example, the USDA APHIS National Animal Health Surveillance System conducts surveillance of several important livestock and poultry diseases, including avian influenza, bluetongue, bovine spongiform encephalopathy, brucellosis, bovine tuberculosis, classical swine fever, and others. These surveillance systems are vital to protecting the health and safety of livestock and livestock products, in addition to protecting the U.S. from potential incursions of foreign animal diseases or biological threat agents.

Beyond reportable and foreign animal diseases, information about the incidence and prevalence of livestock diseases that may require antimicrobial treatment could be helpful to inform risk/decision analysis tools for infectious disease prevention and management practices. More frequently collected animal health data could assist in understanding geographic and seasonal differences in disease incidence, important to the understanding of how and why antimicrobials are used in livestock. Notably, USDA NAHMS collects, analyzes and disseminates data on national animal health, management, and productivity in the U.S.; however, studies for each commodity group are conducted only every 5 to 10 years. While these studies provide for important animal health and

management information geared towards producers' needs, there remains a need for a regular and more frequent data collection component, in particular for diseases that could provide more insight into the reasons for antimicrobial use in livestock.

8.1.2 Enhanced antimicrobial resistance data

Compared to resistance in human and foodborne bacterial pathogens, there is less information available about the emergence and dissemination of antimicrobial resistance occurring in animal pathogens. National programs that could track antimicrobial resistance in bacterial pathogens important in animal health are needed to assist in the advancement of strategies to minimize the development and spread of resistance in these pathogens and also to help incentivize the research and development of alternatives to antimicrobials. There is a strong need for this type of data to be collected and reported on an ongoing basis since therapy of animal diseases caused by animal pathogens is the main driver for antimicrobial use in animals. Enhanced information about antimicrobial resistance in animal pathogens would also help guide antimicrobial stewardship programs.

This report provided a brief overview and initial results of some of the progress being made in this area; for example, the USDA APHIS NAHLN program and the FDA Vet-LIRN programs are piloting methodologies for animal pathogen resistance data collection and reporting. Expansion of these programs into national and sustainable data collection platforms is an important goal. To contribute to the development of these efforts, more work and investments are needed to establish animal species-specific clinical breakpoints for antimicrobial susceptibility testing which are required for veterinarians to make strong treatment decisions for animal patients.

The role of animal environments and animal feed in the ecology and spread of antimicrobial-resistant organisms represents another knowledge gap. As described in this report, the NARMS program intends to incorporate a full One Health approach to surveillance and reporting of resistance in foodborne bacteria including ***E. coli***, *Salmonella*, *Campylobacter*, and *Enterococcus*. With expansion of the NARMS program and recent development of the NARMS Strategic Plan for 2021-2025, new strategic goals build on progress made. These goals incorporate the One Health principle of an interdisciplinary approach to human, animal, and environmental health and intend to explore animal pathogen and environmental testing. Pilot projects will be planned to explore antimicrobial resistance in additional food commodities, bacterial species, and environments. The NARMS program held a public meeting in October of 2020 to obtain public input on the proposed plan and reinforced the need for stakeholder input as pilot projects are designed, conducted, and reported.

8.1.3 Antimicrobial use data and alternatives to antimicrobials

Antimicrobials are an important management tool for therapy of bacterial infections in animals. Antimicrobial use information is needed to assist in the development of antimicrobial stewardship strategies so that antimicrobial effectiveness can be preserved for both humans and animals. While national antimicrobial sales data are collected as described in this report, sales data are most appropriate for examining broad shifts in marketplace trends and not necessarily for examining the linkages between specific use practices and development of antimicrobial resistance, nor for the assessment of antimicrobial stewardship. As described earlier in this report, some pilot antimicrobial use data collection projects have been conducted under cooperative agreements with

FDA and some antimicrobial use surveys have been conducted by NAHMS for feedlot cattle and swine operations. Using the results and experience gained from these types of studies, next steps will involve ongoing collaboration with stakeholders and government partners to develop and support long-term and sustained, mutually agreeable antimicrobial use data collection strategies.

There are also alternatives to antimicrobials that may play a role in decreasing the incidence of animal diseases for which antimicrobial therapies are frequently used. Studies are needed to better determine the types of animal husbandry or management practices aimed at disease prevention, that will be most effective in reducing the need for antimicrobials. More research is needed with regard to developing and implementing new strategies for preventing, controlling, and treating animal diseases that do not result in the creation of selection pressure. Advances in research and development in the area of animal vaccines, immunomodulators, bacteriophages, and probiotics or other types of non-antimicrobial substances may help preserve the effectiveness of antimicrobials. USDA's Agricultural Research Service maintains a resource center about some of the current research on alternatives to antimicrobials in animal production.

8.1.4 Data integration

While the data presented in this report provide some insights into antimicrobial use practices and antimicrobial resistance trends in animal agriculture and along the food chain, there remains a need to better identify strategies for the most appropriate use of these data to assess the relationships between antimicrobial use, resistance, and animal health and production. Considering the complexities of antimicrobial resistance epidemiology and the myriad potential contributing factors, it is challenging to present these data all together in one report without risk of oversimplifying complex relationships. This report should be viewed as descriptive of data that is currently available to FDA. As more data and knowledge about antimicrobial use and resistance in animal agriculture and the related food chain become available, future reports may provide additional analyses and understanding of the inferences that can be made from these data and how best to use them to inform risk assessments and risk management practices.

Overall, the total amount of medically important antimicrobials sold for use in food-producing species has decreased by about 26% between 2016 (prior to completion of GFI #213 implementation) and 2019. While antimicrobial sales data do not indicate how or why antimicrobials are being used, the decrease in sales does indicate that the changes brought about by GFI #213 have had some impact on overall antimicrobial use. As noted in this report, some shifts in on-farm antimicrobial use patterns were also evident between 2016 and 2017, based on the limited amount of data collected thus far in the antimicrobial use data collection pilot projects. It is also important to consider whether these changes in antimicrobial use are having an adverse effect on animal health outcomes. More research is clearly needed in this area.

Some of the changes in antimicrobial resistance for the organisms monitored by the NARMS program were also highlighted in this report, for the time period between 2018 and 2019. Currently, more data are needed to establish how trends in antimicrobial sales or use will relate to trends in antimicrobial resistance. The relationships are not always clear; for example, consider below the changes in macrolide sales and macrolide (azithromycin and/or erythromycin) resistance in foodborne bacteria monitored through the NARMS program for each of the four major food-producing species:

CATTLE

- Estimated macrolide sales (biomass-adjusted) for cattle increased between 2016 and 2019 by about 41%.
  - Decreased susceptibility to azithromycin (DSA) was not detected in ***E. coli*** isolates from retail ground beef or dairy cattle cecal samples in 2019, and only one of 759 ***E. coli*** isolates from beef cattle cecal samples showed DSA.
  - No DSA was detected in 2019 in ***Salmonella*** isolates from retail ground beef and dairy cattle cecal samples. For beef cattle cecal samples, only 2 of 225 ***Salmonella*** isolates showed DSA.
  - Between 2018 and 2019, macrolide (erythromycin) resistance in ***C. jejuni*** isolates from dairy cattle cecal samples decreased (below 1%) and there was no macrolide resistance detected for beef cattle cecal samples. For ***C. coli*** in the same time period, macrolide resistance remained stable for beef and dairy cattle cecal isolates.
  - For ***E. faecalis***, macrolide (erythromycin) resistance increased in beef cattle cecal samples between 2018 and 2019, but decreased for dairy cattle cecal samples and was stable in retail ground beef samples. In retail ground beef, erythromycin resistance in ***E. faecalis*** isolates was essentially stable between 2018 and 2019. For ***E. faecium*** isolates, macrolide resistance in retail ground beef samples significantly decreased, in beef cattle cecal samples it decreased, and was stable for dairy cattle cecal samples.

SWINE

- Estimated macrolide sales (biomass-adjusted) for swine decreased by nearly 48% between 2016 and 2019.
  - In 2019, DSA was detected in only two (of 229) ***E. coli*** isolates from retail pork samples. For ***E. coli*** isolates from swine ceca, there were small decreases in DSA in market swine and sow cecal samples.
  - No ***Salmonella*** isolates with DSA from retail pork and sow ceca were detected in 2019, and there was a small increase in ***Salmonella*** isolates with DSA detected in market swine cecal samples (remains <2%).
  - Macrolide resistance (erythromycin) for ***C. coli*** and ***C. jejuni*** showed decreases for swine cecal samples between 2018 and 2019.
  - Between 2018 and 2019, macrolide (erythromycin) resistance in ***E. faecalis*** from retail pork and sow cecal samples increased, but significantly decreased for market swine cecal samples. For ***E. faecium*** isolates, erythromycin resistance decreased for retail pork, but increased for market swine and remained zero for sow cecal samples.

CHICKENS

- Estimated macrolide sales (biomass-adjusted) for chickens decreased by nearly 88% between 2016 and 2019.
  - In 2019, no DSA was detected in chicken cecal ***E. coli*** isolates, and only one (of 304) ***E. coli*** isolates from retail chicken showed DSA.
  - In 2019, no DSA was detected in ***Salmonella*** isolates from retail chicken or chicken cecal samples.
  - No macrolide (azithromycin or erythromycin) resistance was detected on antimicrobial susceptibility testing for ***C. jejuni*** isolates from chicken ceca in 2019. For retail chicken, macrolide resistance was detected in only one (of 428) ***C. jejuni*** isolates. Between 2018 and 2019, macrolide resistance remained essentially stable in ***C. coli*** isolates from retail chickens and chicken ceca.
  - Between 2018 and 2019, macrolide (erythromycin) resistance in ***E. faecalis*** isolates from retail chicken increased a small amount, but decreased for chicken cecal samples. For ***E. faecium***, macrolide resistance decreased for retail chicken and chicken cecal samples.

TURKEYS

- Estimated macrolide sales (biomass-adjusted) for turkeys increased by about 69% between 2016 and 2019.
  - During 2019, no DSA was detected in ***E. coli*** isolates from turkey cecal samples and was detected in only one (of 496) retail chicken isolates.
  - During 2019, no DSA was detected in ***Salmonella*** isolates from retail ground turkey or turkey cecal samples.
  - No macrolide (azithromycin or erythromycin) resistance was detected on antimicrobial susceptibility testing for ***C. jejuni*** from turkey samples in 2019. Between 2018 and 2019, macrolide resistance increased a small amount for ***C. coli*** isolates from turkey ceca.
  - Between 2018 and 2019, macrolide (erythromycin) resistance in ***E. faecalis*** isolates from turkey samples remained stable. For ***E. faecium***, macrolide resistance decreased by small amounts for turkey samples.

While this was just one example using the macrolides, it shows that trends in antimicrobial resistance in foodborne organisms may not always follow the directional trends in sales and/or use of the same class of antimicrobials. It is very likely that more time needs to pass between changes in sales trends or changes in antimicrobial use patterns, before changes in resistance trends are evident (Zawack, 2018). Factors unrelated to antimicrobial use in animals are likely also driving selection pressures. For example, the use of biocides (as disinfectants or antiseptics) and the use of heavy metals in animal agriculture (as feed supplements or components of foot baths) may contribute to the spread of antimicrobial-resistant bacteria through co-selection. Exposure to these types of agents could induce or select for bacterial adaptations that result in decreased susceptibility to one or more antimicrobials, perhaps occurring by selection of genetic determinants for resistance to these agents that are linked to genes for antimicrobial resistance (Figueiredo et al, 2019; Wales et al, 2015). Future reports may allow for additional analyses once more data are available.

8.2 Summary

In summary, based on the antimicrobial sales, use, and resistance data currently available, the U.S. continues to progress in our understanding of the impact these data have on efforts to support judicious use of medically important antimicrobials in food-producing animals when necessary for animal health, in particular the antimicrobials that are also important to human health.

CVM remains committed to promoting the implementation of good antimicrobial stewardship practices in veterinary settings as part of our mission to protect human and animal health. It is through CVM's goals to align antimicrobial drug product use with the principles of antimicrobial stewardship, foster antimicrobial stewardship in veterinary settings, and enhance monitoring of antimicrobial resistance and use in animals, that we aim to slow the emergence of resistant bacteria and to further preserve antimicrobials to ensure human and animal health. Continued collaborations and partnerships between U.S. government agencies, the animal production industry, academia, veterinary and public health organizations, and other stakeholders are critical to the advancement of knowledge and research about this critically important issue for the health of humans, animals, and our environment.

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APPENDIX 1

Examples of U.S. Federal Government Agency Roles in Combating Antimicrobial Resistance

This table is not intended to be an exhaustive list of U.S. government activities related to antimicrobial resistance. Department and Agency websites should be consulted for more information.

Department	Agency	Antimicrobial use and antimicrobial resistance -related activities
Department of Health and Human Services	Centers for Disease Control and Prevention	• Conducts surveillance and outbreak investigation of antimicrobial-resistant bacteria and other microorganisms affecting human health in community and healthcare settings. • Collects human enteric/intestinal disease surveillance data through PulseNet, FoodNet, the National Outbreak Reporting System, and the National Antimicrobial Resistance Monitoring System (NARMS). • Provides guidance and conducts research on antimicrobial stewardship in human healthcare settings and leads the collection of national healthcare antimicrobial use data. (https://www.cdc.gov/drugresistance/index.html)
	Food and Drug Administration	• Approves antimicrobials for humans and animals and conducts post-approval monitoring of regulated products; provides guidance to industry on new drug development. • CVM provides guidance on judicious antimicrobial use in food-producing animals and antimicrobial stewardship in animals. • Conducts surveillance and reports on antimicrobial resistance in select bacteria from food and animal sources through the NARMS and Veterinary Laboratory Information Response Network (VetLIRN) programs. • Reports annual sales data for antimicrobials sold for use in food-producing animals. (https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance)
	National Institutes of Health	• National Institute of Allergy and Infectious Diseases funds and conducts research on antimicrobial resistance and hospital-acquired infections. • National Center for Biotechnology and Information maintains a global genomic antimicrobial resistance database. (https://www.niaid.nih.gov/research/antimicrobial-resistance)

Department	Agency	Antimicrobial use and antimicrobial resistance -related activities
Department of Agriculture	**Food Safety and Inspection Service**	Conducts and reports antimicrobial susceptibility testing and whole genome sequencing of bacterial isolates recovered from cecal samples and Hazard Analysis and Critical Control Point (HACCP) sampling for the livestock and poultry section of NARMS. (https://www.fsis.usda.gov/wps/portal/fsis/topics/data-collection-and-reports/microbiology/antimicrobial-resistance/narms)
	Agricultural Research Service	Conducts research on antimicrobial resistance in animal production environments and antimicrobial alternatives. (https://www.ars.usda.gov/nutrition-food-safetyquality/food-safety-animal-and-plant-products/docs/antimicrobial-resistance-amr/)
	Animal and Plant Health Inspection Service	National Animal Health Monitoring System conducts periodic on-farm surveys of antimicrobial resistance and antimicrobial use. (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/monitoring-and-surveillance/nahms) National Animal Health Laboratory Network monitors antimicrobial resistance among clinical samples from animals submitted to partner laboratories. (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/lab-info-services/nahln/) National Veterinary Accreditation Program maintains educational modules, including modules related to judicious antimicrobial use and the Veterinary Feed Directive. (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/nvap) National Veterinary Services Laboratory conducts antimicrobial susceptibility testing, whole genome sequencing, and other tests. (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/lab-info-services/sa_about_nvsl/ct_about_nvsl)
	Economic Research Service	Conducts research to explore economic impacts of antimicrobial use in U.S. agricultural production. Manages and conducts Agricultural and Resource Management Surveys, collects information on farm finances and practices, including antimicrobial use. (https://www.ers.usda.gov/topics/animal-products/animal-policy-regulatory-issues/)
	National Institute for Food and Agriculture	Researches role of agriculture in antimicrobial resistance and strategies for mitigating antimicrobial resistance in the food chain; supports education and extension projects. (https://nifa.usda.gov/antimicrobial-resistance)
Department of Defense	**Armed Forces Health Surveillance Branch**	Conducts surveillance projects to address epidemiology and resistance mechanisms for wound and healthcare-associated infections in humans (U.S. military). (https://www.health.mil/Military-Health-Topics/Combat-Support/Armed-Forces-Health-Surveillance-Division)
Department of the Interior	**U.S. Geologic Survey**	Investigates contaminants of emerging concern in the natural environment, including antimicrobials, antimicrobial-resistant bacteria and genes. (https://www.usgs.gov/programs/environmental-health-program)
	Environmental Protection Agency	Evaluates the safety and efficacy of antimicrobial pesticides. (https://www.epa.gov/pesticides/antimicrobial-pesticides) Conducts research and surveillance of antimicrobial-resistant bacteria from wastewater effluents and other environmental water sources. (https://www.epa.gov/npdes and https://www.epa.gov/national-aquatic-resource-surveys)

APPENDIX 2:
Animal Drug Approval and Post-Approval Monitoring

CVM is responsible for ensuring that animal drugs are safe and effective for their approved conditions of use. To accomplish this, CVM conducts an extensive pre-approval review of the safety and effectiveness data for each animal drug, including antimicrobials. After approval, CVM continues to monitor the safety and effectiveness of each drug once it is marketed.

The following information is intended as a brief background for understanding CVM's pre- and post-approval regulatory activities related to antimicrobials used in food-producing animals. FDA-regulated products, including animal drugs and food additives, are regulated under The Federal Food, Drug, and Cosmetic Act (FFDCA, the Act), a federal law enacted by Congress in 1938. FDA develops regulations based on the laws set forth in the FFDCA or other laws under which FDA operates. FDA regulations can be found in Title 21 of the Code of Federal Regulations (CFR).

A2.1 Overview of the Animal Drug Approval Process

As required by Section 512 of the FFDCA, an animal drug must be approved by FDA before a drug sponsor (the person, company, or other entity working to get a drug approved) can legally market the drug. During the pre-approval review process, CVM evaluates information submitted by the sponsor to make sure the drug is safe and effective for its intended use and that the drug is properly manufactured and adequately labeled and packaged. "Safe" includes safety to the treated animal, safety to the environment, safety to humans administering the drug

to animals, and safety of food products obtained from treated food-producing animals. "Effective" means the drug consistently does what it is expected to do based on its approved indication.

FDA approves animal drugs for major and minor species, and minor uses. The seven major species are horses, dogs, cats, cattle, pigs, chickens, and turkeys. All other animals, such as fish, ferrets, and goats, are minor species. A minor use is the use of a drug for a disease or condition that occurs in a small number of animals each year, either because the disease or condition is rare or because it only occurs in a limited part of the country.

After an approved brand name animal drug has been on the market for a number of years, another drug sponsor can start the approval process for a generic copy. Two additional pathways to the marketplace are available for drugs used in animals depending on certain situations: conditional approval and indexing. These pathways became available with passage of the Minor Use and Minor Species Animal Health Act of 2004. The conditional approval pathway is available for certain drugs intended for use in minor species or for minor uses (see https://www.fda.gov/animal-veterinary/resources-you/conditional-approval-explained-resource-veterinarians). Indexing is a pathway available only for drugs for non-food producing minor species (see https://www.fda.gov/animal-veterinary/minor-useminor-species/drug-indexing).

FDA also reviews and approves drugs for use in or on animal feed (i.e., medicated feed). Manufacturers of medicated feed can mix a drug into feed only for the specific uses and at the specific levels allowed by FDA's approval. Medically important antimicrobials intended for use in food-producing animals and administered in feed are approved as veterinary feed directive (VFD) drugs. Use of a VFD drug requires a VFD issued by a licensed veterinarian in the course of the veterinarian's professional practice. A VFD is a written order that authorizes the client (the owner or other animal caretaker) to obtain and use a VFD drug in or on animal feed in conformance with the approved labeling.

During the drug evaluation process, the drug sponsor submits certain required information in seven 'technical sections' briefly described below:

- **Target Animal Safety:** The drug sponsor must show that the drug is safe for the target animal species when used according to the label (the target animal species is the specific animal species for which the drug is intended for use).
- **Effectiveness:** The drug sponsor must demonstrate that the drug is effective when administered to animals according to the label.
- **Environmental Safety:** Under the National Environmental Policy Act, CVM evaluates the potential impacts of the drug on the environment. There may be a finding of no significant impact, or an environmental impact statement may be prepared.
- **Chemistry, Manufacturing, and Controls:** CVM evaluates information about the drug's ingredients, manufacturing process, packaging, and storage conditions to ensure that these processes and procedures are adequate to preserve the drug's identity, strength, quality, and purity.
- **Human Food Safety:** For drugs intended for use in food-producing animals, CVM evaluates the safety of drug residues that may remain in food (meat, milk, eggs, and honey) derived from treated animals. Studies may include toxicology, residue chemistry, microbial food safety, and analytical methods development.

- **Labeling:** CVM evaluates the product labeling to ensure it is accurate and not misleading. The product must be properly labeled to inform the user how to appropriately use it, including safety considerations and storage and handling procedures.
- **All Other Information:** CVM evaluates other information submitted by the drug sponsor that was not part of the technical sections. For example, the sponsor may submit published scientific literature and information about experience with the drug in foreign markets.

As part of the drug evaluation process, CVM also determines the appropriate marketing status for the product: over-the-counter (OTC), prescription (Rx), or VFD drug. If CVM determines that adequate directions for use can be written on the drug's label in such a way that a non-veterinarian can use the drug for an animal safely and effectively, then it is marketed OTC; if not, the drug must be marketed as either Rx or VFD. Veterinary oversight essentially means that a licensed veterinarian's education and experience are necessary to make a diagnosis and direct the safe and effective use of animal drugs to manage an individual animal's or group of animals' disease or condition.

More information about the drug approval process can be found on CVM's website at https://www.fda.gov/animal-veterinary/animal-health-literacy/idea-marketplace-journey-animal-drug-through-approval-process. Also, CVM maintains a publicly-available searchable database (AnimalDrugs@FDA) that includes most FDA-approved and conditionally approved animal drugs. It includes drug label information and supporting documents such as Freedom of Information summaries and Environmental Assessments. The database can be searched using several parameters, including proprietary (trade or brand) name and active ingredient.

A2.2 Post-Approval Monitoring for Animal Drugs

After an animal drug is approved and marketed, CVM continues to monitor its safety and effectiveness during the drug's entire lifecycle. Two of the main methods for monitoring include adverse event report evaluation and monitoring of the drug's labeling, promotion, and advertising.

- **Adverse Event Reporting:** CVM reviews reports of adverse drug events submitted by the drug sponsor, veterinarians, and the public. As new information becomes available, CVM determines if any post-approval actions are warranted to address new issues related to the safety and effectiveness of the drug. For example, CVM may determine that certain information about adverse events or other information may need to be added to the product's labeling to increase its safe and effective use.
- **Drug Labeling, Promotion, and Advertising:** CVM evaluates promotional and advertising materials used by drug sponsors to ensure the information presented to veterinarians and consumers is truthful and consistent with approved product labeling.
- **Other Post-approval Information:** CVM may also evaluate other information related to a drug's safety and effectiveness during the post-approval period, such as published literature or information from foreign markets.

CVM currently has two additional post-approval monitoring activities specific to antimicrobials approved for use in food-producing species:

- **Antimicrobial Sales and Distribution Data:** CVM reviews annual reports submitted by drug sponsors detailing the amount of each antimicrobial drug product sold or distributed for use in the major food-producing species (cattle, swine, chickens, and turkeys). See Chapter 3 for more details.
- **Antimicrobial Resistance Monitoring:** For antimicrobials intended for use in food-producing animals, CVM monitors antimicrobial resistance trends among key foodborne bacteria through the National Antimicrobial Resistance Monitoring System (NARMS). NARMS is a collaborative program of state and local health departments and universities, FDA, the CDC, and the U.S. Department of Agriculture's Food Safety and Inspection Service (FSIS) which tracks antimicrobial resistance in foodborne bacteria from humans, retail meats, and food-producing animals. NARMS data are used by CVM to make regulatory decisions designed to preserve the effectiveness of antimicrobials for humans and animals. See Chapter 3 for more information about NARMS.

Changes to the approved conditions of use may be made during the post-approval period as part of CVM's risk mitigation strategies to ensure that animal drugs continue to be safe and effective. Changing the marketing status, prohibiting extralabel use, or withdrawing a drug's approval are some examples of risk mitigation strategies which CVM has utilized for certain antimicrobials.

APPENDIX 3: Regulations, Guidance and Policies Related to Judicious Use of Medically Important Antimicrobials in Food-Producing Animals

FDA has a long history of risk mitigation strategies related to antimicrobial use and resistance in animals. This section describes examples of actions CVM has taken, providing important groundwork for our continued efforts in support of judicious use of antimicrobials in animals. We also provide a brief description of more recent activities such as the successful implementation of FDA Guidance for Industry #213. A timeline of CVM's actions related to antimicrobial resistance is provided on our website.

A3.1 Historical Regulations and Policies

A few examples of historical regulations and policies which have contributed to antimicrobial resistance risk mitigation are those related to veterinary oversight for antimicrobials, extralabel drug use, and actions taken related to certain antimicrobial drug classes. Guidance pertaining to the risk assessment of antimicrobials approved for use in food-producing animals is also described in this section.

A3.1.1 Historical Provisions for Veterinary Oversight of Animal Drugs Approved for Use in Food-Producing Animals

As mentioned previously, during the pre-approval evaluation process CVM determines whether the animal drug product will require veterinary oversight for its safe and effective use. Prior to 1996, Rx and OTC were the only marketing status options for approved animal drugs. With passage of the Animal Drug Availability Act (ADAA) in 1996, a new regulatory category of VFD drugs was created. VFD drugs are approved animal drugs intended for use in or on animal feed which are limited to use under the professional supervision of a licensed veterinarian. Any animal feed containing a VFD drug can only be fed to animals based upon an order, called a veterinary feed directive, issued by a licensed veterinarian in the course of the veterinarian's professional practice. In the ADAA, Congress delegated authority to CVM to publish regulations consistent with the ADAA; these regulations are referred to as the VFD rule. The final regulations implementing the VFD-related provisions of the ADAA were published in December of 2000 and the rule was effective January 8, 2001 (an update to this rule was subsequently published in 2015, as noted later in this chapter).

In creating this category of VFD drugs, Congress determined that certain new animal drugs, vital to animal health, should be approved for use in animal feed only if these medicated feeds were administered under a veterinarian's order and professional supervision. For example, veterinarians are essential for controlling the use of certain antimicrobials, in order to ensure their judicious use. Safety concerns relating to difficulty of diagnosis of disease conditions, high toxicity, or other reasons may also dictate that the administration of a medicated feed be permitted only under the supervision of a licensed veterinarian. CVM has provided a wealth of information about VFDs on CVM's website, including historical information, guidance for industry, and frequently asked questions. As discussed later in this chapter, all medically important antimicrobials administered in the feed or water of food-producing animals have required veterinary oversight since January 2017. Remaining dosage forms (e.g., injectable, etc.) will also require veterinary oversight once implementation of additional guidance (Guidance for Industry #263, 'OTC-to-Rx') is completed (see Section 2.3.3).

Box A3-1

Extralabel Use

One of the main conditions of legal ELU is the requirement for a valid veterinarian-client-patient-relationship, or VCPR. The definition of VCPR is published in regulation at the federal level (21 CFR 530.3(i)) and some states also define a VCPR specific to that state's veterinary practice regulations.

The key elements of a valid VCPR include the veterinarian's engagement with the client (animal producer or owner) to assume responsibility for making clinical judgments about the animal patient's or patients' health, the veterinarian's knowledge of the patient(s) through examination and/or facility visit, and the veterinarian's availability to provide necessary follow-up evaluation or care.

A veterinarian's authority to allow for ELU is limited; for example, ELU is limited to circumstances where the health of an animal is threatened, or suffering or death may result from failure to treat. Important limitations also include (among others) no ELU is permitted by laypersons except under veterinary supervision, and no ELU is permitted in or on animal feed. Additional specific limitations apply to ELU in food-producing animals, found in 21 CFR Part 530.

A3.1.2 Extralabel Use of Animal Drugs – Background

The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 (Pub. L. 103-396) amended the FFDCA, allowing veterinarians to prescribe certain approved human and animal drugs for extralabel uses in animals under specified conditions, which are listed in FDA regulations (21 CFR Part 530). Extralabel use (ELU) is defined by regulation (21 CFR §530.3(a)) as: "actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease and other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from labeled withdrawal time based on these different uses." Given the relatively limited number of approved animal drugs available to veterinarians, AMDUCA created the professional flexibility that veterinarians need in order to adequately administer therapy to animals when their health is threatened. Also, many of the minor species have few or no drugs approved for use, making it very difficult for a veterinarian to provide the best care possible. With the creation of legal ELU, many of these issues can be addressed and animals may be more likely to be relieved of illness and suffering. **Box A3-1** describes some of the conditions and limitations related to ELU (21 CFR Part 530 contains full information).

Box A3-2: Antimicrobial Drug Extralabel Use Prohibitions

Fluoroquinolones

Fluoroquinolones are a class of medically important antimicrobial drugs that are used in the treatment of severe and invasive infections in humans and are also considered very important therapies in veterinary medicine. The fluoroquinolones were the first group of antimicrobials prohibited by FDA from ELU in food-producing animals based solely on their potential to compromise treatment of human infections due to antimicrobial resistance development. They may be used in human medicine for treatment of multi-drug resistant Salmonella infections (Werth, 2020a). In 1997, FDA issued a final rule prohibiting the ELU of all fluoroquinolones (and glycopeptides) in food-producing animals. The Agency issued this order after determining that some ELU of these drug classes could increase the level of antimicrobial-resistant zoonotic pathogens in treated animals at the time of slaughter. All uses of fluoroquinolones in poultry were later withdrawn. The prohibition of glycopeptides at the same time was primarily a precautionary measure, since none have been approved for use in animals.

Cephalosporins (Certain ELU)

Cephalosporins are medically important antimicrobials vital for therapy of infections in both humans and animals. In human medicine, cephalosporins are widely used for treatment of pneumonia, skin and soft tissue infections. Newer cephalosporins are used in hospital settings to treat patients with life-threatening infections such as those caused by Salmonella spp. and Shigella spp. (Werth, 2020b). Cephalosporins were considered for prohibition from certain types of ELU because of the increased emergence of cephalosporin-resistant zoonotic foodborne pathogens, particularly Salmonella spp., believed to be associated with cephalosporin ELU in food-producing animals. Between 1996 and 2009, antimicrobial resistance data collected by the NARMS program had revealed an increase in ceftiofur-resistant Salmonella spp. from both humans and food-producing animals (USDA and CDC NARMS, 2011). Ceftiofur is not used in human medicine; however, concerns about the movement of foodborne bacteria between animals and humans and cross-resistance led the FDA to consider certain types of cephalosporin ELU a risk to public health and safety. After extensive consultations, in 2012 FDA issued a final order prohibiting certain uses of cephalosporins (not including cephapirin) in cattle, swine, chickens, and turkeys. Specifically, the prohibited uses include cephalosporin drugs at unapproved dose levels, frequencies, durations or routes of administration, using cephalosporins in cattle, swine, chickens, or turkeys that are not specifically approved for use in that species, and using cephalosporins (except cephapirin) for disease prevention.

As discussed more fully later in this chapter, medically important antimicrobials approved for use in the feed or water of food-producing animals have been transitioned from OTC to VFD or Rx status, respectively. Consistent with AMDUCA, ELU of other dosage forms of antimicrobials (e.g., oral, injectable, ophthalmic, topical, intramammary) is permitted if the appropriate regulations are followed. With reference to medically important antimicrobials administered in drinking water that transitioned from OTC to Rx marketing status, legal ELU is permitted. However, for medically important antimicrobials that transitioned from OTC to VFD marketing status, ELU is not permitted, with few exceptions (e.g., for minor species under certain circumstances – see the Compliance Policy Guide 615.115, Extralabel Use of Medicated Feeds for Minor Species).

A3.1.3 ELU Prohibitions of Certain Antimicrobial Drugs in Animals

Under the AMDUCA provisions, FDA has the authority to prohibit extralabel uses of drugs in animals. For example, FDA may prohibit the ELU of an approved animal or human drug (or class of drugs) in food-producing animals if FDA determines that the ELU of the drug or class of drugs represents a risk to public health. A prohibition may be a general ban on the ELU of a drug or class of drugs, or it may be limited to certain species, indications, dosage forms, routes of administration, or any combination of factors (21 CFR §530.21). Some examples of antimicrobials, or classes of antimicrobials, that are prohibited from extralabel use in food-producing animals include chloramphenicol, glycopeptides, fluoroquinolones, and sulfonamides in lactating dairy cattle (except for approved uses of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine). In addition, cephalosporins (except cephapirin) in cattle, swine, chickens, and turkeys are prohibited for prevention purposes, as well as for uses in unapproved species or production classes, at unapproved doses, frequencies, durations, and routes of administration. The full list of substances currently prohibited for ELU in animals can be found in regulations (21 CFR 530.41). The ELU prohibitions for two notable classes of antimicrobials for use in food-producing animals for reasons related to antimicrobial resistance are described in **Box A3-2**: fluoroquinolones and certain extralabel uses of cephalosporins.

A3.1.4 Withdrawal of Approval for Fluoroquinolone Use in Poultry

In 2005, FDA took additional actions for fluoroquinolones, withdrawing the previously approved uses in poultry. Two fluoroquinolone products had been approved for prescription use in poultry in 1995 (sarafloxacin) and 1996 (enrofloxacin) for the control of mortality associated with *E. coli* in chickens and for control of mortality associated with *E. coli* and *Pasteurella multocida* in turkeys. The NARMS surveillance program subsequently revealed an increase in fluoroquinolone-resistant *Campylobacter* spp. in poultry, which was linked to an increased incidence of infection with resistant *Campylobacter* spp. in humans. By 1998, CDC had reported that 13.6% of *Campylobacter* human isolates were resistant to fluoroquinolones and further increases in resistance were seen in 1999. In 1998 it had also been found that nearly 12% of the *Campylobacter jejuni* isolated from chicken carcasses at federally inspected slaughter plants in the U.S. were fluoroquinolone-resistant. In addition, retail meat samples taken in 1999 indicated even higher levels (~24%) of fluoroquinolone-resistant *Campylobacter* in retail chicken (see the Federal Register Volume 65, Number 211, 2000, pp. 64954-64965).

Based on these data, the established temporal relationship between approval of fluoroquinolones in poultry and subsequent increases in resistance, as well as published literature and other sources, FDA concluded that

the use of fluoroquinolones in poultry was a significant cause of fluoroquinolone-resistant *Campylobacter* on poultry carcasses and therefore could significantly contribute to the incidence of fluoroquinolone-resistant *Campylobacter* infections in humans. Therefore, in October 2000 FDA proposed a withdrawal of fluoroquinolone products labeled for use in poultry on the basis of the determination that they posed a risk to human health. A hearing was requested by one of the sponsors of the affected products and ultimately a final decision was issued in August of 2005, withdrawing the approval of enrofloxacin products for use in poultry (see the Federal Register, Volume 70, Number 146, 2005, p. 44105).

A3.1.5 Microbial Food Safety of Antimicrobials Used in Food-Producing Animals

As part of the human food safety assessment for new antimicrobials intended for use in food-producing animals, CVM includes a microbial food safety assessment to evaluate potential risks associated with development of antimicrobial-resistant bacteria of public health concern. In addition, CVM has provided guidance for drug sponsors outlining an approach to evaluate the safety of residues of veterinary drugs in human food, related to the safety of potential antimicrobial residues and their effect on the human intestinal flora (see FDA GFI #159, "*Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food; General Approach to Establish a Microbiological Acceptable Daily Intake (ADI)*." This section briefly describes the microbial food safety assessment, including information about a qualitative risk assessment process. For more information about this assessment, as well as the evaluation of safety of veterinary antimicrobial residues on human intestinal flora, see CVM's website.

MICROBIAL FOOD SAFETY ASSESSMENT

To address potential antimicrobial resistance concerns surrounding the use of antimicrobial new animal drugs in food-producing animals, CVM evaluates the ability of these drugs to exert pressure towards the emergence or selection of antimicrobial-resistant bacteria of human health concern. This regulatory framework is outlined in FDA's Guidance for Industry (GFI) #152, "*Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern*." The objective of the microbial food safety assessment is to mitigate the risk of development of antimicrobial resistance among pathogens of human health concern, which in turn mitigates the risk of clinical therapy failures for human illnesses.

The guidance provides an outline for a qualitative risk assessment that considers risks to human health through consumption of animal-derived food products by evaluating potential effects of antimicrobials on non-target (food-borne) bacteria (e.g., *E. coli, Salmonella* spp., *Campylobacter* spp., and *Enterococcus* spp.); however, other bacterial hazards may be considered in the risk assessment process. Concerns outlined in GFI #152 are usually addressed if the antimicrobial new animal drug, including the drug's metabolites, is/are:

- regularly considered to have properties that would exert pressure towards the emergence or selection of resistant bacteria of public health concern;
- used to treat zoonotic gastroenteritis or other bacterial diseases in humans;
- under development to treat bacterial diseases in humans; or
- indicated for a bacterial disease in food-producing animals.

In the context of the risk assessment process, FDA GFI #152 defines the hazard as a human illness, caused by antimicrobial-resistant bacteria attributable to an animal-derived food commodity, and treated with the human antimicrobial drug of interest. The qualitative antimicrobial resistance risk assessment is comprised of three components: the ***release***, ***exposure,*** and ***consequence*** assessments. **Box A3-3** briefly describes these components.

Results from the ***release***, ***exposure***, and ***consequence*** assessments are then integrated to determine an ***overall risk estimation*** for the proposed use of the drug. Because GFI #152 provides a qualitative approach, the overall risk estimation ranks the risk as high, medium, or low to represent the potential for human health to be adversely impacted by the selection or emergence of antimicrobial-resistant foodborne bacteria resulting from use of a new animal antimicrobial drug in food-producing animals. The overall risk estimation is then used to develop appropriate risk management measures to mitigate antimicrobial resistance concerns surrounding the use of the proposed drug. For example, antimicrobial new animal drugs that are considered to be high risk could have risk management conditions such as a prohibition of ELU or being limited to use under veterinary oversight only. Additional risk management steps, such as post-approval resistance monitoring through the NARMS program, may be implemented to mitigate the human exposure of high risk antimicrobial new animal drugs.

GFI #152 contains Appendix A, which provides a ranking of antimicrobial drugs according to their importance in human medicine. Currently, Appendix A ranks antimicrobial drugs as important, highly important, or critically important. This list is sometimes referred to as FDA's list of medically-important antimicrobials. It is a

Box A3-3: Microbial Food Safety - Qualitative Risk Assessment Components

Release Assessment:
The boundaries of the release assessment span from the point the antimicrobial is administered to the animal to the point the animal is harvested for slaughter. The release assessment describes in detail factors related to an antimicrobial new animal drug and its use in animals that contribute to the emergence or selection of resistant bacteria or resistance determinants in the animals. Some of these factors describing the veterinary drug product include, but are not limited to: mechanism and type of antimicrobial action, spectrum of activity, and pharmacokinetic /pharmacodynamic properties. Bacterial resistance mechanisms and genetics, occurrence and rate of transfer of resistance determinants, resistance selection pressures, and the baseline prevalence of resistance are considered; data from the NARMS program are a critical part of this evaluation. The outcome of the release assessment estimates the probability that resistant organisms will emerge or be selected for as a consequence of the proposed use of an antimicrobial new animal drug in a food-producing animal.

Exposure assessment:
CVM assumes the probability that bacteria in or on the animal at slaughter can be used as an estimate of the probability of human exposure to that bacterial species in the primary food commodity. This evaluation is based on relative rates of both consumption of the food commodity derived from the treated animal, and contamination of the food commodity with organisms of human health concern. The outcome of the exposure assessment describes the likelihood of human exposure to food-borne bacteria of human health concern through the consumption of animal-derived food products.

Consequence assessment:
This estimates the probability that human exposure to resistant bacteria could result in an adverse health consequence. This component focuses on the human health consequence of exposure to resistant bacteria based on the importance of the drug (or related drugs) in human medicine. Thus, the outcome of the consequence assessment is related to the rankings of medically-important antimicrobials currently provided in Appendix A of GFI #152.

critical component of the overall microbial food safety risk assessment process where ranking of importance determines the result of the consequence assessment. Recently, CVM published a concept paper describing a potential approach for updating and revising the list and ranking of medically important antimicrobials (see Chapter 2). Antimicrobial resistance concerns may also be considered for other drug products (e.g., those not listed in Appendix A) as long as the drug product is known to have antibacterial activity and its use could exert pressure towards the emergence or selection for resistance in bacteria of public health concern. For example, avilamycin, approved by FDA in 2015 and in 2016 as a Type A Medicated Article for use in weaned pigs and broiler chickens, is not considered to be medically-important since it is not used in human medicine. However, because the drug product is an antimicrobial and thus has antibacterial activity which could potentially exert pressure on the emergence or selection of antimicrobial resistance among bacteria of human health concern, a microbial food safety risk assessment as outlined in GFI #152 was required for its approval. In addition, post-approval resistance monitoring of avilamycin is conducted through the NARMS program.

The microbial food safety assessment serves to ensure that medically important antimicrobials are used judiciously, which should minimize antimicrobial resistance development. It is important to note that since no new antimicrobials have been approved for production uses in food-producing animals since the publication of GFI #152 in 2003, the microbial food safety for these indicated uses was not evaluated using the current approach. To address this concern, FDA published guidance in 2012 (GFI #209) and 2015 (GFI #213) to provide a framework and strategy for judicious use of medically important antimicrobials in food-producing animals so that these drugs are used in a manner to minimize antimicrobial selection pressure and thus help preserve effective therapies in both humans and animals. GFI #209 and GFI #213, as well as other recent regulatory and policy changes related to VFD antimicrobial drugs, are described in the next section.

A3.2 Recent Regulations and Policies (2012-2017)

Building upon the foundations established in historical regulations and policies related to marketing status and ELU of antimicrobial drugs, as well as the pre-approval microbial food safety assessment for antimicrobials described in the previous section, CVM continues to take actions aimed at addressing the threat of antimicrobial resistance arising from the use of medically important antimicrobials in food-producing animals. Between 2012 and 2015, CVM published three core documents to announce and implement a policy framework for the judicious use of medically important antimicrobials in food-producing animals. Judicious use of antimicrobials is an integral part of good veterinary practice. In general, judicious use refers to drug use practices aimed at maximizing therapeutic efficacy while minimizing the selection of resistant microorganisms.

A3.2.1 Guidance for Industry (GFI) #209: The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals

GFI #209, entitled "*The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals*," was finalized in April of 2012. It summarized some of the key reports and scientific literature that had been

published over the prior 40 years related to the use of antimicrobials in animal agriculture, and set forth CVM's framework for judicious use. This guidance document included two main measures that CVM considered essential for judicious use: (1) limiting medically important antimicrobial drugs approved for use in the feed or water of food-producing animals to uses that are considered necessary for assuring animal health, and (2) limiting such drugs to uses in food-producing animals that include veterinary oversight or consultation. These measures would effectively eliminate the feed and water uses of medically important antimicrobials for production purposes (e.g., growth promotion; improved feed efficiency) in food-producing animals, and bring all remaining therapeutic uses of such drugs under the oversight of licensed veterinarians.

A3.2.2 Guidance for Industry (GFI) #213: New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals

GFI #213, entitled "*New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209*," was published in December 2013. It outlined a detailed process and timeline for implementing the measures identified in GFI #209. On January 3, 2017, CVM announced that it had completed implementation of GFI #213. CVM achieved voluntary compliance from all drug sponsors for all of the affected applications with implementation of GFI #209 and #213 policies. This process successfully transitioned medically important antimicrobials used in the feed or drinking water of food-producing animals from OTC status to VFD or Rx status requiring veterinary oversight and eliminated production uses. Completing implementation of GFI #213 was a significant milestone in U.S. efforts to address the use of medically important antimicrobials in food-producing animals. Of the 292 new animal drug applications initially affected by GFI #213:

- 84 were completely withdrawn;
- 208 applications transitioned to either Rx or VFD marketing status:
  - Rx: 93 applications for products intended for use in water converted from OTC to Rx marketing status
  - VFD: 115 applications for products intended for use in feed converted from OTC to VFD marketing status; and
- Production indications were withdrawn from all applications (31) that had included such indications for use.

A3.2.3 Veterinary Feed Directive (VFD) Final Rule

The VFD Rule is the third core policy document of CVM's judicious use strategy. (https://www.federalregister.gov/documents/2015/06/03/2015-13393/veterinary-feed-directive). Given that most of the products affected by GFI #213 were feed-use antimicrobial drugs transitioning from OTC to VFD marketing status, the VFD regulation has an important role since it outlines the requirements associated with veterinary authorization, distribution, and use of VFD drugs in animal feed. In June of 2015, CVM published a final rule revising the VFD regulations in 21 CFR Part 558. The final rule amended the regulations in order to improve the efficiency of the existing VFD program. The final rule became effective in October of 2015. A draft GFI was also published with the final rule, GFI #120, entitled '*Veterinary Feed Directive Regulation Questions and Answers*.'

The VFD final rule outlines the process for authorizing the use of VFD drugs and provides veterinarians in all states with a framework for authorizing the use of medically important antimicrobials in feed when needed for specific animal health purposes. Like the initial VFD regulation, the VFD final rule continues to require veterinarians to issue all VFDs within the context of a VCPR. The final rule requires veterinarians to follow state-defined VCPR requirements; however, in states where CVM determines that no applicable or appropriate state VCPR requirements exist, veterinarians need to issue VFDs in compliance with federally defined VCPR requirements. The rule facilitates veterinary oversight in a way that allows for the flexibility needed to accommodate the diversity of circumstances that veterinarians encounter, while at the same time ensuring that veterinarians in all states are conducting such oversight in accordance with nationally consistent principles.

As part of the VFD final rule, CVM stated that it intended to use a phased enforcement strategy for implementation of the final rule as OTC drugs became VFD drugs under GFI #213. Leading up to full implementation of GFI #213, CVM provided multiple education and training opportunities in a variety of formats for stakeholders subject to the final rule, such as veterinarians, animal producers, and medicated feed manufacturers and distributors. These education and training efforts were important for supporting effective implementation and compliance with the final rule. In addition, CVM clarified specific questions related to VFD issues such as the use of medically important antimicrobials in bees, and free-choice feeding options for control of anaplasmosis in cattle. As additional opportunities for clarification on a wide range of topics related to the VFD final rule arose, CVM published updates to draft GFI #120 in September 2015 and March 2019, and additional updates to the guidance are expected to publish in the near future. In addition, FDA GFI #233, entitled '*Veterinary Feed Directive Common Format Questions and Answers*', was published in September 2016.

APPENDIX 4
Animal Populations and Animal Weights Used for Biomass Denominator Calculations

Animal Populations Used in Biomass Denominator Calculations, 2016-2019

Animal Category	Population				Ref #
	2016	2017	2018	2019	
Cattle -- commercial and farm slaughtered	30,676,100	32,280,600	33,099,800	33,655,900	1
Calves -- commercial and farm slaughtered	512,700	536,800	603,600	608,900	1
Cattle imported for immediate slaughter	548,415	491,133	416,996	522,749	5
Cattle imported <90 kg	4,869	7,576	7,515	7,299	5
Cattle imported 90 kg to 199 kg	375,538	455,455	499,883	493,438	5
Cattle imported 200 kg to 319 kg	619,274	752,067	827,233	858,704	5
Cattle imported > 320 kg	144,250	87,910	136,467	150,145	5
Exported cattle for slaughter	68,760	193,058	243,586	307,281	5
Livestock beef cows (Jan 1 following-year inventory)	31,213,200	31,466,200	31,690,700	31,316,700	3
Livestock dairy cows (milk cows, Jan 1 following-year inventory)	9,346,000	9,432,100	9,353,400	9,334,600	3
Hogs -- commercial and farm slaughtered	118,303,900	121,389,700	124,508,400	129,989,000	1
Imported pigs for immediate slaughter ≥50 kg	848,779	753,973	695,080	745,274	5
Imported pigs <7 kg	3,439,010	3,442,477	3,310,252	3,293,979	5
Imported pigs 7 to <23 kg	672,042	673,124	593,988	576,024	5
Imported pigs 23 to <50 kg	626,746	651,837	594,683	441,480	5
Imported pigs ≥50 kg	12,940	16,545	15,931	14,127	5
Exported pigs ≥50 kg	12,305	13,102	8,551	9,749	5
Exported pigs <50 kg	23,303	22,539	33,231	36,373	5
Hogs and pigs, kept for breeding+ (Dec 1 inventory)	6,110,000	6,179,000	6,326,000	6,471,000	4
Chickens -- number slaughtered, total	8,908,986,000	9,050,702,000	9,160,910,000	9,339,249,000	2
Young chickens#	8,768,399,000	8,916,083,000	9.034,504,000	9,224,243,000	2
Chicken imports (<0.185 kg)	5,334,755	4,598,968	3,954,204	1,602,043	5
Chicken imports (>0.185 kg)	244,926	273,093	223,857	218,155	5
Chicken exports (<0.185 kg)	68,295,081	68,069,679	58,678,373	61,895,911	5
Chicken exports (>0.185 kg)	458,680	664,071	282,942	313,759	5
Turkeys -- number slaughtered, total	243,255,000	241,680,000	236,860,000	227,660,000	2

+All hogs and pigs kept for breeding includes boars.
#Young chickens are defined in reference 2 as commercially grown broilers/fryers and other young immature birds such as roasters and capons. This population is used in the calculation of chicken biomass for the lincosamide drug class only. They are a subset of the total number slaughtered in previous row.

Animal Weights Used in Biomass Denominator Calculations, 2016-2019

Animal Category	Weight (kg)*				Ref #
	2016	2017	2018	2019	
Cattle -- commercial and farm slaughtered	618.25	611.90	612.35	609.63	1
Calves -- commercial and farm slaughtered	120.66	113.40	102.51	100.24	1
Cattle imported for immediate slaughter	618.25	611.90	612.35	609.63	1
Cattle imported <90 kg	90.00	90.00	90.00	90.00	5
Cattle imported 90 kg to 199 kg	199.00	199.00	199.00	199.00	5
Cattle imported 200 kg to 319 kg	319.00	319.00	319.00	319.00	5
Cattle imported > 320 kg	618.25	611.90	612.35	609.63	1
Exported cattle for slaughter	618.25	611.90	612.35	609.63	1
Livestock beef cows (Jan 1 following-year inventory)	520.27	520.27	520.27	520.27	7
Livestock dairy cows (milk cows, Jan 1 following-year inventory)	635.03	635.03	635.03	635.03	6,7
Hogs -- commercial and farm slaughtered	127.91	127.91	128.37	129.27	1
Imported pigs for immediate slaughter ⩾50 kg	127.91	127.91	128.37	129.27	1
Imported pigs <7 kg	7.00	7.00	7.00	7.00	5
Imported pigs 7 to <23 kg	23.00	23.00	23.00	23.00	5
Imported pigs 23 to <50 kg	50.00	50.00	50.00	50.00	5
Imported pigs ⩾50 kg	127.91	127.91	128.37	129.27	1
Exported pigs ⩾50 kg	127.91	127.91	128.37	129.27	1
Exported pigs <50 kg	50.00	50.00	50.00	50.00	5
Hogs and pigs, kept for breeding* (Dec 1 inventory)	204.12	204.12	204.12	204.12	8**
Chickens -- number slaughtered, total	2.79	2.81	2.84	2.87	2
Young chickens#	2.79	2.81	2.84	2.87	2
Chicken imports (<0.185 kg)	0.19	0.19	0.19	0.19	5
Chicken imports (>0.185 kg)	2.79	2.81	2.84	2.87	2
Chicken exports (<0.185 kg)	0.19	0.19	0.19	0.19	5
Chicken exports (>0.185 kg)	2.79	2.81	2.84	2.87	2
Turkeys -- number slaughtered, total	13.92	14.02	14.09	14.52	2

*Weight in kilograms was calculated from pounds (1 lb=0.453592 kg), unless based on values were reported in kg; values are rounded to nearest hundredth.

**Average weight is for culled sows; gilts and sows account for the majority of the hog breeding inventory, so the number of boars has minimal impact on the average weight of this category. Reference 8 links to daily or weekly swine reports, in which sow weight ranges are reported as 300 to 550+ lbs; therefore, a midpoint of 450 lbs was chosen to represent average sow weight, in the absence of another published resource for this information.

#Young chickens are defined in reference 2 as commercially grown broilers/fryers and other young immature birds such as roasters and capons. This population is used in the calculation of chicken biomass for the lincosamide drug class only. They are a subset of the total number slaughtered in previous row.

Calculated Biomass Denominators, 2016-2019

Animal Category	Biomass^			
	2016	2017	2018	2019
Cattle -- commercial and farm slaughtered	18,965,372,930	19,752,357,364	20,268,636,050	20,517,567,158
Calves -- commercial and farm slaughtered	61,860,060	60,872,046	61,876,118	61,038,469
Cattle imported for immediate slaughter	339,055,323	300,522,126	255,347,167	318,682,243
Cattle imported <90 kg	438,210	681,840	676,350	656,910
Cattle imported 90 kg to 199 kg	74,732,062	90,635,545	99,476,717	98,194,162
Cattle imported 200 kg to 319 kg	197,548,406	239,909,373	263,887,327	273,926,576
Cattle imported > 320 kg	89,181,970	53,791,743	83,565,458	91,532,543
Exported cattle for slaughter	42,510,588	118,131,342	149,159,692	187,326,993
Livestock beef cows (Jan 1 following-year inventory)	16,239,291,564	16,370,919,874	16,487,720,489	16,293,139,509
Livestock dairy cows (milk cows, Jan 1 following-year inventory)	5,934,979,165	5,989,655,144	5,939,678,378	5,927,739,836
Hogs -- commercial and farm slaughtered	15,132,600,136	15,527,313,898	15,982,712,011	16,804,161,589
Imported pigs for immediate slaughter ≥50 kg	108,569,821	96,442,906	89,225,012	96,344,342
Imported pigs <7 kg	24,073,070	24,097,339	23,171,764	23,057,853
Imported pigs 7 to <23 kg	15,456,966	15,481,852	13,661,724	13,248,552
Imported pigs 23 to <50 kg	31,337,300	32,591,850	29,734,150	22,074,000
Imported pigs ≥50 kg	1,655,193	2,116,320	2,045,007	1,826,250
Exported pigs ≥50 kg	1,573,969	1,675,915	1,097,662	1,260,289
Exported pigs <50 kg	1,165,150	1,126,950	1,661,550	1,818,650
Hogs and pigs, kept for breeding (Dec 1 inventory)	1,247,151,204	1,261,235,236	1,291,240,346	1,320,837,224
Chickens -- number slaughtered, total	24,892,835,831	25,453,021,334	26,012,274,959	26,772,838,557
Young chickens#	24,500,017,938	25,074,436,305	25,653,346,902	26,443,150,691
Chicken imports (<0.185 kg)	986,930	850,809	731,528	296,378
Chicken imports (>0.185 kg)	684,354	768,011	635,639	625,385
Chicken exports (<0.185 kg)	12,634,590	12,592,891	10,855,499	11,450,744
Chicken exports (>0.185 kg)	1,281,610	1,867,547	803,410	899,453
Turkeys -- number slaughtered, total	3,385,185,854	3,387,385,140	3,338,092,481	3,305,504,799

^Biomass calculations were performed using unrounded raw data, and resulting figures were rounded to a whole number. Biomass denominator calculations are performed by multiplying the population of an animal category by that animal category's weight in kilograms.

#Young chickens are used in the calculation of chicken biomass for the lincosamide drug class only. They are a subset of the total number slaughtered in previous row.

References

1	USDA Livestock Slaughter Summary
2	USDA Poultry Slaughter Summary
3	USDA NASS Cattle Report, first yearly publication of biannual report
4	USDA NASS Quarterly Hogs and Pigs Report, December publication of quarterly report (use March report showing December 1 inventory of prior year)
5	USDA Foreign Agricultural Service, Global Agricultural Trade System (GATS) using the link at https://apps.fas.usda.gov/gats/ProductGroup.aspx?GROUP=BICO-HS10
6	Bovine Alliance on Management and Nutrition; HEIFER GROWTH AND ECONOMICS: TARGET GROWTH;
7	USDA NAHMS Beef 2007-08 Part IV: Reference of Beef Cow-calf Management Practices in the United States
8	USDA AMS Swine Direct Reports

Formulas for Target Animal Biomass (TAB) as applied to the mg/TAB Calculations for Biomass-Adjusted Antimicrobial Sales Data in Chapters 4-7 of the report:

Cattle TAB = (Cattle, commercial and farm slaughtered) + (Calves, commercial and farm slaughtered) - (Imported cattle: all weight categories) + (Exported cattle for slaughter) + (Livestock beef cows) + (Livestock daily cows). No subcategory exclusions applied.

Swine TAB = (Hogs, commercial and farm slaughtered) + (Exported pigs: all weight categories) + (Hogs and pigs kept for breeding) – (Imported pigs: all weight categories). No subcategory exclusions applied.

Chicken TAB = (Chickens, number slaughtered, total) - (Imported chickens: all categories) + (Exported chickens: all categories).

Young chicken TAB is calculated separately and applied to the lincosamide drug class only.

Turkey TAB = (Turkeys, number slaughtered, total). No subcategory exclusions applied. Note: no import or export categories are included for turkeys, as the GATS database does not report on turkeys separately from other species.

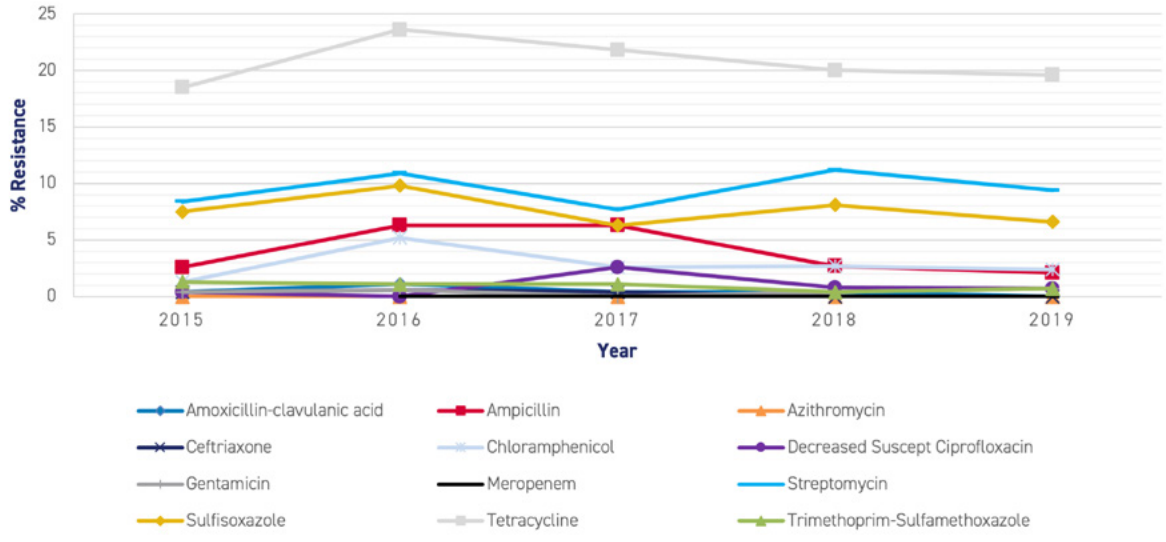
APPENDIX 5

NARMS Antimicrobial Resistance Data for Cattle Sample Types, 2015-2019

E. coli

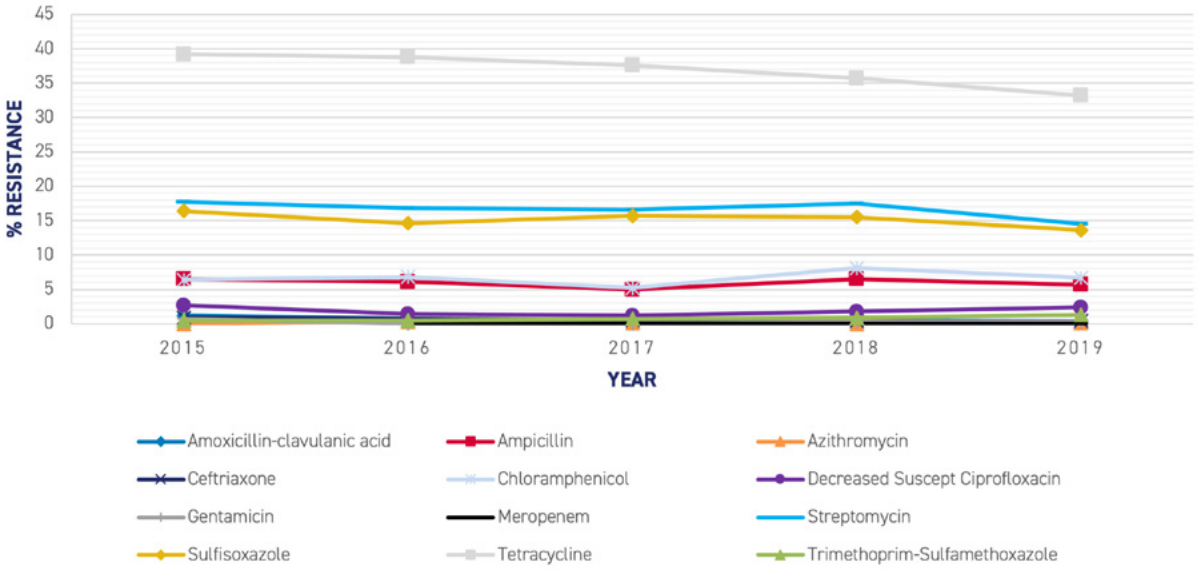
Figures A5.1 through A5.3 below show the percentage resistance for antimicrobials from ten antimicrobial drug classes tested, for *E. coli* isolates from retail ground beef, beef cattle cecal samples, and dairy cattle cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *E. coli* isolates from cattle sample types are shown in **Figure A5.4.**

Figure A5.1: Percentage resistance in *E. coli* isolates from retail ground beef samples, 2015-2019



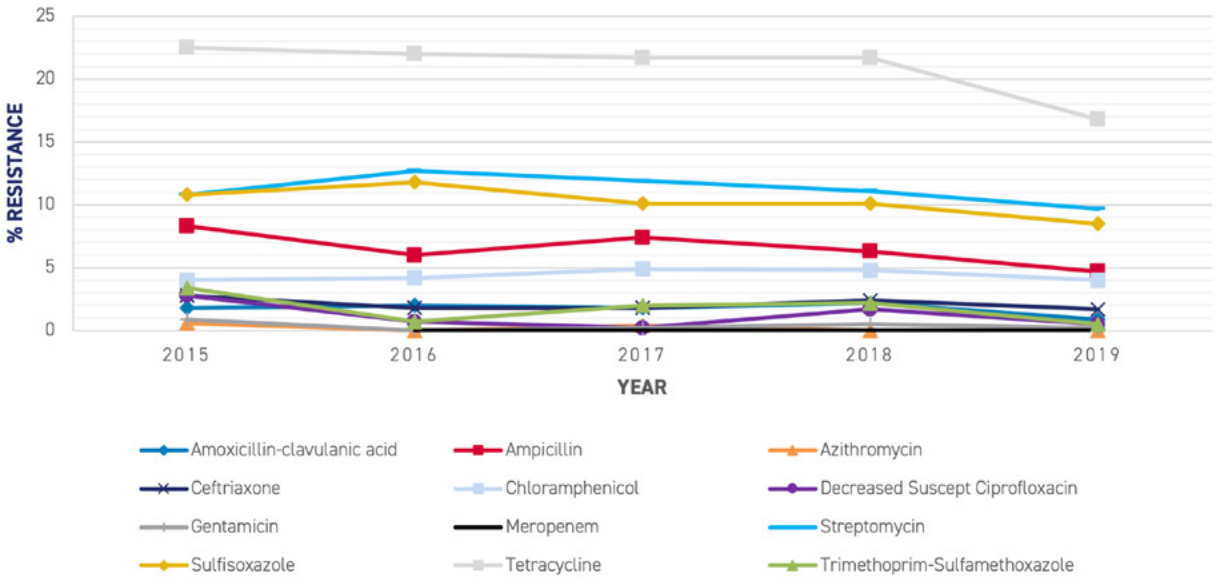
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, folate pathway inhibitors, penicillins, amphenicols, carbapenems, tetracyclines, macrolides, and quinolones.

Figure A5.2: Percentage resistance in *E. coli* isolates from beef cattle cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, folate pathway inhibitors, penicillins, amphenicols, carbapenems, tetracyclines, macrolides, and quinolones.

Figure A5.3: Percentage resistance in *E. coli* isolates from dairy cattle cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, folate pathway inhibitors, penicillins, amphenicols, carbapenems, tetracyclines, macrolides, and quinolones.

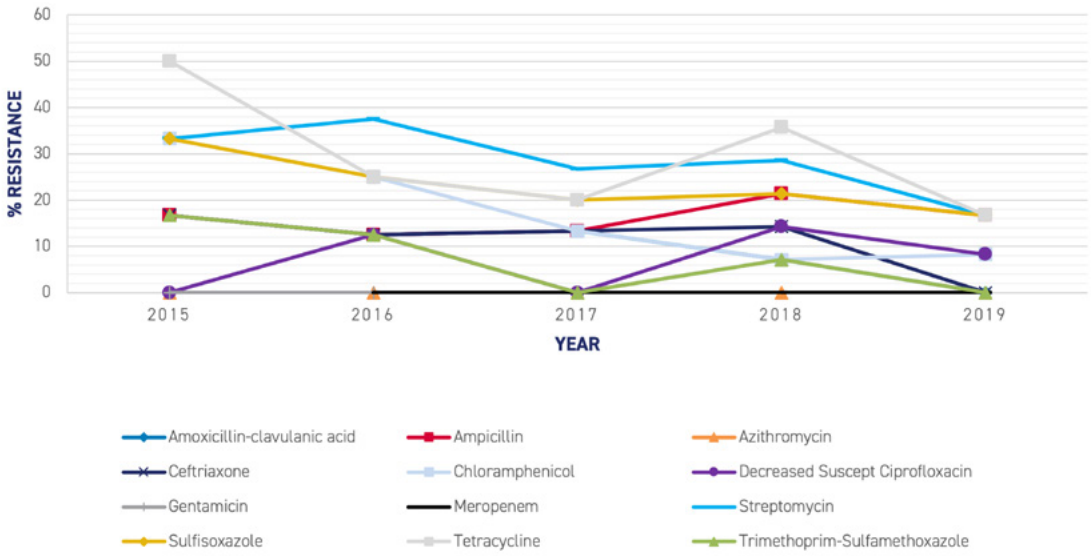
Figure A5.4: Percentage of *E. coli* isolates with multidrug resistance by cattle sample type, 2015-2019

Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Salmonella

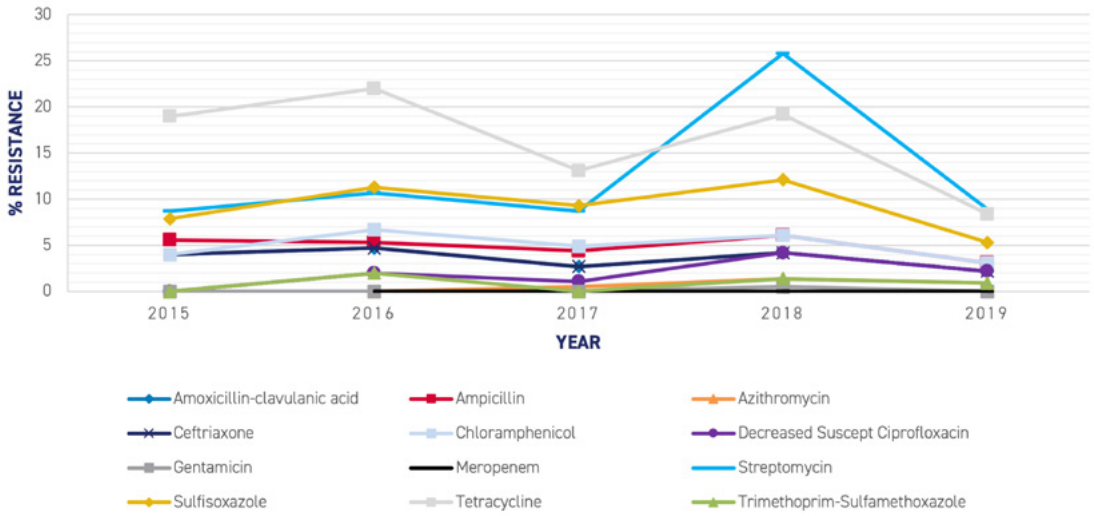
Figures A5.5 through A5.7 below show the percentage resistance for antimicrobials from ten antimicrobial drug classes tested, for nontyphoidal *Salmonella* isolates from retail ground beef, beef cattle cecal samples, and dairy cattle cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. The charts show data for all nontyphoidal *Salmonella* serotypes combined. Complete data, including information for isolates obtained from the USDA-FSIS Pathogen Reduction/Hazard Analysis and Critical Control Point (PR/HACCP) sampling program, are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Salmonella* isolates from cattle sample types are shown in **Figure A5.8.**

Figure A5.5: Percentage resistance in *Salmonella* isolates from retail ground beef samples, 2015-2019



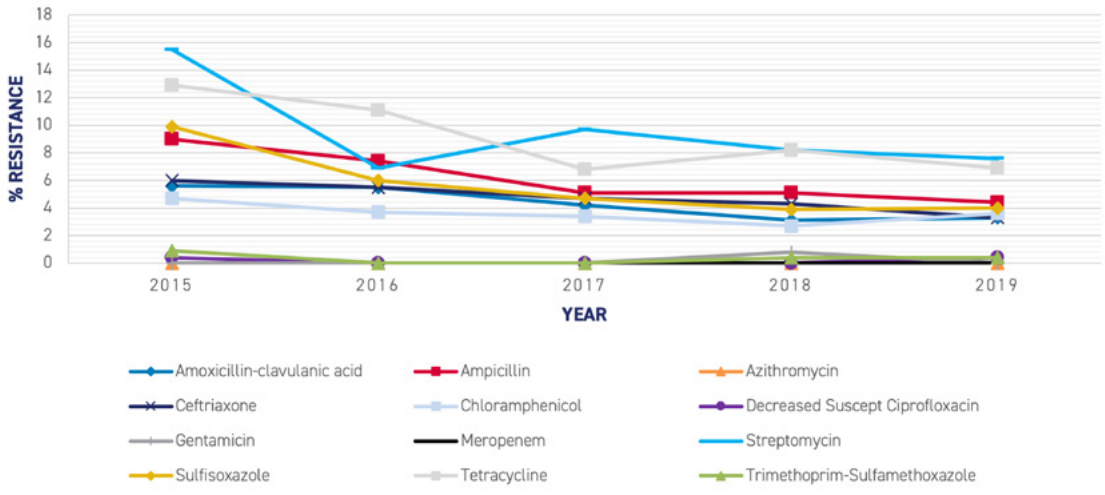
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, folate pathway inhibitors, penicillins, amphenicols, carbapenems, tetracyclines, macrolides, and quinolones.

Figure A5.6: Percentage resistance in *Salmonella* isolates from beef cattle cecal samples, 2015-2019



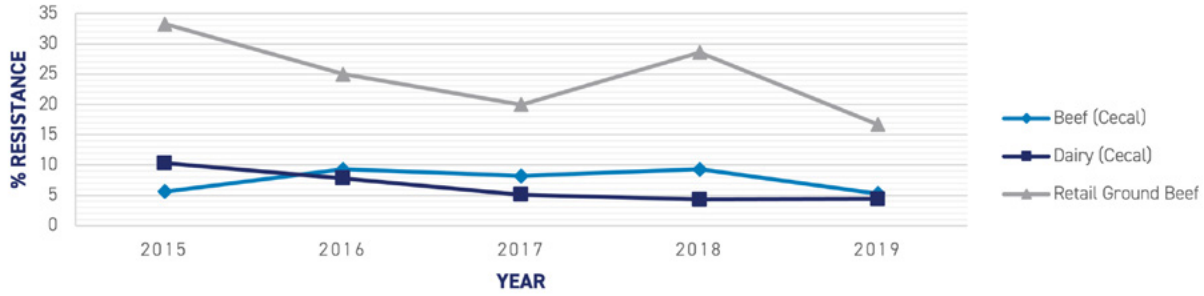
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, folate pathway inhibitors, penicillins, amphenicols, carbapenems, tetracyclines, macrolides, and quinolones.

Figure A5.7: Percentage resistance in *Salmonella* isolates from dairy cattle cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, folate pathway inhibitors, penicillins, amphenicols, carbapenems, tetracyclines, macrolides, and quinolones.

Figure A5.8: Percentage of *Salmonella* isolates with multidrug resistance by cattle sample type, 2015-2019

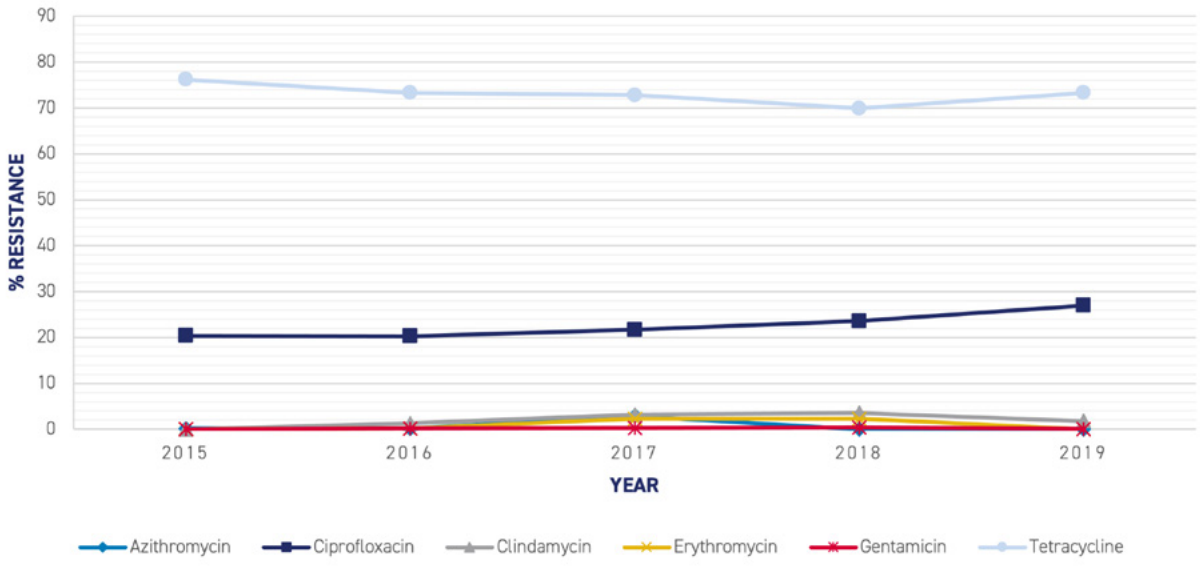


Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Campylobacter spp.

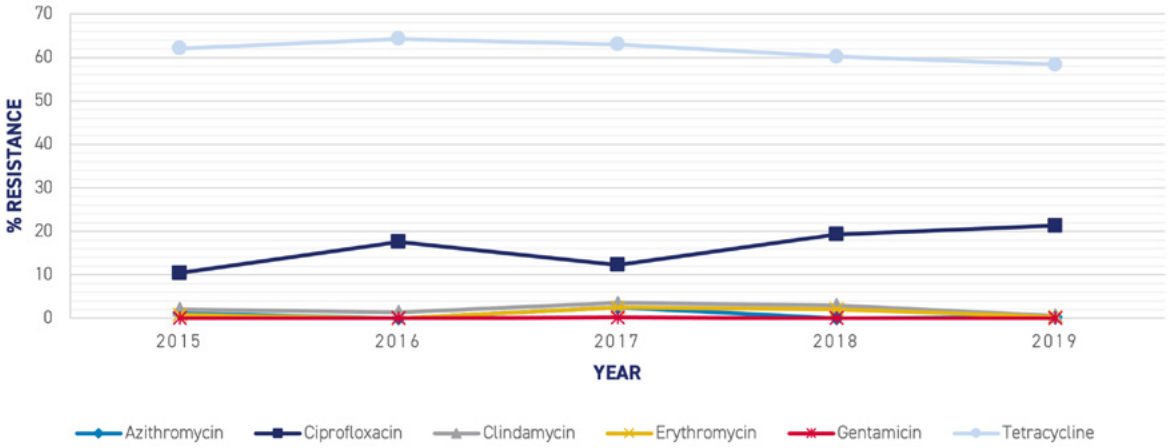
Figures A5.9 and A5.10 and **Figures A5.12 and A5.13** below show the percentage resistance for antimicrobials from five of the antimicrobial drug classes tested, for *Campylobacter jejuni (C. jejuni)* and *Campylobacter coli (C. coli)* isolates from beef cattle and dairy cattle cecal samples, respectively. Retail ground beef has not been cultured for *Campylobacter* in the NARMS retail meat program since 2008, due to the low recovery of isolates. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Campylobacter* spp. isolates from cattle cecal sample types are shown in **Figure A5.11 and A5.14.**

Figure A5.9: Percentage resistance in *Campylobacter jejuni* isolates from beef cattle cecal samples, 2015-2019



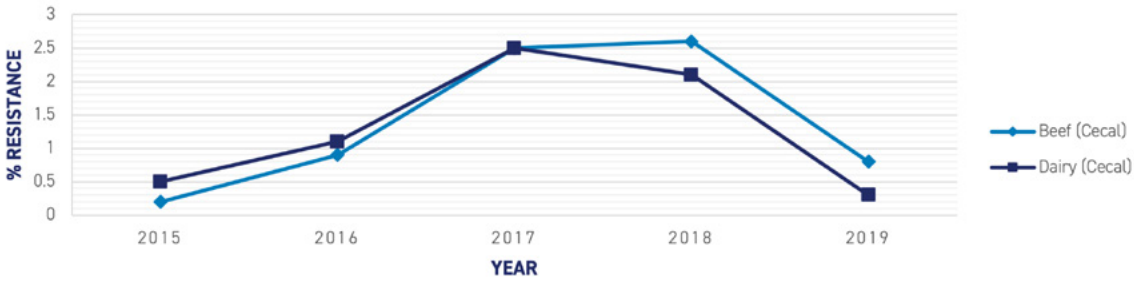
Antimicrobials shown are from the following antimicrobial classes: quinolones, lincosamides, macrolides, , aminoglycosides, and tetracyclines.

Figure A5.10: Percentage resistance in *Campylobacter jejuni* isolates from dairy cattle cecal samples, 2015-2019



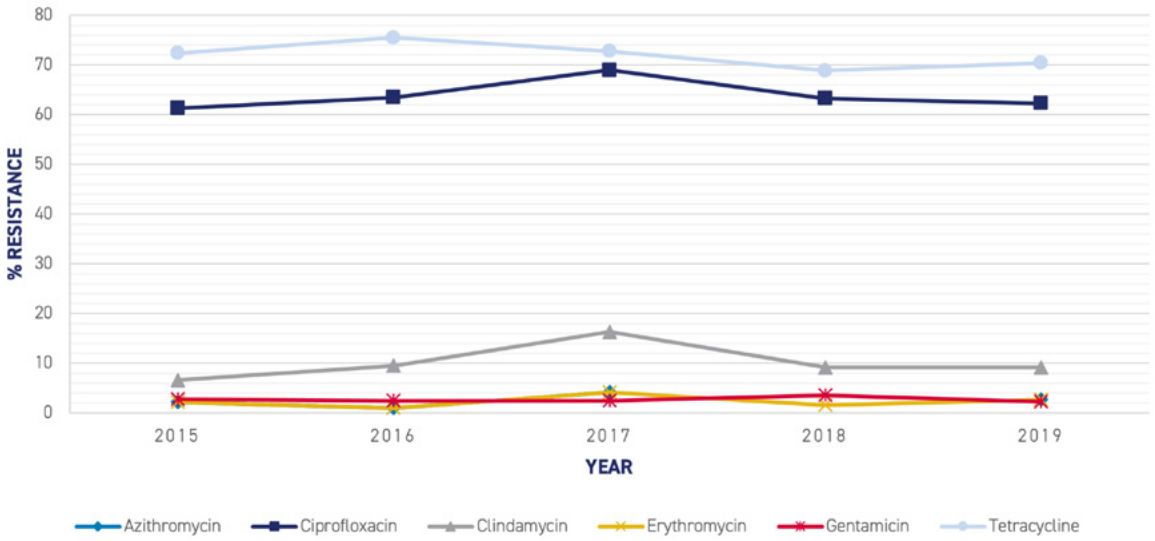
Antimicrobials shown are from the following antimicrobial classes: quinolones, lincosamides, macrolides, , aminoglycosides, and tetracyclines.

Figure A5.11: Percentage of *Campylobacter jejuni* isolates with multidrug resistance by cattle cecal sample type, 2015-2019



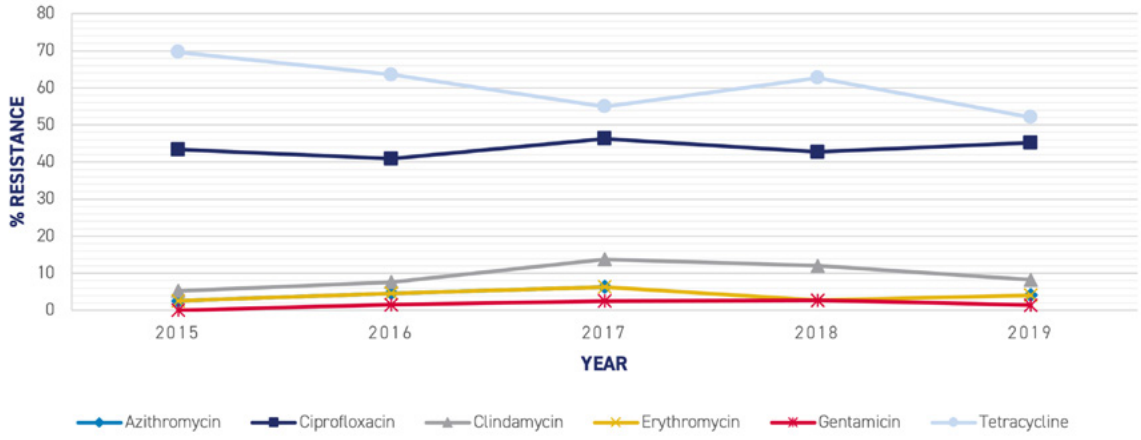
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Figure A5.12: Percentage resistance in *Campylobacter coli* isolates from beef cattle cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: quinolones, lincosamides, macrolides, , aminoglycosides, and tetracyclines.

Figure A5.13: Percentage resistance in *Campylobacter coli* isolates from dairy cattle cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: quinolones, lincosamides, macrolides, aminoglycosides, and tetracyclines.

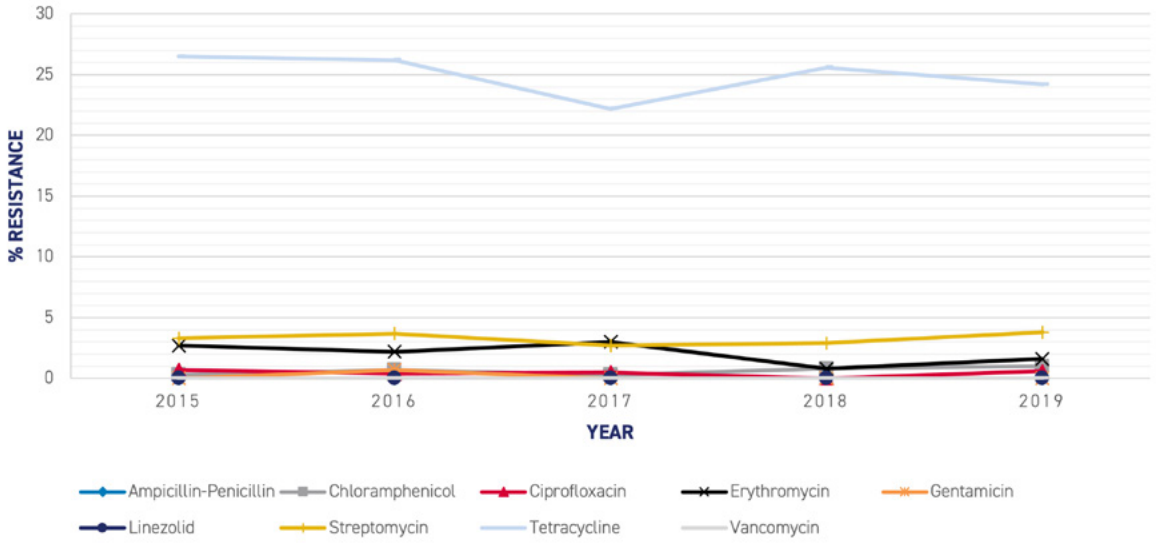
Figure A5.14: Percentage of *Campylobacter coli* isolates with multidrug resistance by cattle cecal sample type, 2015-2019

Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Enterococcus spp.

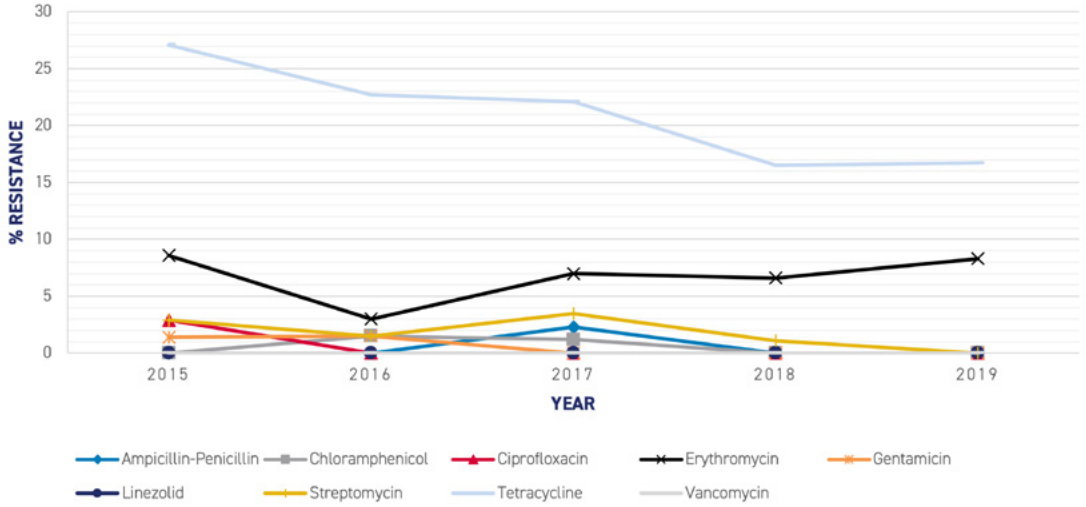
Figures A5.15 through A5.17 and **Figures A5.19 and A5.21** below show the percentage resistance for antimicrobials from eight or nine of the antimicrobial drug classes tested, for *Enterococcus faecalis (E. faecalis)* and *Enterococcus faecium (E. faecium)* isolates from retail ground beef, beef cattle cecal samples, and dairy cattle cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Enterococcus* spp. isolates from cattle sample types are shown in **Figure A5.18 and A5.22.**

Figure A5.15: Percentage resistance in *Enterococcus faecalis* isolates from retail ground beef samples, 2015-2019



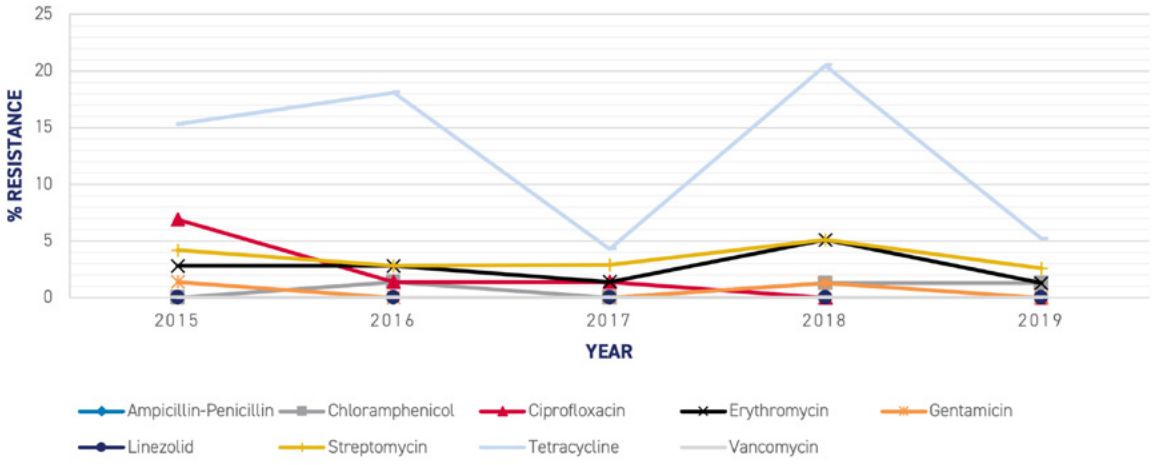
Antimicrobials shown are from the following antimicrobial classes: amphenicols, penicillins, quinolones, aminoglycosides, macrolides, tetracyclines, glycopeptides, and oxazolidinones.

Figure A5.16: Percentage resistance in *Enterococcus faecalis* isolates from beef cattle cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: amphenicols, penicillins, quinolones, aminoglycosides, macrolides, tetracyclines, glycopeptides, and oxazolidinones.

Figure A5.17: Percentage resistance in *Enterococcus faecalis* isolates from dairy cattle cecal samples, 2015-2019

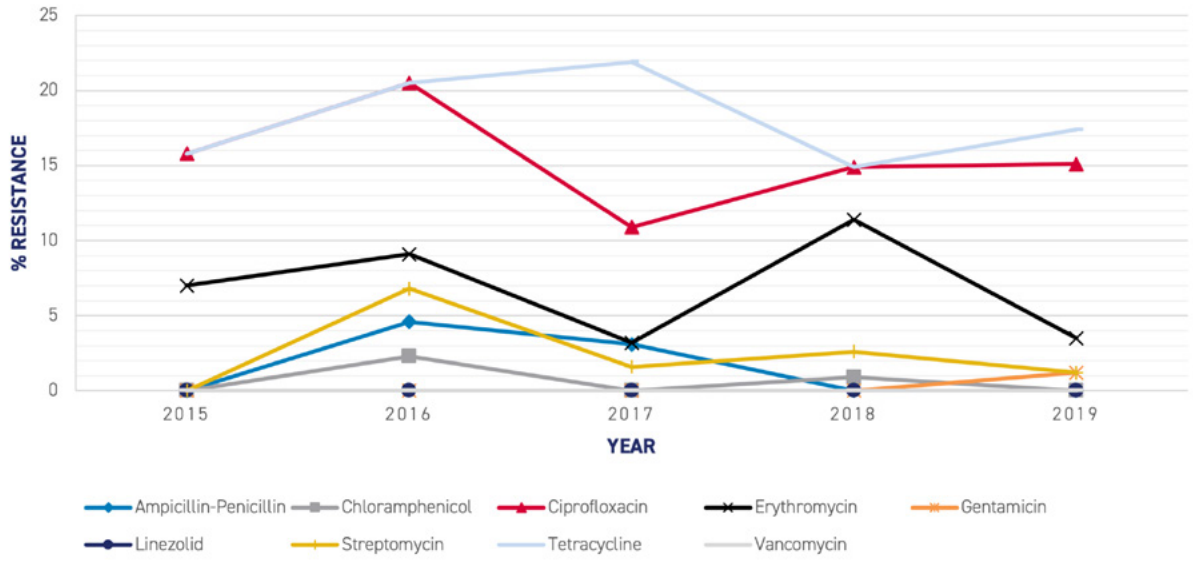


Antimicrobials shown are from the following antimicrobial classes: : amphenicols, penicillins, quinolones, aminoglycosides, macrolides, tetracyclines, glycopeptides, and oxazolidinones.

Figure A5.18: Percentage of *Enterococcus faecalis* isolates with multidrug resistance by cattle sample type, 2015-2019

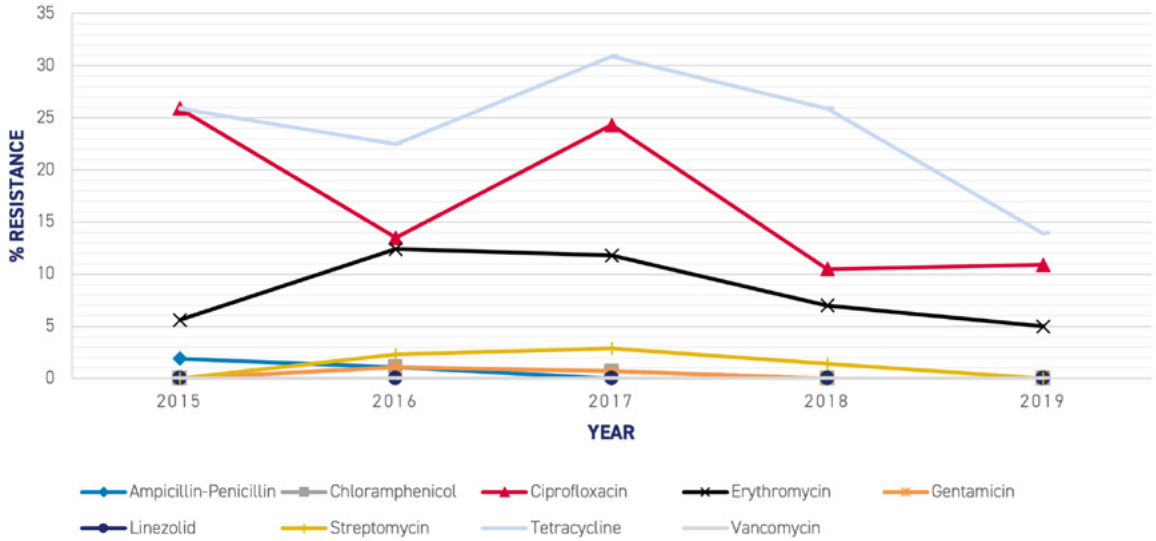
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Figure A5.19: Percentage resistance in *Enterococcus faecium* isolates from retail ground beef samples, 2015-2019



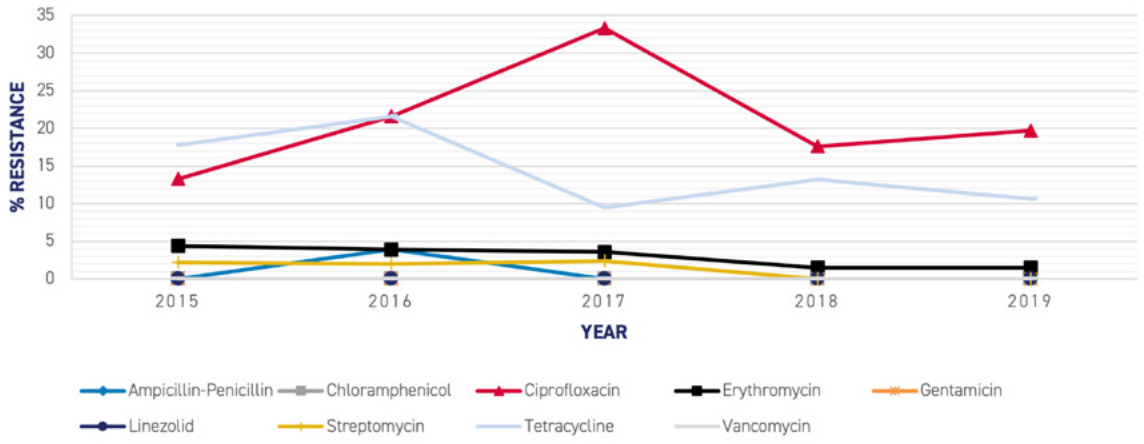
Antimicrobials shown are from the following antimicrobial classes: amphenicols, oxazolidinones, tetracyclines, quinolones, penicillins, glycopeptides, macrolides, streptogramins, and aminoglycosides.

Figure A5.20: Percentage resistance in *Enterococcus faecium* isolates from beef cattle cecal samples, 2015-2019



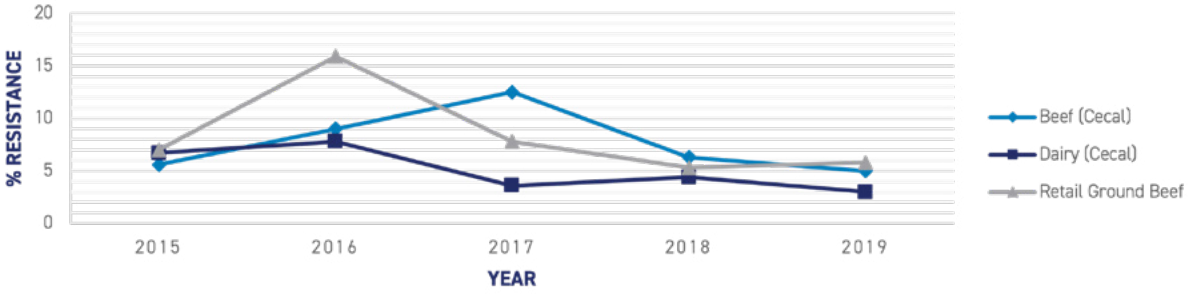
Antimicrobials shown are from the following antimicrobial classes: amphenicols, oxazolidinones, tetracyclines, quinolones, penicillins, glycopeptides, macrolides, streptogramins, and aminoglycosides.

Figure A5.21: Percentage resistance in *Enterococcus faecium* isolates from dairy cattle cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: amphenicols, oxazolidinones, tetracyclines, quinolones, penicillins, glycopeptides, macrolides, streptogramins, and aminoglycosides.

Figure A5.22: Percentage of *Enterococcus faecium* isolates with multidrug resistance by cattle sample type, 2015-2019



Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

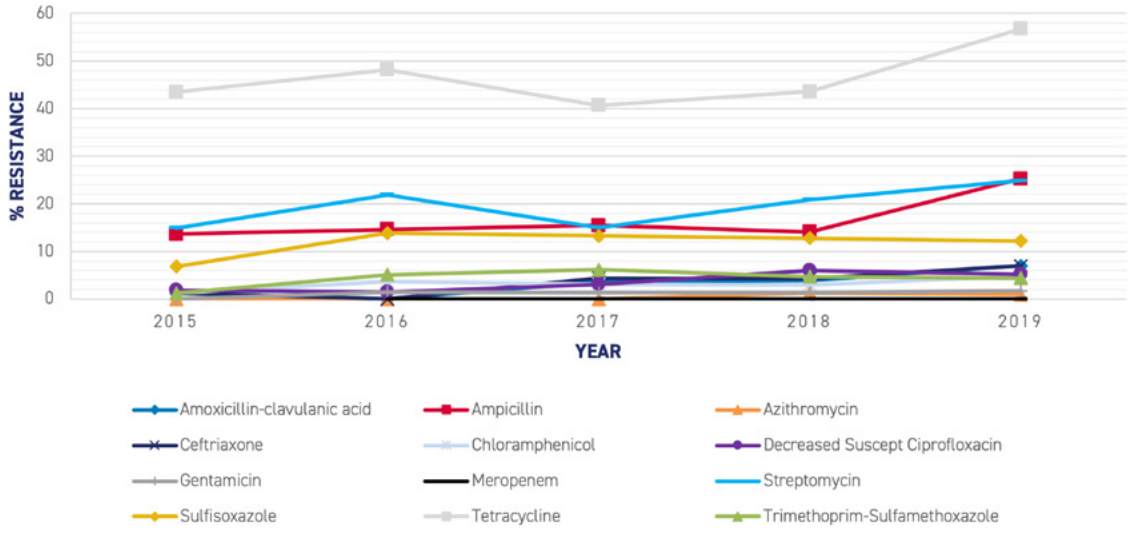
APPENDIX 6

NARMS Antimicrobial Resistance Data for Swine Sample Types, 2015-2019

E. coli

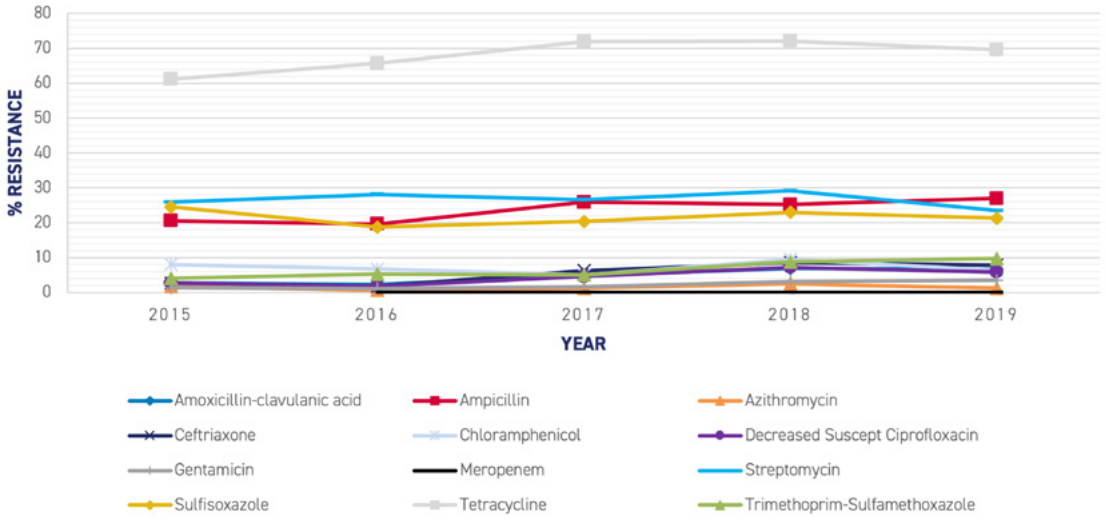
Figures A6.1 through A6.3 below show the percentage resistance for antimicrobials from ten antimicrobial drug classes tested, for *E. coli* isolates from retail pork, market swine cecal samples, and sow cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *E. coli* isolates from swine sample types are shown in **Figure A6.4.**

Figure A6.1: Percentage resistance in *E. coli* isolates from retail pork samples, 2015-2019



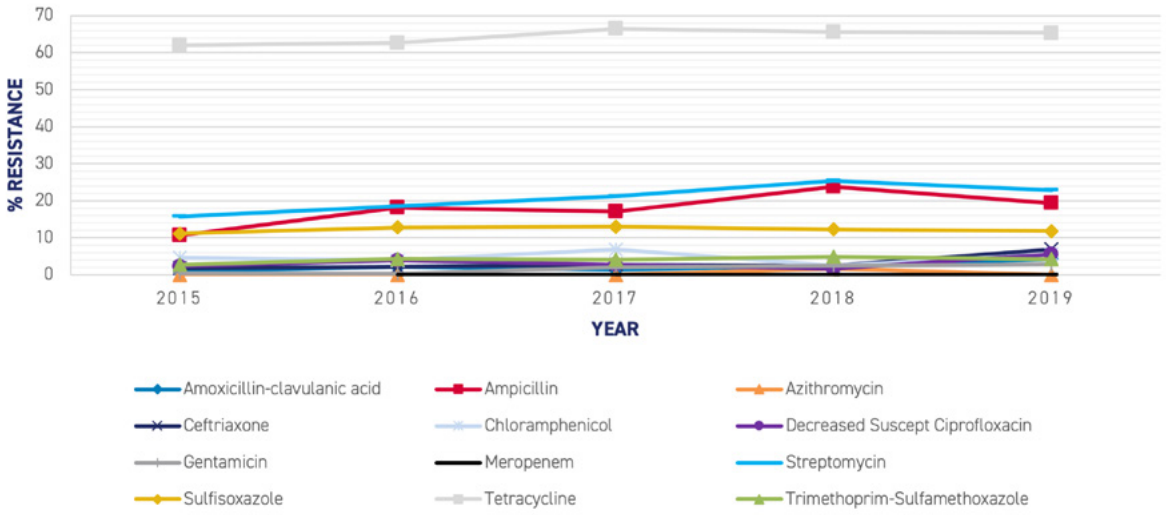
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A6.2: Percentage resistance in *E. coli* isolates from market swine cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes:=β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A6.3: Percentage resistance in *E. coli* isolates from sow cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

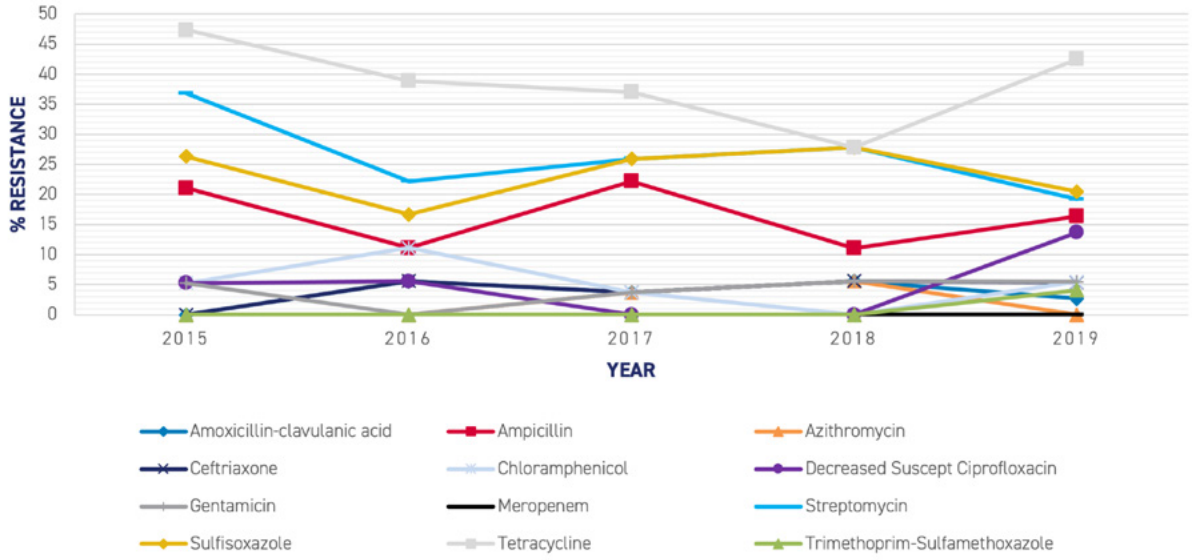
Figure A6.4: Percentage of *E. coli* isolates with multidrug resistance by swine sample type, 2015-2019

Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Salmonella

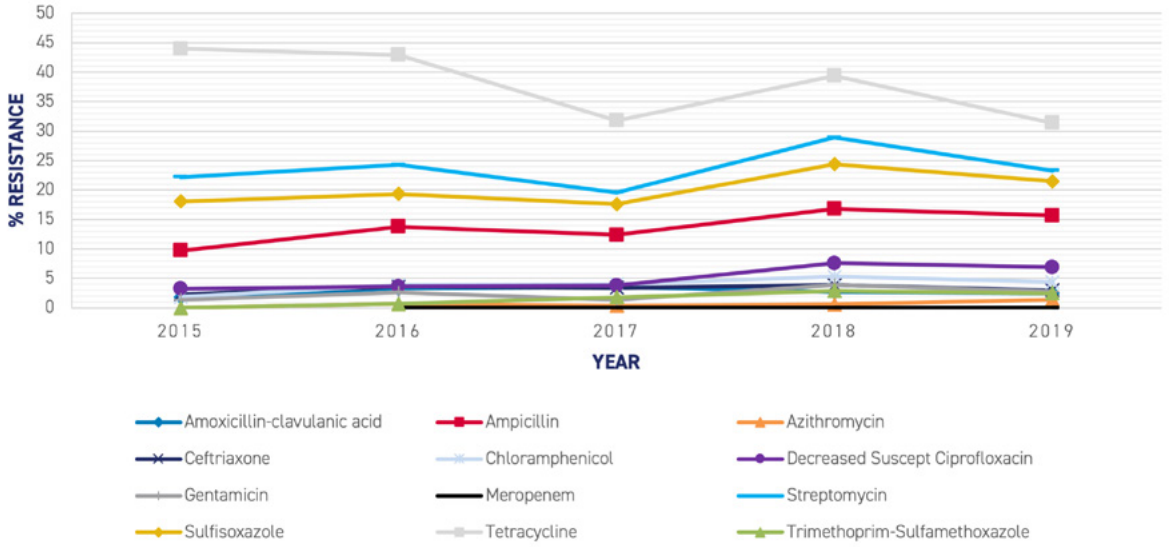
Figures A6.5 through A6.7 below show the percentage resistance for antimicrobials from ten antimicrobial drug classes tested, for nontyphoidal *Salmonella* isolates from retail pork, market swine cecal samples, and sow cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. The charts show data for all nontyphoidal *Salmonella* serotypes combined. Complete data, including information for isolates obtained from the USDA-FSIS Pathogen Reduction/Hazard Analysis and Critical Control Point (PR/HACCP) sampling program, are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Salmonella* isolates from swine sample types are shown in **Figure A6.8.**

Figure A6.5: Percentage resistance in *Salmonella* isolates from retail pork samples, 2015-2019



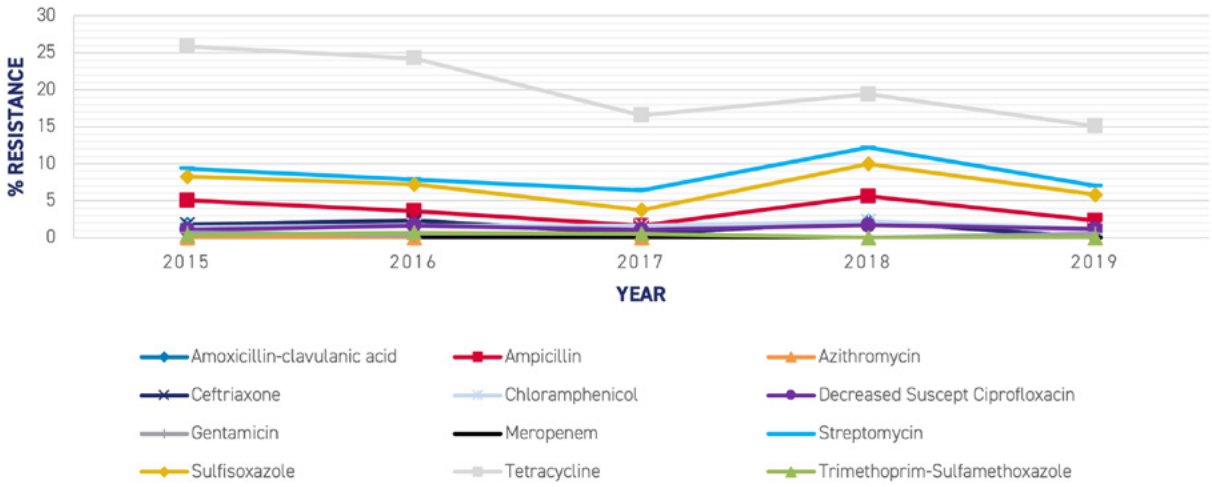
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A6.6: Percentage resistance in *Salmonella* isolates from market swine cecal samples, 2015-2019



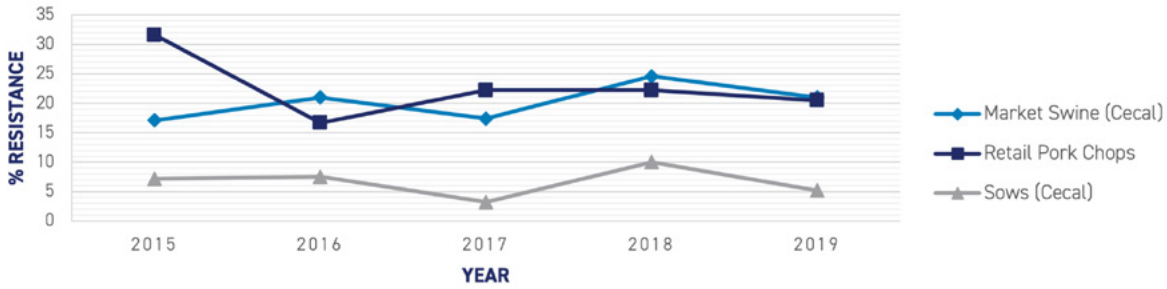
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A6.7: Percentage resistance in *Salmonella* isolates from sow cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A6.8: Percentage of *Salmonella* isolates with multidrug resistance by swine sample type, 2015-2019

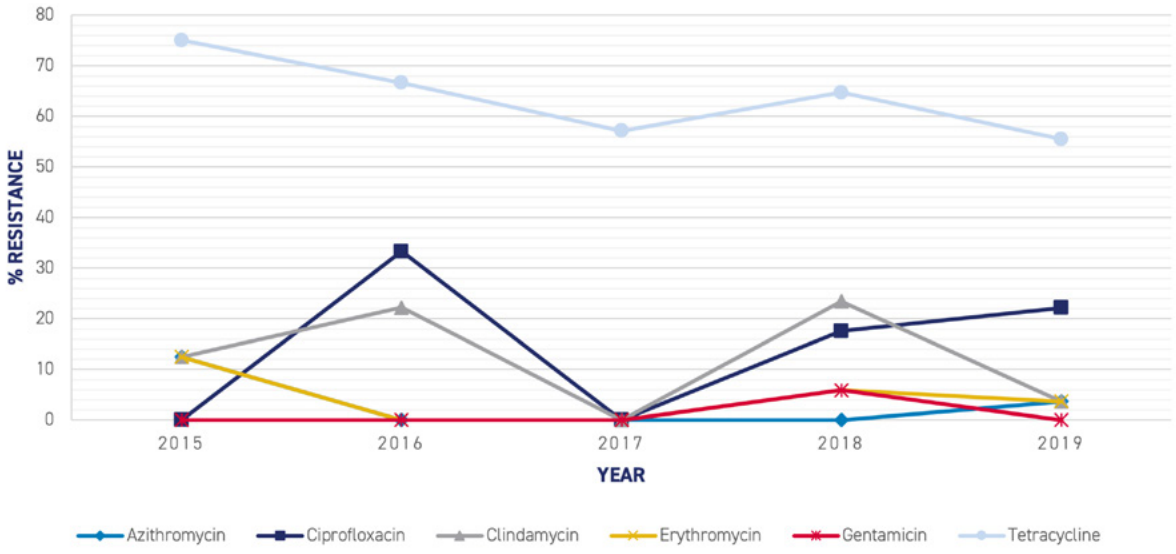


Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Campylobacter spp.

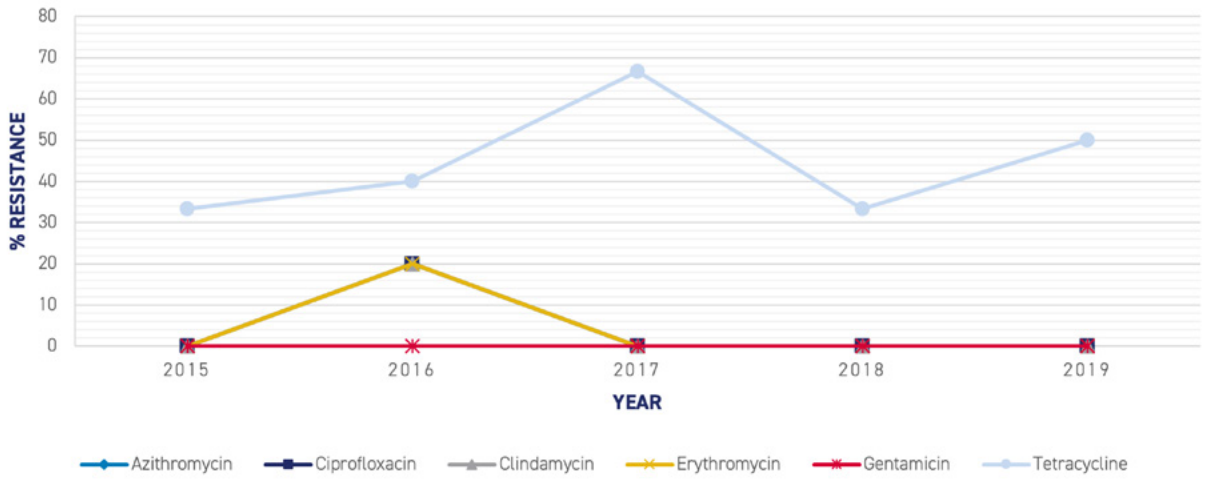
Figures A6.9 and A6.10 and **Figures A6.12 and A6.13** below show the percentage resistance for antimicrobials from five of the antimicrobial drug classes tested, for *Campylobacter jejuni (C. jejuni)* and *Campylobacter coli (C. coli)* isolates from market swine and sow cecal samples, respectively. Retail pork has not been cultured for *Campylobacter* in the NARMS retail meat program since 2008, due to the low recovery of isolates. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Campylobacter* spp. isolates from swine cecal sample types are shown in **Figure A6.11 and A6.14.**

Figure A6.9: Percentage resistance in *Campylobacter jejuni* isolates from market swine cecal samples, 2015-2019



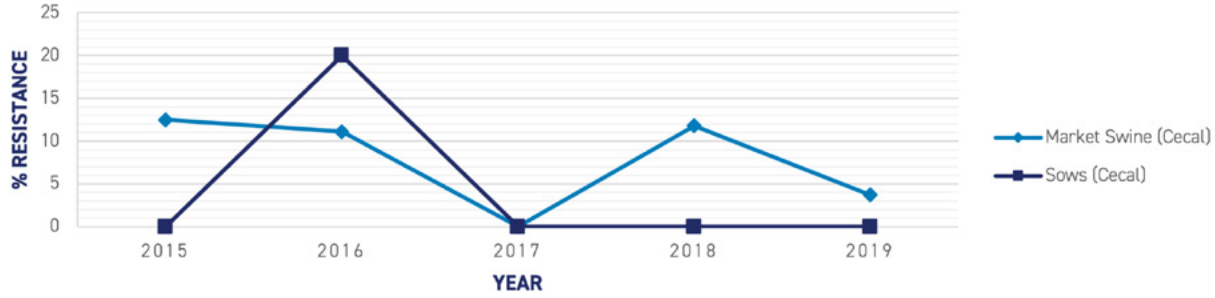
Antimicrobials shown are from the following antimicrobial classes: quinolones, lincosamides, macrolides, aminoglycosides, and tetracyclines.

Figure A6.10: Percentage resistance in *Campylobacter jejuni* isolates, sow cecal samples, 2015-2019



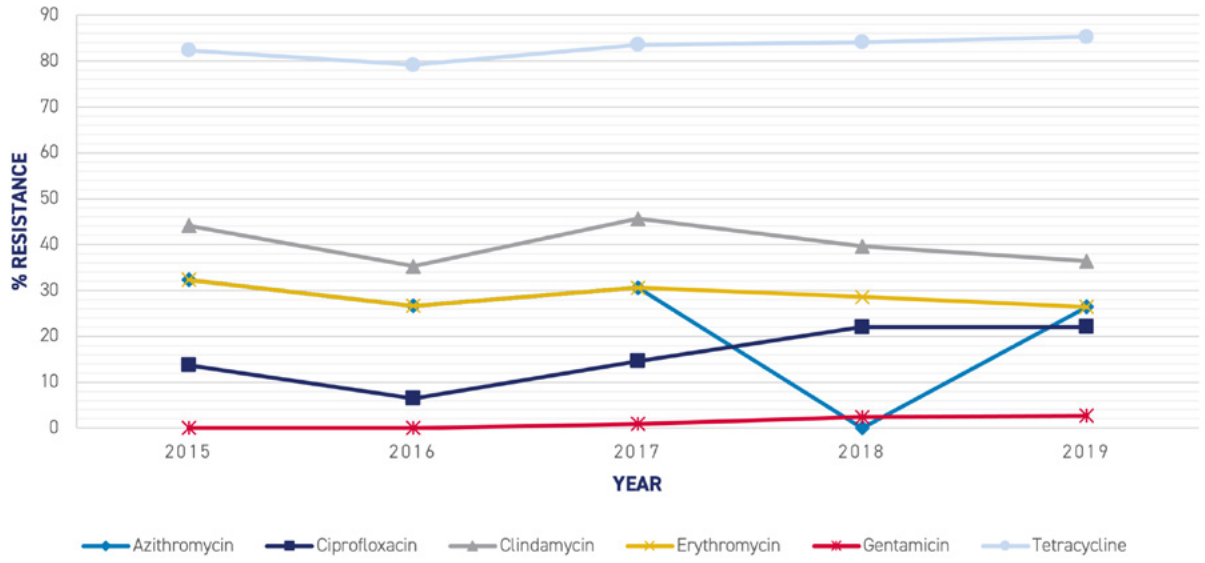
Antimicrobials shown are from the following antimicrobial classes: quinolones, lincosamides, macrolides, aminoglycosides, and tetracyclines.

Figure A6.11: Percentage of *Campylobacter jejuni* isolates with multidrug resistance by swine cecal sample type, 2015-2019



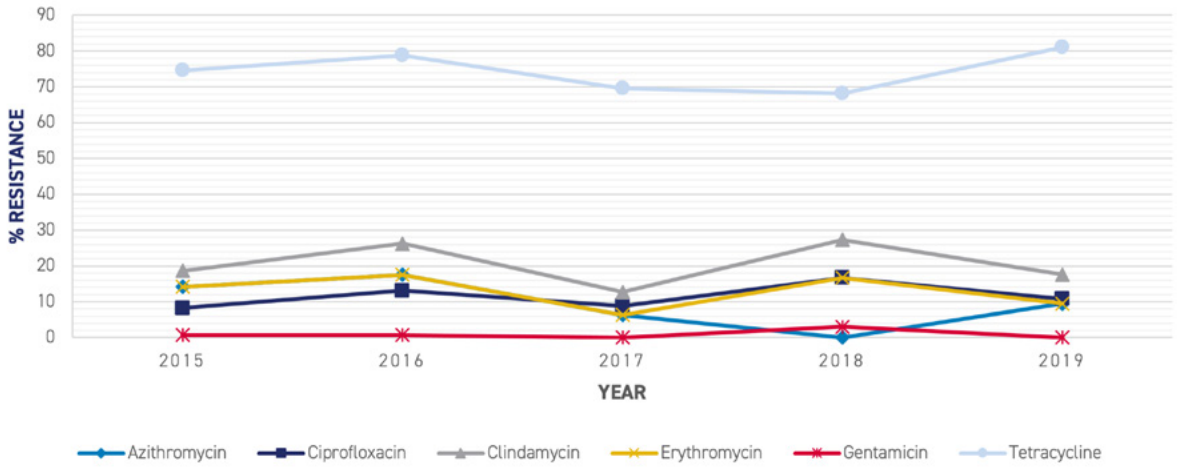
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Figure A6.12: Percentage resistance in *Campylobacter coli* isolates from market swine cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: quinolones, lincosamides, macrolides, aminoglycosides, and tetracyclines.

Figure A6.13: Percentage resistance in *Campylobacter coli* isolates, sow cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: quinolones, lincosamides, macrolides, aminoglycosides, and tetracyclines.

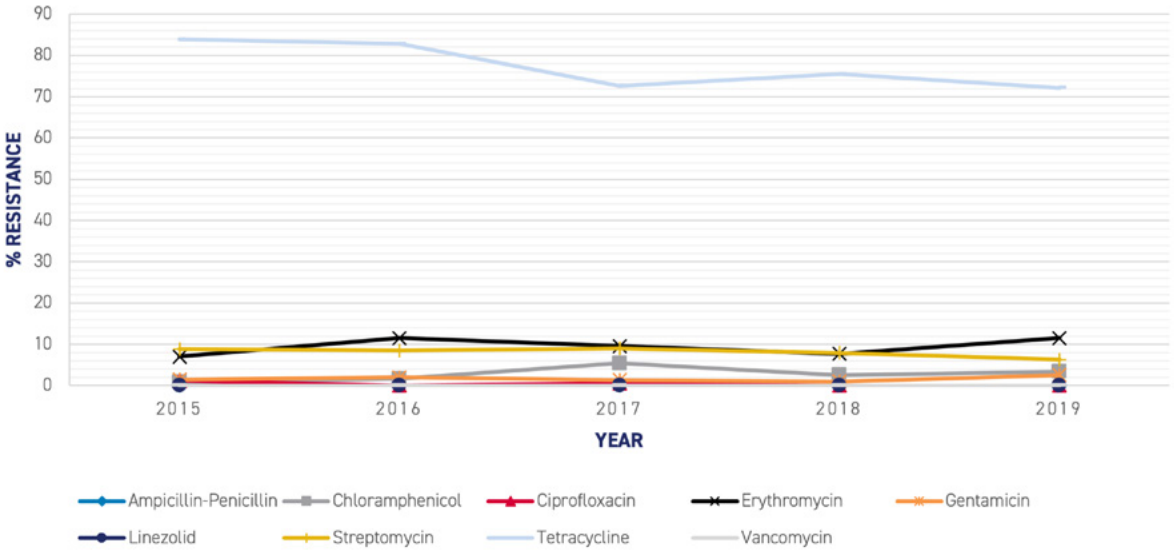
Figure A6.14: Percentage of *Campylobacter coli* isolates with multidrug resistance by swine cecal sample type, 2015-2019

Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Enterococcus spp.

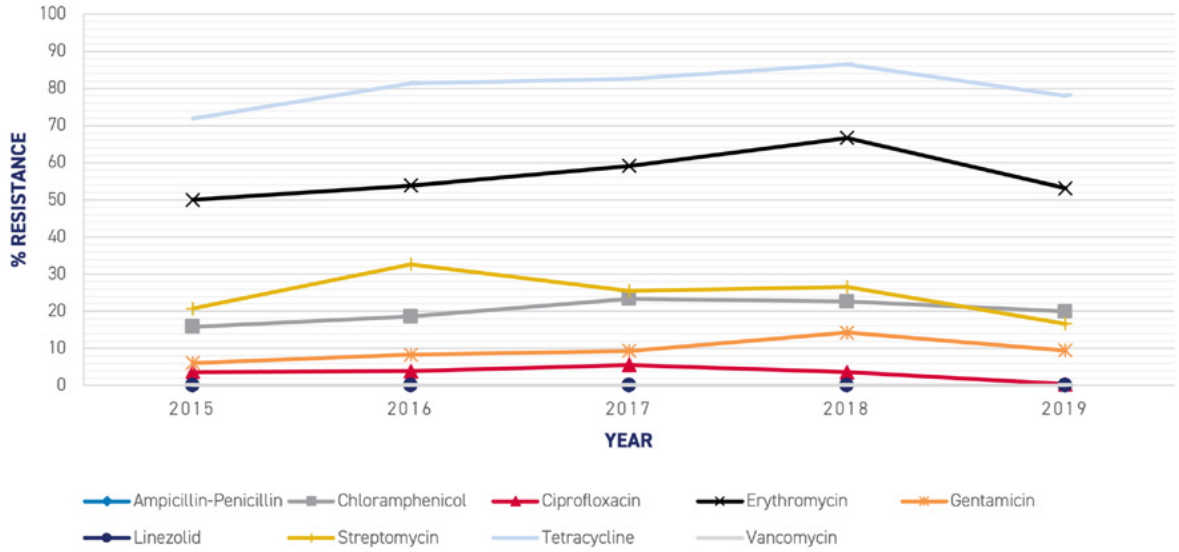
Figures A6.15 through A6.17 and **Figures A6.19 through A6.21** below show the percentage resistance for antimicrobials from eight or nine of the antimicrobial drug classes tested, for *Enterococcus faecalis (E. faecalis)* and *Enterococcus faecium (E. faecium)* isolates from retail pork, market swine cecal samples, and sow cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Enterococcus* spp. isolates from swine sample types are shown in **Figure A6.18 and A6.22.**

Figure A6.15: Percentage resistance in *Enterococcus faecalis* isolates from retail pork samples, 2015-2019



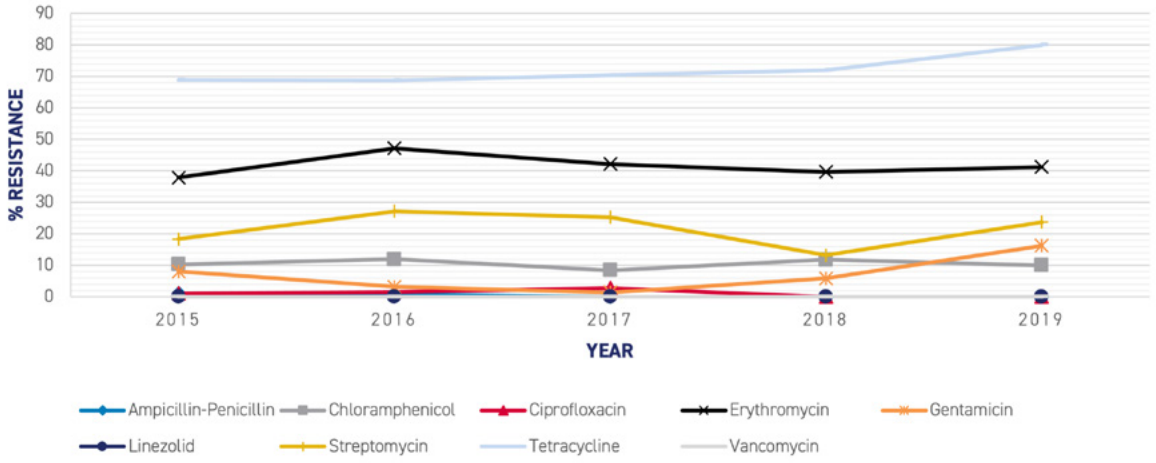
Antimicrobials shown are from the following antimicrobial classes: penicillins, oxazolidinones, amphenicols, aminoglycosides, quinolones, tetracyclines, macrolides, and glycopeptides.

Figure A6.16: Percentage resistance in *Enterococcus faecalis* isolates from market swine cecal samples, 2015-2019



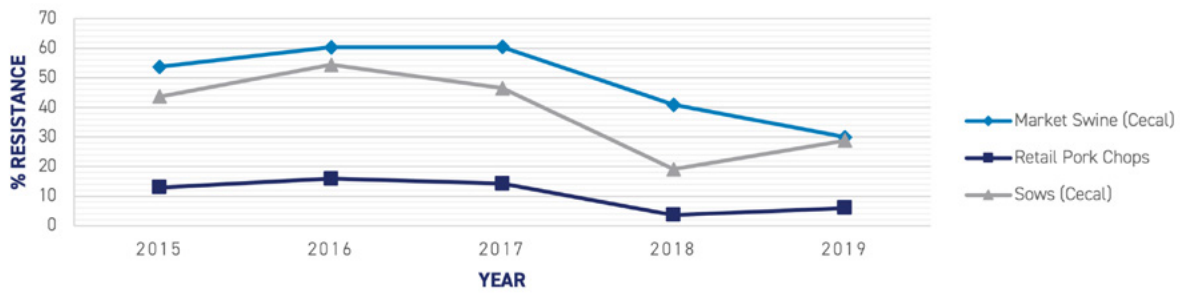
Antimicrobials shown are from the following antimicrobial classes: penicillins, oxazolidinones, amphenicols, aminoglycosides, quinolones, tetracyclines, macrolides, and glycopeptides.

Figure A6.17: Percentage resistance in *Enterococcus faecalis* isolates, sow cecal samples, 2015-2019



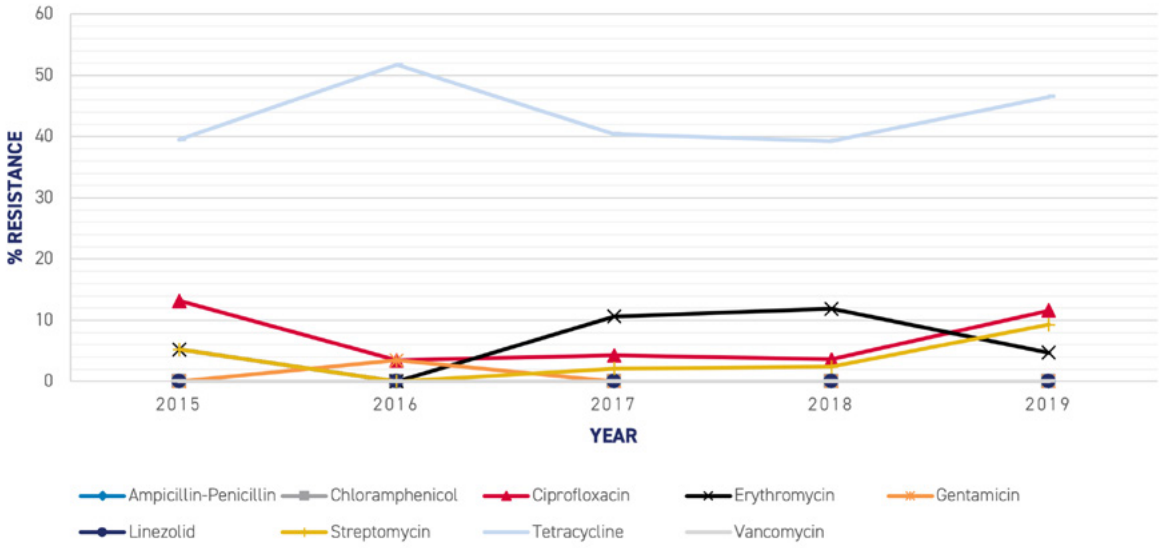
Antimicrobials shown are from the following antimicrobial classes: penicillins, oxazolidinones, amphenicols, aminoglycosides, quinolones, tetracyclines, macrolides, and glycopeptides.

Figure A6.18: Percentage of *Enterococcus faecalis* isolates with multidrug resistance by swine sample type, 2015-2019



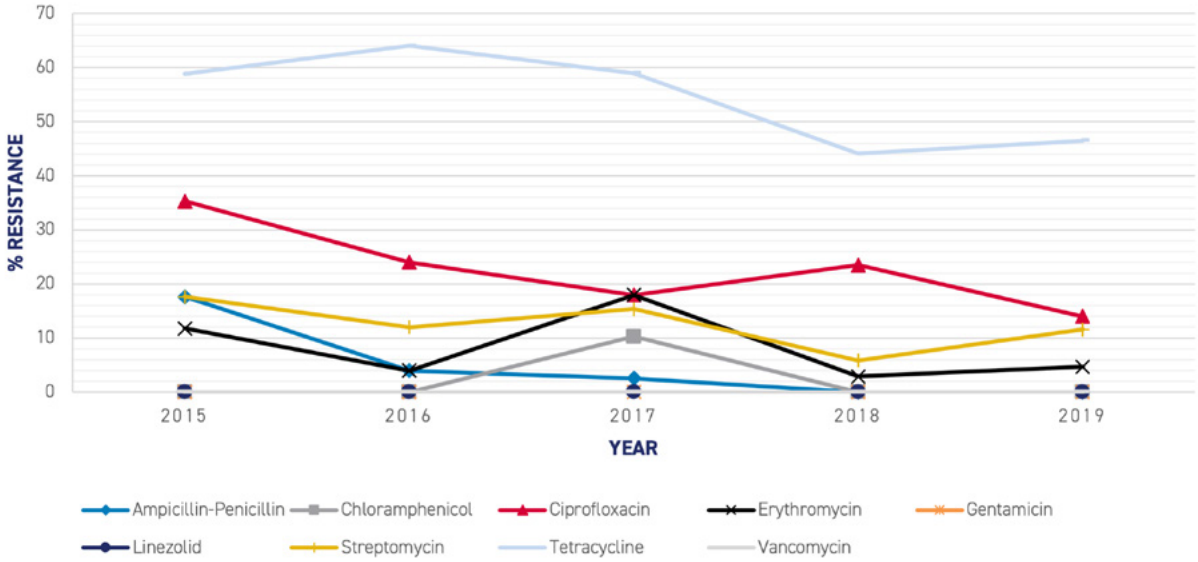
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Figure A6.19: Percentage resistance in *Enterococcus faecium* isolates from retail pork samples, 2015-2019



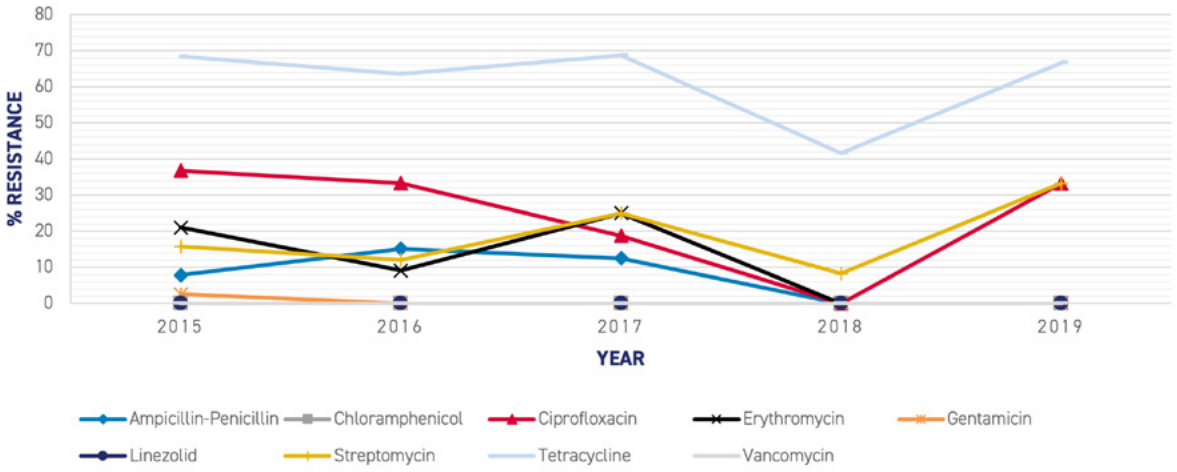
Antimicrobials shown are from the following antimicrobial classes: penicillins, aminoglycosides, tetracyclines, amphenicols, oxazolidinones, glycopeptides, quinolones, streptogramins, and macrolides.

Figure A6.20: Percentage resistance in *Enterococcus faecium* isolates from market swine cecal samples, 2015-2019



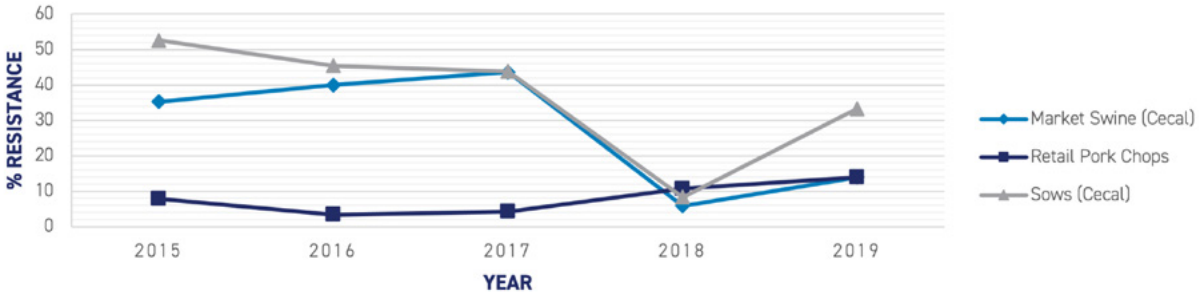
Antimicrobials shown are from the following antimicrobial classes: penicillins, aminoglycosides, tetracyclines, amphenicols, oxazolidinones, glycopeptides, quinolones, streptogramins, and macrolides.

Figure A6.21: Percentage resistance in *Enterococcus faecium* isolates, sow cecal samples, 2015-2019

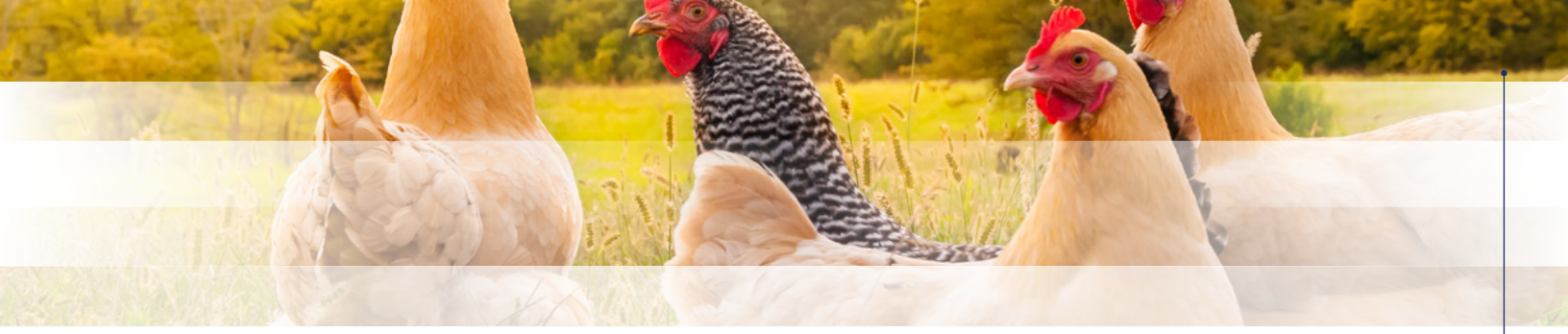


Antimicrobials shown are from the following antimicrobial classes: penicillins, aminoglycosides, tetracyclines, amphenicols, oxazolidinones, glycopeptides, quinolones, streptogramins, and macrolides.

Figure A6.22: Percentage of *Enterococcus faecium* isolates with multidrug resistance by swine sample type, 2015-2019



Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.



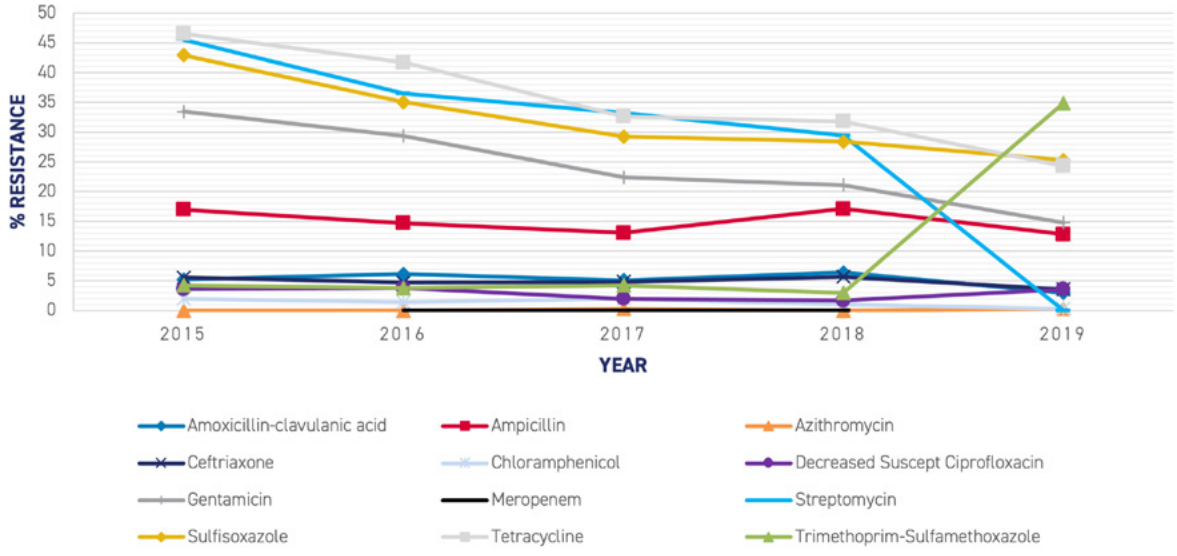
APPENDIX 7

NARMS Antimicrobial Resistance Data for Chicken Sample Types, 2015-2019

E. coli

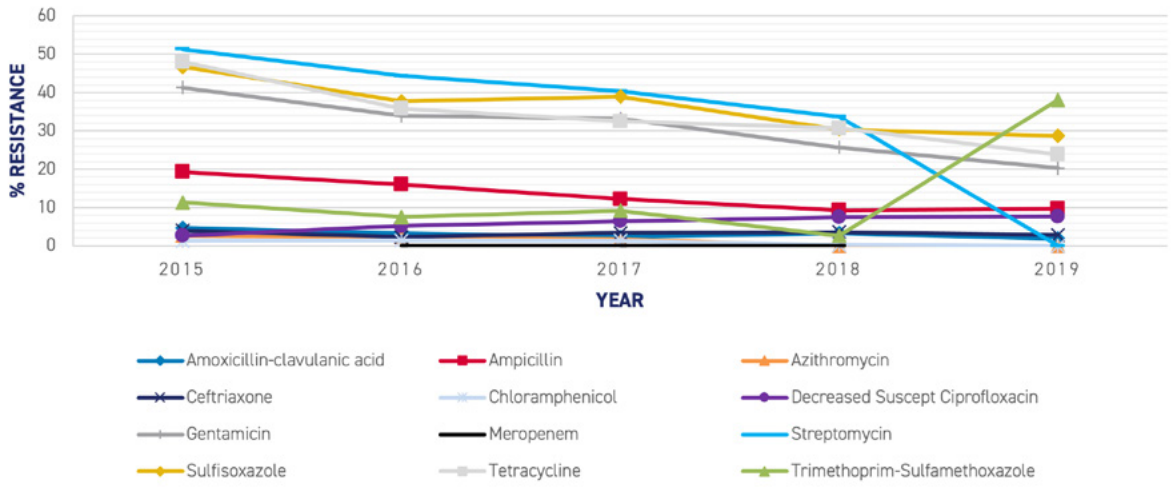
Figures A7.1 and A7.2 below show the percentage resistance for antimicrobials from ten antimicrobial drug classes tested, for *E. coli* isolates from retail chicken and chicken cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *E. coli* isolates from chicken sample types are shown in **Figure A7.3.**

Figure A7.1: Percentage resistance in *E. coli* isolates from retail chicken samples, 2015-2019



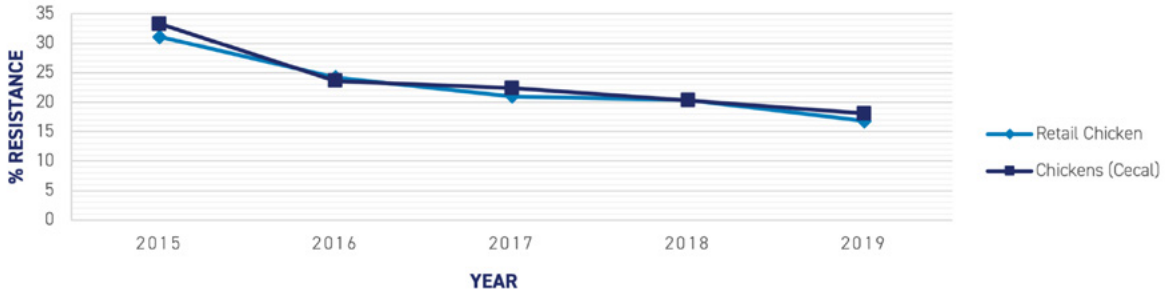
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A7.2: Percentage resistance in *E. coli* isolates from chicken cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A7.3: Percentage of *E. coli* isolates with multidrug resistance by chicken sample type, 2015-2019

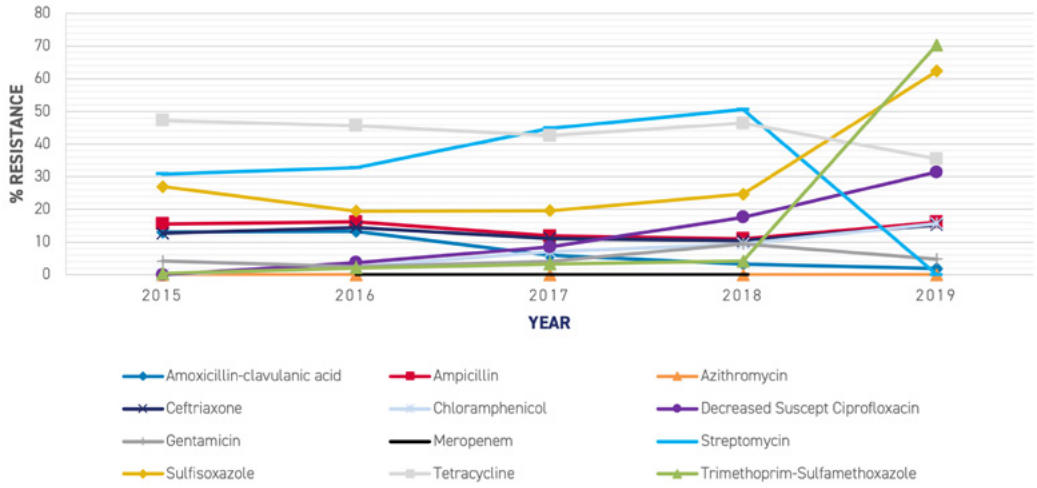


Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Salmonella

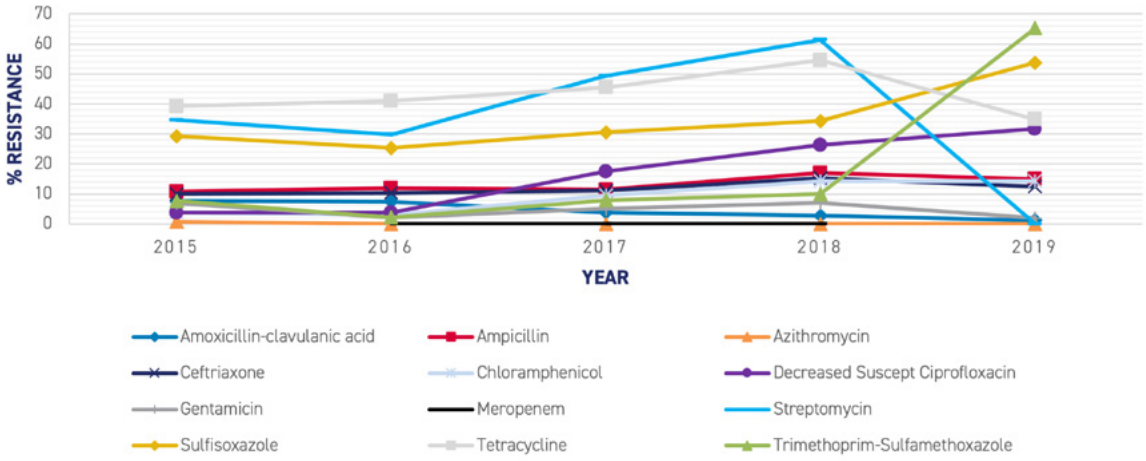
Figures A7.4 and A7.5 below show the percentage resistance for antimicrobials from ten antimicrobial drug classes tested, for nontyphoidal *Salmonella* isolates from retail chicken and chicken cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. The charts show data for all nontyphoidal *Salmonella* serotypes combined. Complete data, including information for isolates obtained from the USDA-FSIS Pathogen Reduction/Hazard Analysis and Critical Control Point (PR/HACCP) sampling program, are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Salmonella* isolates from chicken sample types are shown in **Figure A7.6.**

Figure A7.4: Percentage resistance in *Salmonella* isolates from retail chicken samples, 2015-2019



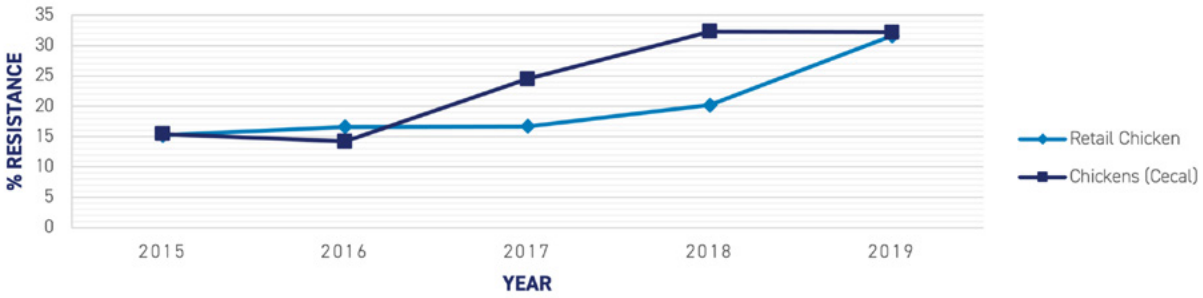
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A7.5: Percentage resistance in *Salmonella* isolates from chicken cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A7.6: Percentage of *Salmonella* isolates with multidrug resistance by chicken sample type, 2015-2019

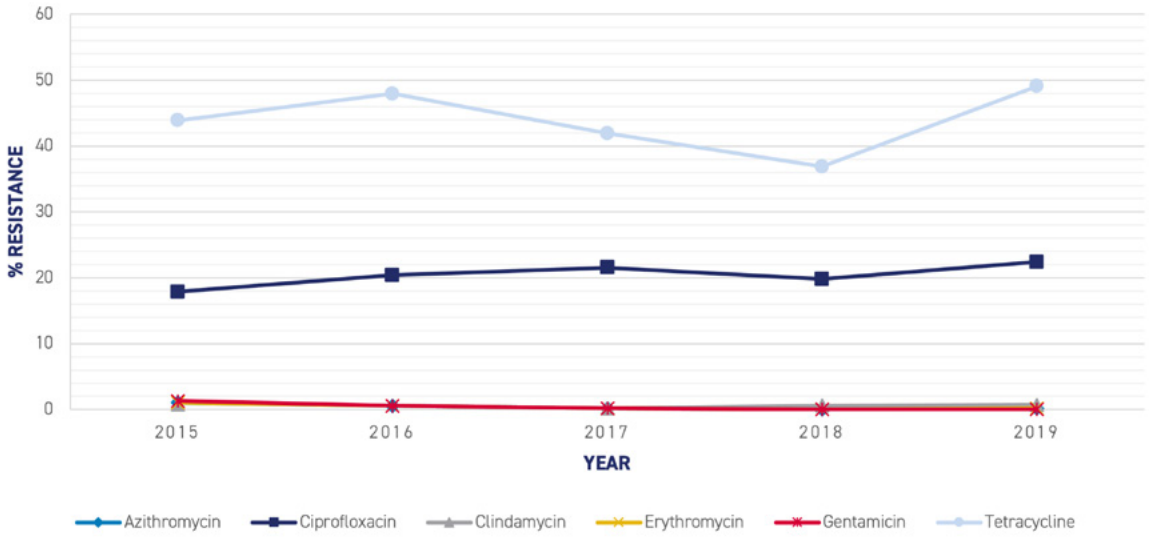


Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Campylobacter spp.

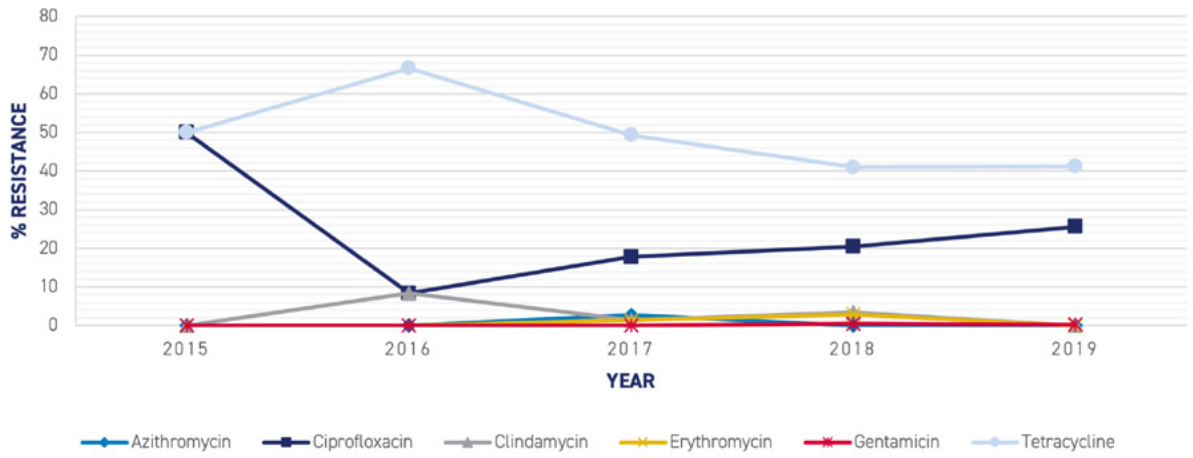
Figures A7.7 and A7.8 and **Figures A7.10 and A7.11** below show the percentage resistance for antimicrobials from five of the antimicrobial drug classes tested, for *Campylobacter jejuni (C. jejuni)* and *Campylobacter coli (C. coli)* isolates from retail chicken and chicken cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Campylobacter* spp. isolates from chicken cecal sample types are shown in **Figure 7.9 and A7.12.**

Figure A7.7: Percentage resistance in *Campylobacter jejuni* isolates from retail chicken samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: macrolides, quinolones, lincosamides, aminoglycosides, and tetracyclines.

Figure 7.8: Percentage resistance in *Campylobacter jejuni* isolates from chicken cecal samples, 2015-2019

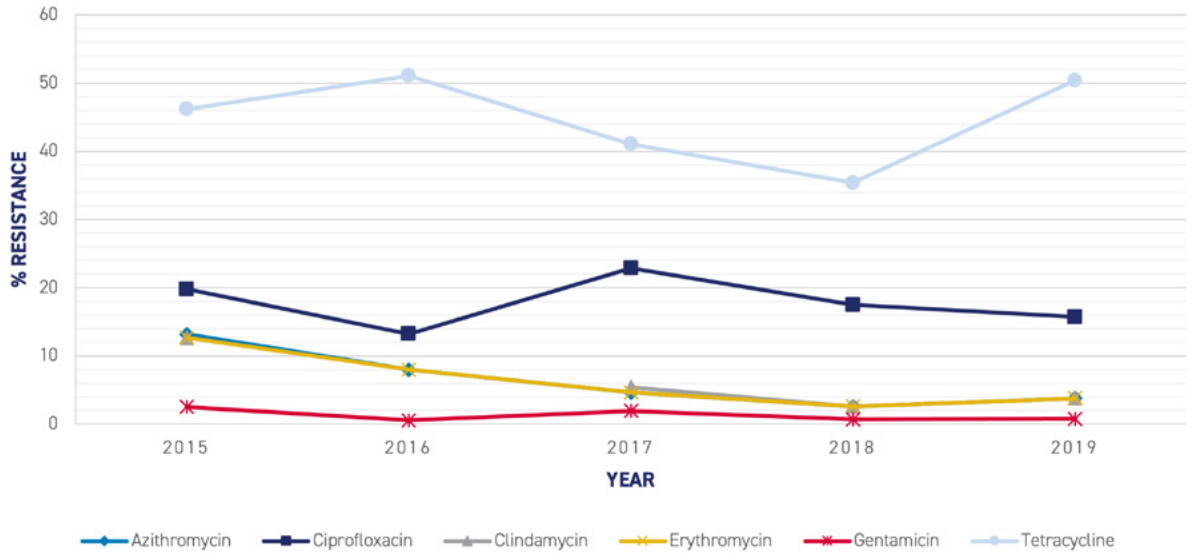


Antimicrobials shown are from the following antimicrobial classes: macrolides, quinolones, lincosamides, aminoglycosides, and tetracyclines.

Figure 7.9: Percentage of *Campylobacter jejuni* isolates with multidrug resistance by chicken sample type, 2015-2019

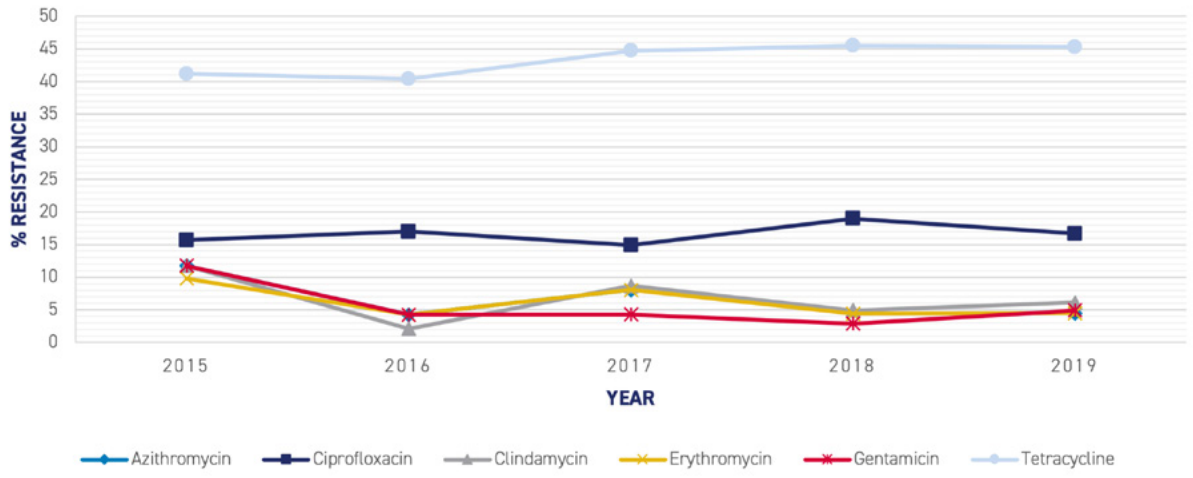
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Figure A7.10: Percentage resistance in *Campylobacter coli* isolates from retail chicken samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: macrolides, quinolones, lincosamides, aminoglycosides, and tetracyclines.

Figure A7.11: Percentage resistance in *Campylobacter coli* isolates from chicken cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: macrolides, quinolones, lincosamides, aminoglycosides, and tetracyclines.

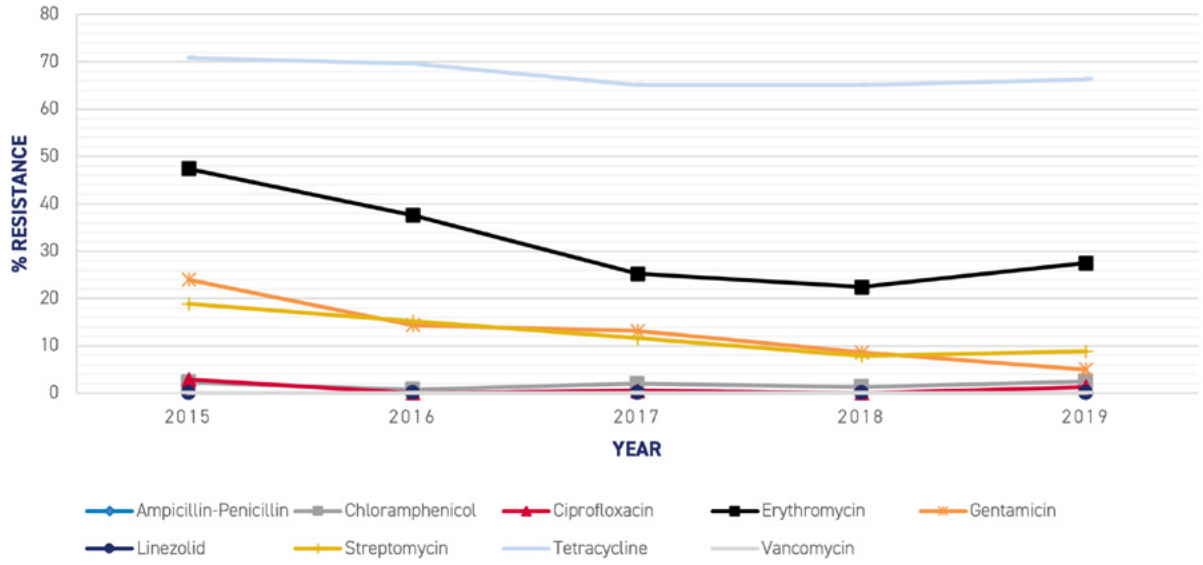
Figure A7.12: Percentage of *Campylobacter coli* isolates with multidrug resistance by chicken sample type, 2015-2019

Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Enterococcus spp.

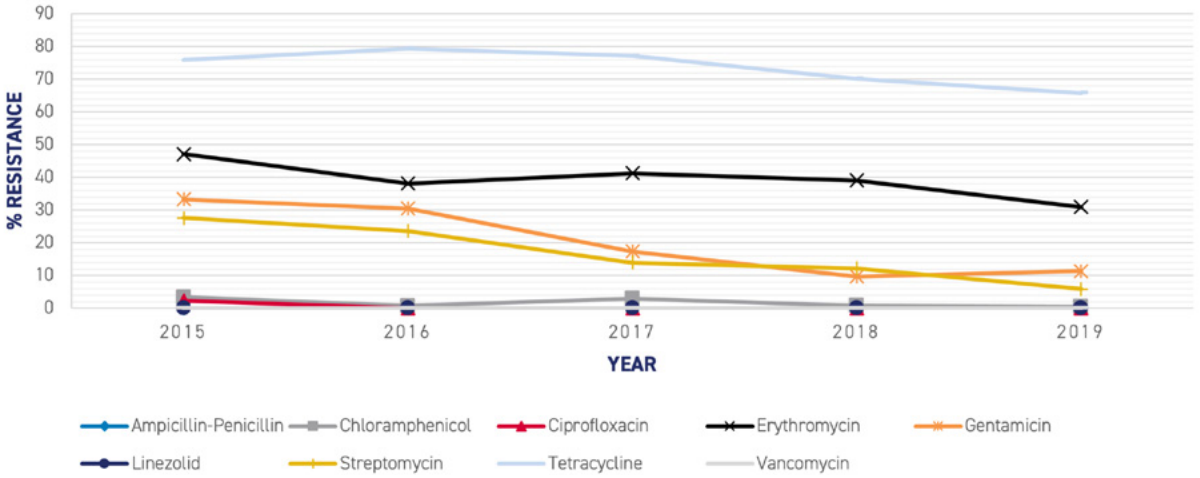
Figures A7.13 and A7.14 and **Figures A7.16 and A7.17** below show the percentage resistance for antimicrobials from eight or nine of the antimicrobial drug classes tested, for *Enterococcus faecalis (E. faecalis)* and *Enterococcus faecium (E. faecium)* isolates from retail chicken and chicken cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Enterococcus* spp. isolates from chicken sample types are shown in **Figure A7.15 and A7.18.**

Figure A7.13: Percentage resistance in *Enterococcus faecalis* isolates from retail chicken samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: penicillins, oxazolidinones, amphenicols, aminoglycosides, quinolones, tetracyclines, macrolides, and glycopeptides.

Figure A7.14: Percentage resistance in *Enterococcus faecalis* isolates from chicken cecal samples, 2015-2019

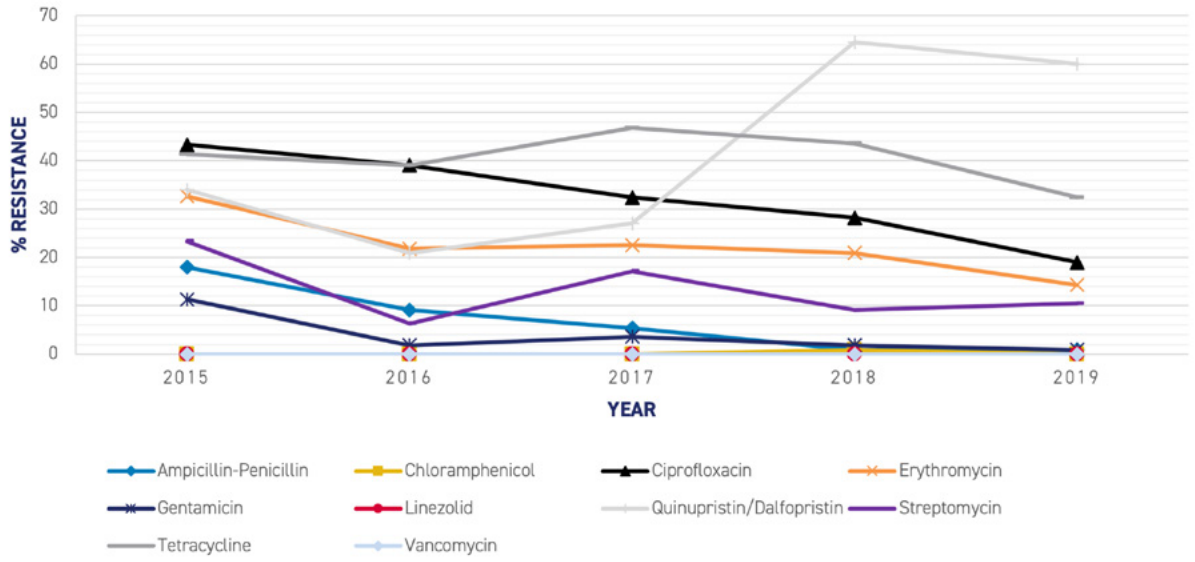


Antimicrobials shown are from the following antimicrobial classes: penicillins, oxazolidinones, amphenicols, aminoglycosides, quinolones, tetracyclines, macrolides, and glycopeptides.

Figure A7.15: Percentage of *Enterococcus faecalis* isolates with multidrug resistance by chicken sample type, 2015-2019

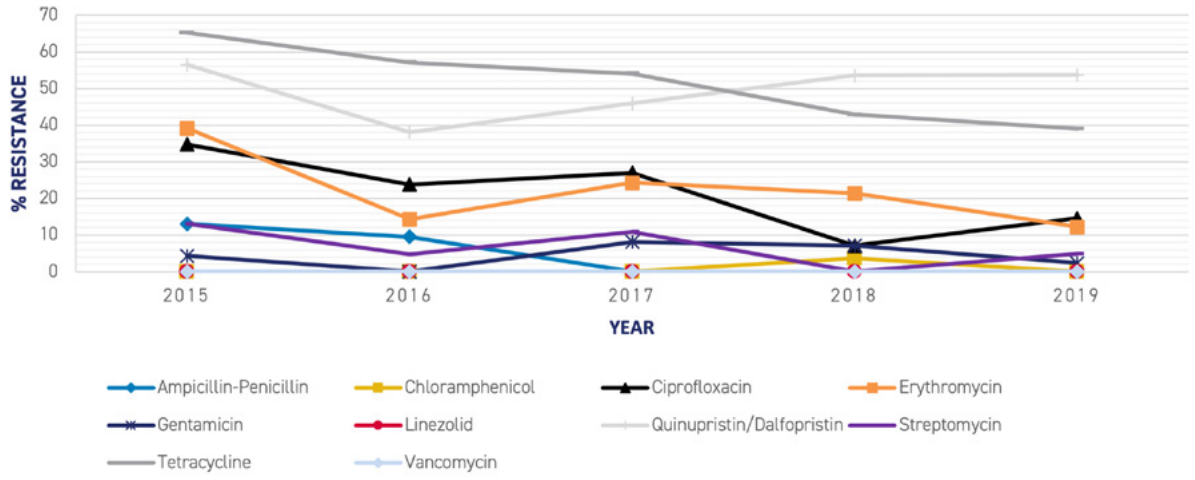
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Figure A7.16: Percentage resistance in *Enterococcus faecium* isolates from retail chicken samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: penicillins, aminoglycosides, tetracyclines, amphenicols, oxazolidinones, glycopeptides, quinolones, streptogramins, and macrolides.

Figure A7.17: Percentage resistance in *Enterococcus faecium* isolates from chicken cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: penicillins, aminoglycosides, tetracyclines, amphenicols, oxazolidinones, glycopeptides, quinolones, streptogramins, and macrolides.

Figure A7.18: Percentage of *Enterococcus faecium* isolates with multidrug resistance by chicken sample type, 2015-2019

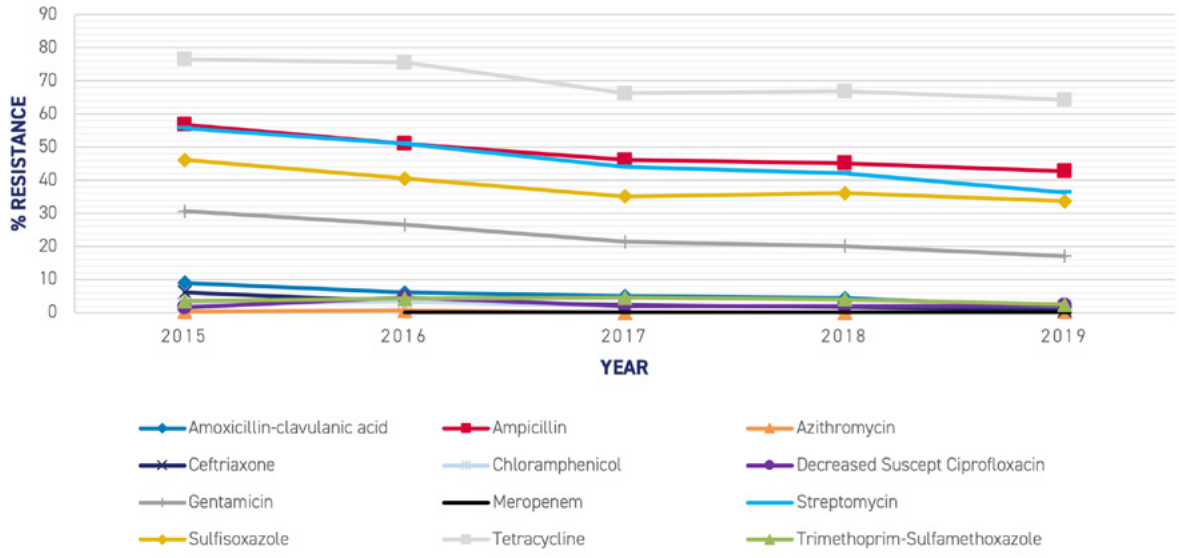
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

APPENDIX 8
NARMS Antimicrobial Resistance Data for Turkey Sample Types, 2015-2019

E. coli

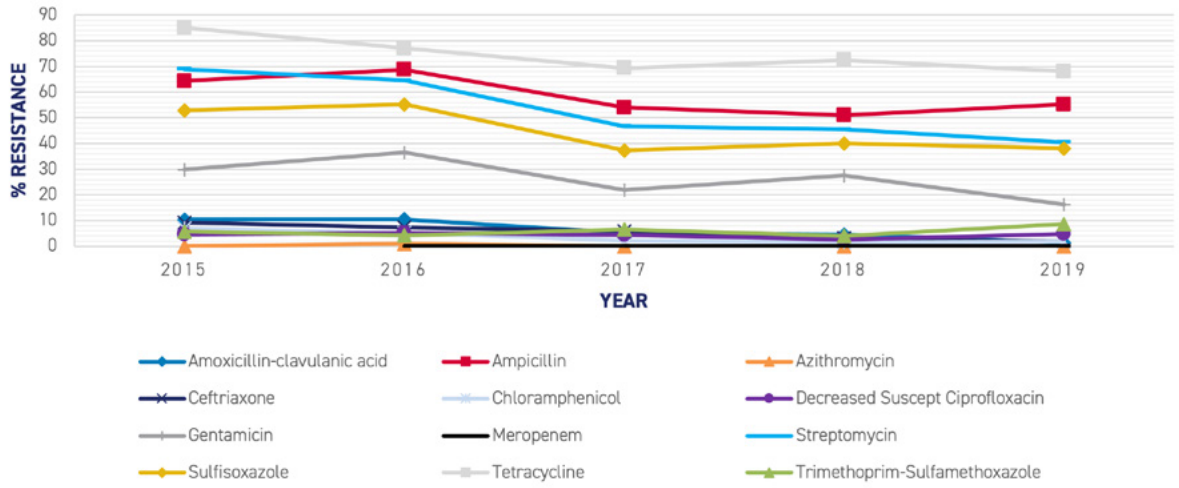
Figures A8.1 and A8.2 below show the percentage resistance for antimicrobials from ten antimicrobial drug classes tested, for *E. coli* isolates from retail ground turkey and turkey cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *E. coli* isolates from turkey sample types are shown in **Figure A8.3.**

Figure A8.1: Percentage resistance in *E. coli* isolates from retail ground turkey samples, 2015-2019



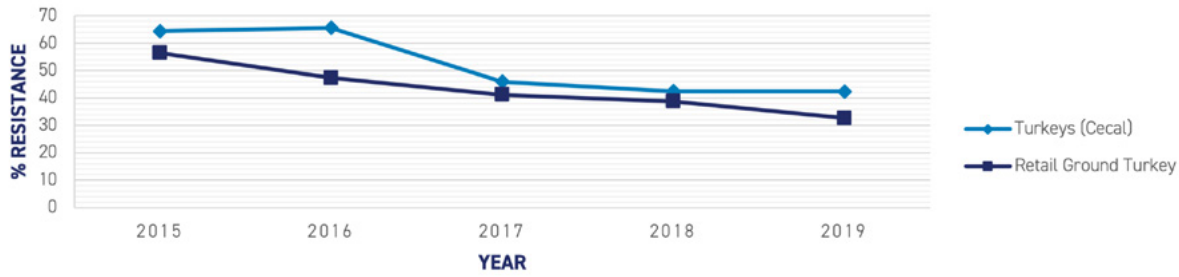
Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A8.2: Percentage resistance in *E. coli* isolates from turkey cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A8.3: Percentage of *E. coli* isolates with multidrug resistance by turkey sample type, 2015-2019

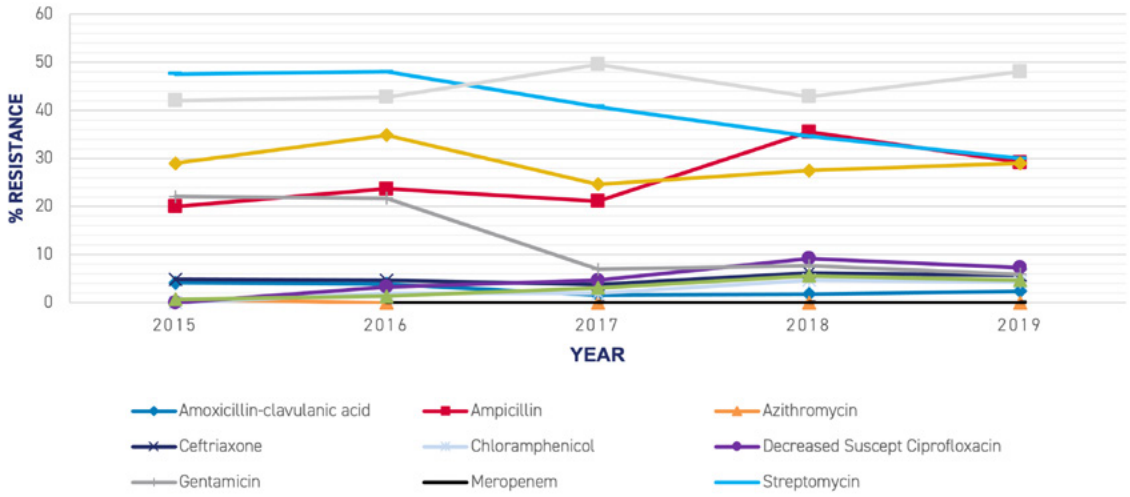


Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Salmonella

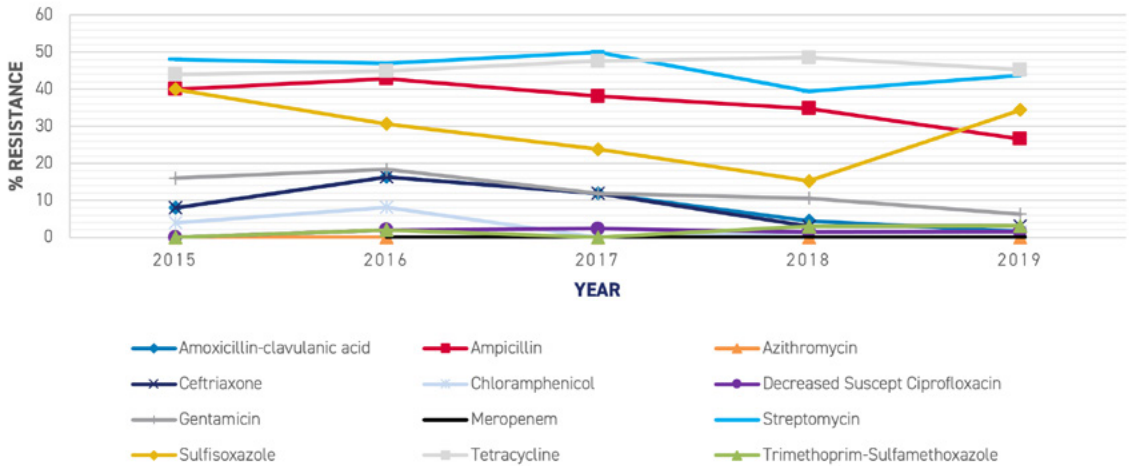
Figures A8.4 and A8.5 below show the percentage resistance for antimicrobials from ten antimicrobial drug classes tested, for nontyphoidal *Salmonella* isolates from retail ground turkey and turkey cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. The charts show data for all nontyphoidal *Salmonella* serotypes combined. Complete data, including information for isolates obtained from the USDA-FSIS Pathogen Reduction/Hazard Analysis and Critical Control Point (PR/HACCP) sampling program, are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Salmonella* isolates from turkey sample types are shown in **Figure A8.6.**

Figure A8.4: Percentage resistance in *Salmonella* isolates from retail ground turkey samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

Figure A8.5: Percentage resistance in *Salmonella* isolates from turkey cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: β-lactam/β-lactamase inhibitor combinations, cephalosporins, aminoglycosides, tetracyclines, penicillins, amphenicols, carbapenems, folate pathway inhibitors, macrolides, and quinolones.

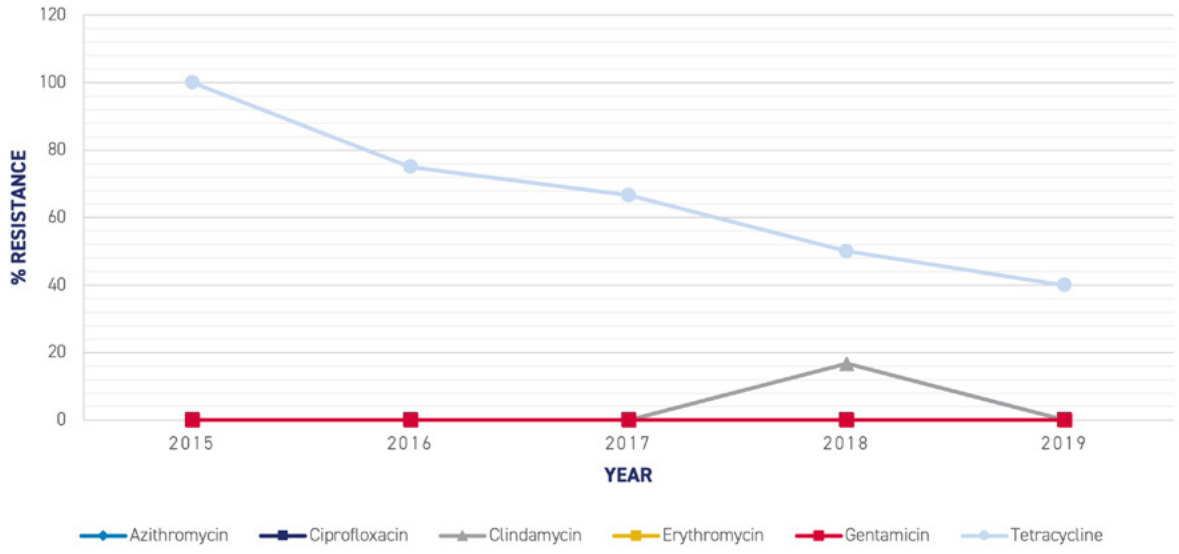
Figure A8.6: Percentage of *Salmonella* isolates with multidrug resistance by turkey sample type, 2015-2019

Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Campylobacter spp.

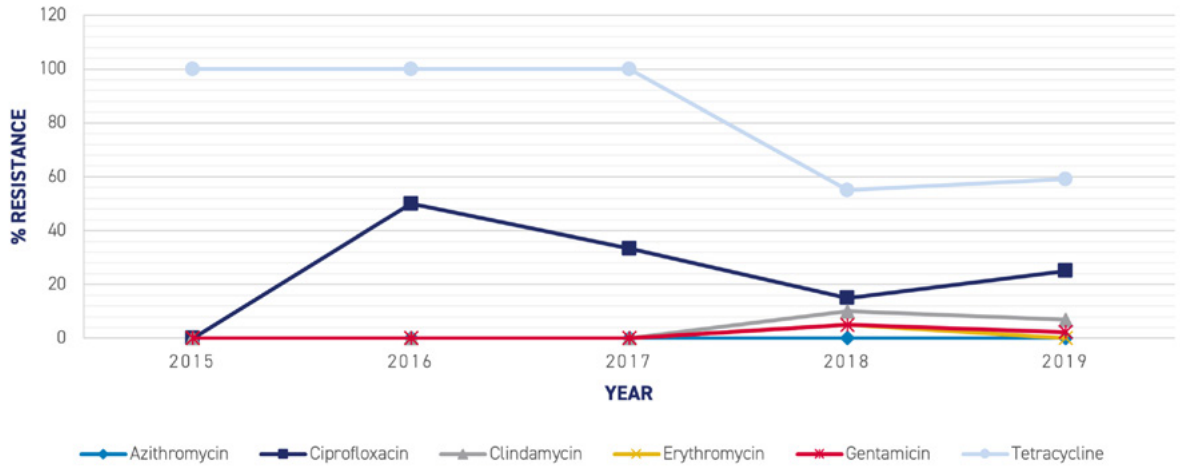
Figures A8.7 and A8.8 and **Figures A8.10 and A8.11** below show the percentage resistance for antimicrobials from five of the antimicrobial drug classes tested, for *Campylobacter jejuni (C. jejuni)* and *Campylobacter coli (C. coli)* isolates from retail ground turkey and turkey cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *C. jejuni* and *C. coli* isolates from turkey cecal samples are shown in **Figure A8.9 and A8.12.** For *C. jejuni*, only one of 44 isolates showed MDR in 2019, and retail ground turkey is not tested for MDR for either *C. jejuni* or *C. coli*.

Figure A8.7: Percentage resistance in *Campylobacter jejuni* isolates from retail ground turkey samples, 2015-2019



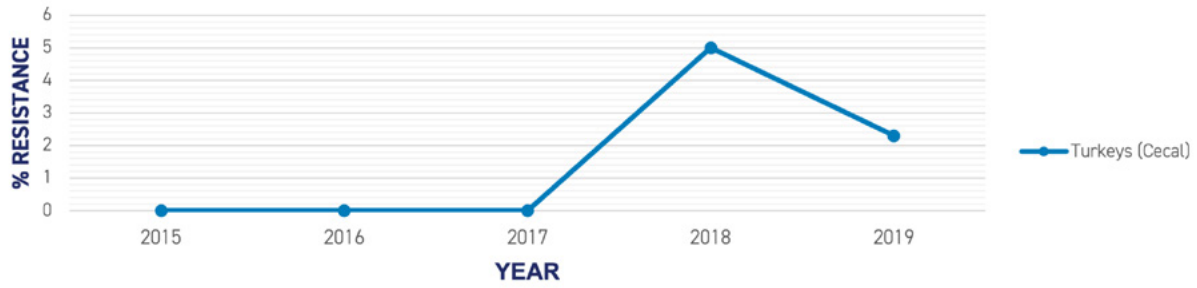
Antimicrobials shown are from the following antimicrobial classes: macrolides, quinolones, lincosamides, aminoglycosides, and tetracyclines.

Figure A8.8: Percentage resistance in *Campylobacter jejuni* isolates from turkey cecal samples, 2015-2019



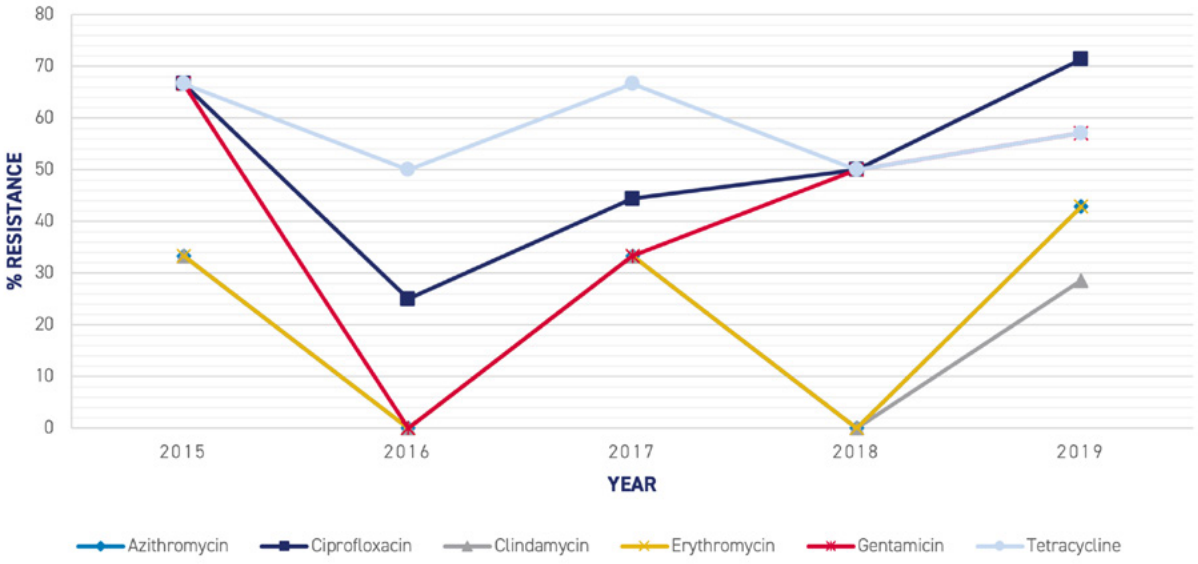
Antimicrobials shown are from the following antimicrobial classes: macrolides, quinolones, lincosamides, aminoglycosides, and tetracyclines.

Figure A8.9: Percentage of *Campylobacter jejuni* isolates with multidrug resistance for turkey cecal samples, 2015-2019



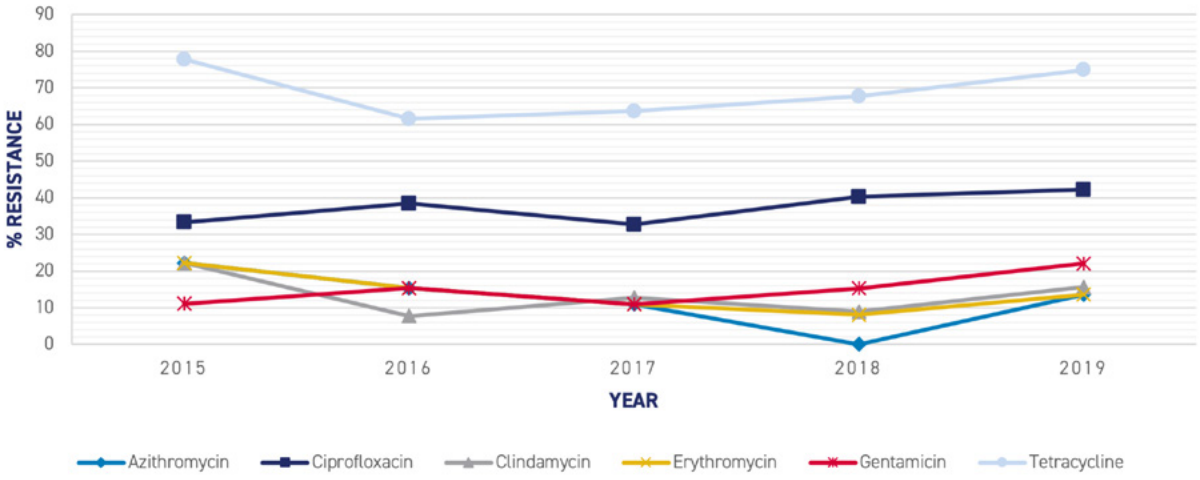
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Figure A8.10: Percentage resistance in *Campylobacter coli* isolates from retail ground turkey samples, 2015-2019



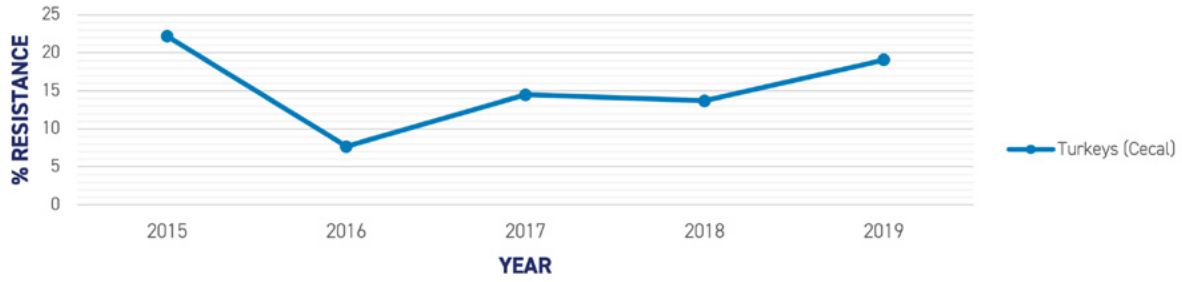
Antimicrobials shown are from the following antimicrobial classes: macrolides, quinolones, lincosamides, aminoglycosides, and tetracyclines.

Figure A8.11: Percentage resistance in *Campylobacter coli* isolates from turkey cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: macrolides, quinolones, lincosamides, aminoglycosides, and tetracyclines.

Figure A8.12: Percentage of *Campylobacter coli* isolates with multidrug resistance for turkey cecal samples, 2015-2019

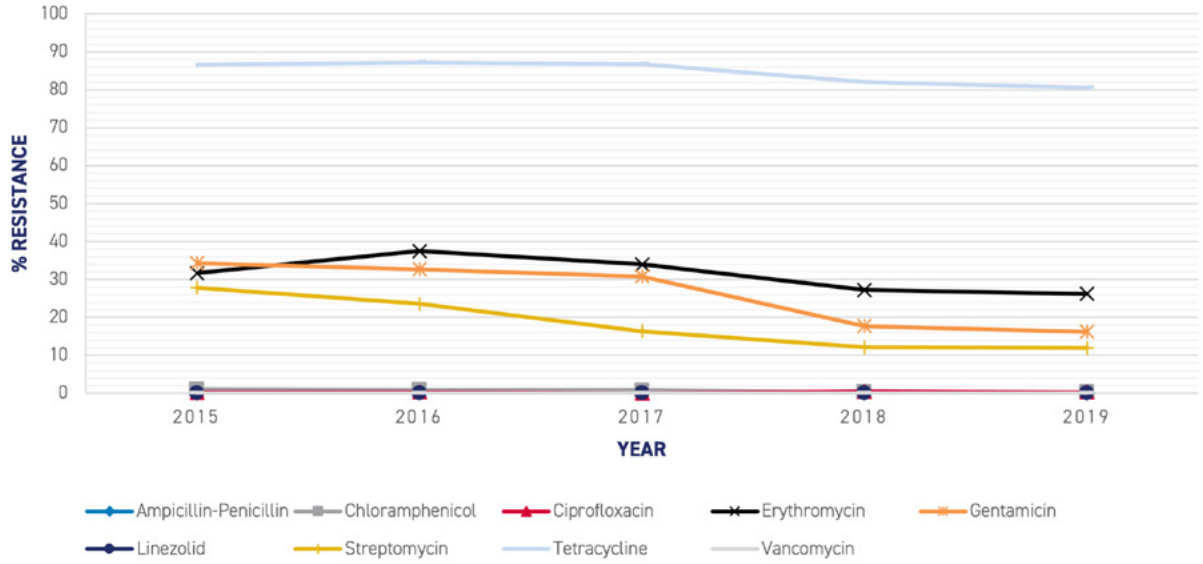


Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Enterococcus spp.

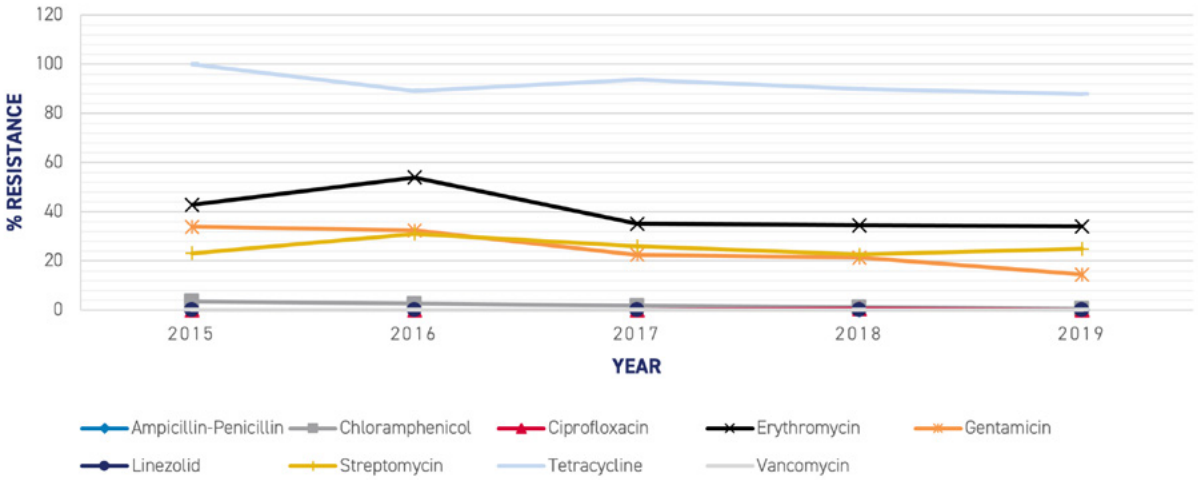
Figures A8.13 and A8.14 and **Figures A8.16 and A8.17** below show the percentage resistance for antimicrobials from eight or nine of the antimicrobial drug classes tested, for *Enterococcus faecalis (E. faecalis)* and *Enterococcus faecium (E. faecium)* isolates from retail ground turkey and turkey cecal samples, respectively. Data for 2015 through 2019 are included to show trends for a five-year period. Complete data are available on the NARMS website. Data for additional years are also available. Multidrug resistance (MDR; defined as resistance to three or more antimicrobial classes) in *Enterococcus* spp. isolates from turkey sample types are shown in **Figure A5.15 and A5.18.**

Figure A8.13: Percentage resistance in *Enterococcus faecalis* isolates from retail ground turkey samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: penicillins, oxazolidinones, amphenicols, aminoglycosides, quinolones, tetracyclines, macrolides, and glycopeptides.

Figure A8.14: Percentage resistance in *Enterococcus faecalis* isolates from turkey cecal samples, 2015-2019

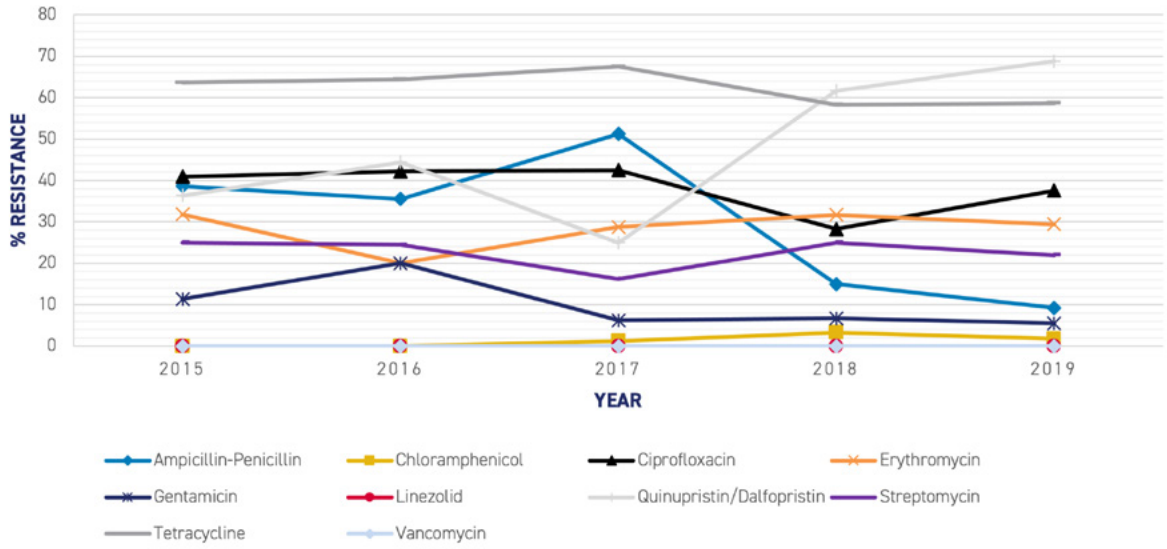


Antimicrobials shown are from the following antimicrobial classes: penicillins, oxazolidinones, amphenicols, aminoglycosides, quinolones, tetracyclines, macrolides, and glycopeptides.

Figure A8.15: Percentage of *Enterococcus faecalis* isolates with multidrug resistance by turkey sample type, 2015-2019

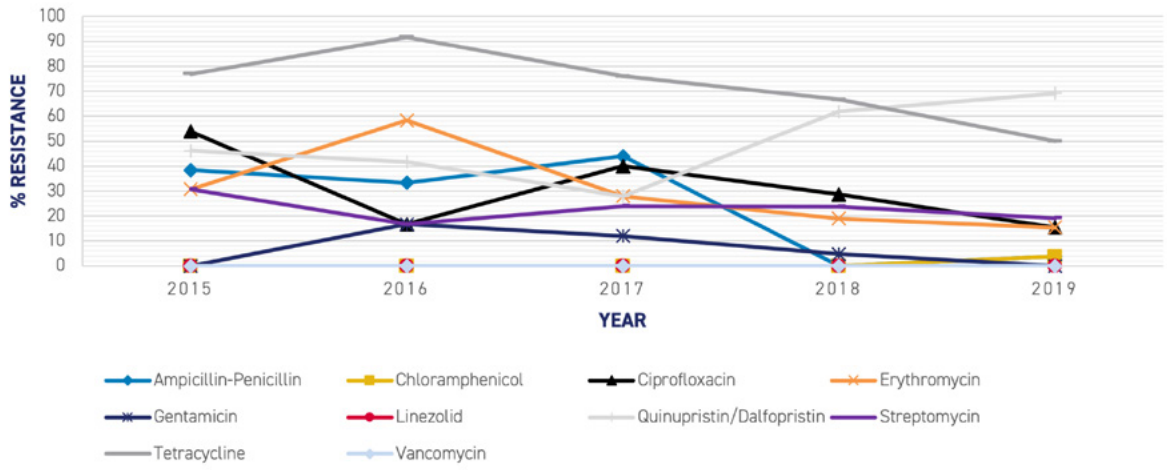
Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

Figure A8.16: Percentage resistance in *Enterococcus faecium* isolates from retail ground turkey samples, 2015-2019



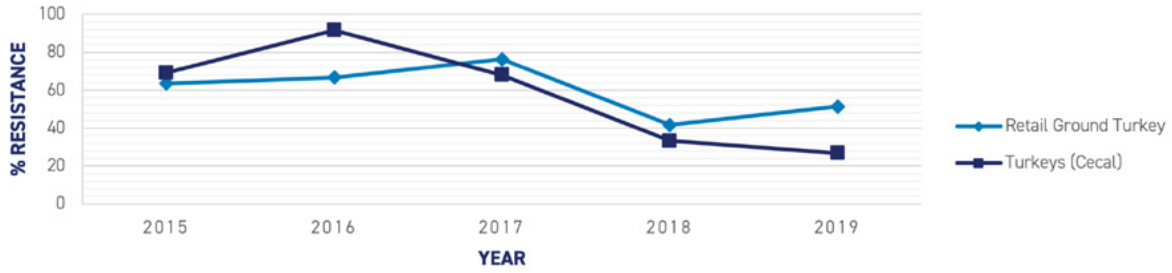
Antimicrobials shown are from the following antimicrobial classes: penicillins, aminoglycosides, tetracyclines, amphenicols, oxazolidinones, glycopeptides, quinolones, streptogramins, and macrolides.

Figure A8.17: Percentage resistance in *Enterococcus faecium* isolates from turkey cecal samples, 2015-2019



Antimicrobials shown are from the following antimicrobial classes: penicillins, aminoglycosides, tetracyclines, amphenicols, oxazolidinones, glycopeptides, quinolones, streptogramins, and macrolides.

Figure A8.18: Percentage of *Enterococcus faecium* isolates with multidrug resistance by turkey sample type, 2015-2019



Multidrug resistance (MDR) is defined as resistance to three or more antimicrobial classes.

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