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Epidemiology of Veterinary Antimicrobial Use in Tennessee and Strategies for Antimicrobial Stewardship

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To the Graduate Council:

I am submitting herewith a dissertation written by John Eddie Ekakoro entitled "Epidemiology of Veterinary Antimicrobial Use in Tennessee and Strategies for Antimicrobial Stewardship." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Comparative and Experimental Medicine.

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Epidemiology of Veterinary Antimicrobial Use in Tennessee and Strategies for Antimicrobial Stewardship

A Dissertation Presented for the

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Degree

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John Eddie Ekakoro

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DEDICATION

To my grandmother Mrs. Mary Amase Ekakoro

I love you. I dedicate this work to you.

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ABSTRACT

Antimicrobial drugs are used for maintaining or improving animal health. Non-judicious antimicrobial use (AMU) is a modifiable factor driving antimicrobial resistance (AMR). Using qualitative and quantitative approaches, this doctoral dissertation examined the epidemiology of veterinary AMU among clinicians at The University of Tennessee Veterinary Medical Center (UTVMC), and cattle producers in Tennessee (TN), and identified strategies for antimicrobial stewardship (AMS). First, an online survey was sent to UTVMC clinicians to identify factors influencing their AMU practices, analyze their concerns regarding AMU and AMR. Compared to clinicians who obtained their veterinary degree from 1970–1999, those who graduated from 2000–2009 and 2010–2016 were 3.96 ($P = 0.034$) and 5.39 ($P = 0.01$) times less concerned about AMR, respectively. Second, a qualitative study was undertaken to identify and document the factors driving AMU, alternatives, knowledge, and perceptions towards AMU among TN beef cattle producers. The findings suggested that clinical signs, culture & susceptibility testing drive AMU and more awareness of drivers for AMR, and continuing education for producers on prudent AMU is needed. Third, a mixed methods study that was conducted with TN dairy producers showed that use of culture and sensitivity test results for antimicrobial selection was a widespread and common practice, and blanket dry cow therapy was still commonly practiced. Fourth, a survey of TN beef cattle producers was conducted to identify the factors driving their AMU, as well as their alternatives, knowledge, and perceptions towards AMU. The findings showed that controlling for type of cattle operation, age was significantly associated with the producer’s degree of concern about AMR ($P = 0.022$). Additionally, survey findings suggested a need to promote the use of written antimicrobial treatment protocols among TN beef producers, and continued training for producers on infection prevention/control and prudent AMU. Fifth, a

mixed methods study was conducted to identify the perceptions of TN cattle producers regarding the Veterinary Feed Directive. The findings suggested a likely compensatory increase in the use of injectable antimicrobials for therapeutic and prophylactic purposes that should be further investigated. Overall, the entire project identified key strategies for improving AMU in TN.

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LIST OF ABBREVIATIONS AND ACRONYMS

WHO: World Health Organization

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

CDC: Centers for Disease Control and Prevention

FDA: Food and Drug Administration

VRE: Vancomycin-Resistant Enterococci

MRSA: Methicillin-resistant Staphylococcus aureus

ESBL: Extended Spectrum Beta Lactamases

MDR: Multidrug Resistant

AMR: Antimicrobial Resistance

AMS: Antimicrobial Stewardship

AMU: Antimicrobial Use

TN: Tennessee

UTVMC: University of Tennessee Veterinary Medical Center

U.S.: United States

INTRODUCTION

The emergence and spread of antimicrobial resistance (AMR) is a global threat to human and animal health, and is accelerated by non-judicious antimicrobial use (AMU) in animals and humans [1]. Ensuring judicious AMU both in animals and humans is a key strategy for containing AMR [2]. To preserve the efficacy of medically important antimicrobials, the World Health Organization (WHO) recommended complete restriction of AMU for growth promotion and disease prevention in food-producing animals [3]. Interventions, designed to ensure judicious AMU have been implemented and are supported in many countries [4, 5]. To ensure judicious AMU, there is a global call for veterinary practices to develop and implement antimicrobial stewardship (AMS) programs. Beginning January 1, 2017, the United States Food and Drug Administration implemented the Veterinary Feed Directive (VFD) to ensure judicious AMU in food animals [6].

In the United States, AMU for disease management in food-producing animals has minimal veterinary oversight due to lack of food animal veterinarians in some areas and use in food-producing animals for growth promotion or improved feed efficiency is perceived as non-judicious [7]. Data on AMU is generally scarce in many countries. Just like in many parts of the world, current knowledge of veterinary antimicrobial usage in Tennessee and the United States in general is limited due to little research in this area. The overall goal of this dissertation was to fill this knowledge gap by generating veterinary AMU data from clinicians at UTVMC and cattle producers in TN as the starting point. The studies reported in this dissertation contribute new knowledge on AMU by providing insights into: (1) the AMU practices of clinicians at UTVMC, (2) the practices, drivers, alternatives, knowledge, perceptions and concerns of Tennessee beef cattle producers towards AMU, (3) the practices, drivers, alternatives, knowledge, perceptions and concerns of Tennessee dairy cattle producers towards AMU, and (4) perceptions of Tennessee cattle producers regarding the VFD.

Overview of this dissertation

This dissertation is organized in a manuscript format and is composed of a comprehensive literature review and five individual studies that collectively address a common challenge. Overall, there are six chapters presented in this dissertation. Chapter 1 is a review of literature while chapters 2, 3, 4, 5, and 6 are complete individual studies, each with distinct sections (abstract, introduction/background, materials and methods, results, discussion and conclusions).

The overall aims of the studies reported in this dissertation were to:

1. Provide current work that has been performed in the area of AMU (Chapter 1).
2. Provide insight into the AMU practices of clinicians at UTVMC (Chapter 2).
3. Identify and document the factors driving AMU, alternatives, knowledge, and perceptions towards AMU among Tennessee cattle producers (Chapters 3, 4 and 5).
4. Identify the perceptions of TN cattle producers regarding the Veterinary Feed Directive (Chapter 6).

Lastly, presented at the end of the dissertation are general conclusions, recommendations, future research directions, appendices, and my VITA.

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CHAPTER 1

Literature review

Key definitions

This dissertation adopts the WHO definition of the terms antibacterial, antibiotic, antimicrobial, antimicrobial class, and antimicrobial resistance [1] as provided below.

Antibacterial drug: A drug that inhibits bacterial growth or kills bacteria.

Antibiotic: An antibiotic is an agent or substance produced from microorganisms that can kill or inhibit the growth of another living microorganism.

Antimicrobial drug: An antimicrobial drug as an agent or substance, derived from any source (microorganisms, plants, animals, synthetic or semi-synthetic) that acts against any type of microorganism: bacteria (antibacterial), mycobacteria (antimycobacterial), fungi (antifungal), parasite antiparasitic, and viruses (antivirals). All antibiotics are antimicrobials, but not all antimicrobials are antibiotics. Antimicrobial agents or substances that are synthetic or semi-synthetic and antimicrobials of plant or animal origin are not considered antibiotics.

Antimicrobial class: A group of antimicrobial agents with related molecular structures, often with similar mode of action because of interaction with a similar target and thus subject to similar mechanisms of resistance.

Antimicrobial resistance: Antimicrobial resistance (AMR) is a clinical phenomenon in which the clinical efficacy of an antimicrobial is lost because the targeted pathogens have metabolic and other defense mechanisms against the antimicrobial agent. Antimicrobial resistance occurs when microorganisms (e.g. bacteria, fungi, viruses, parasites) change (morphologically, physiologically, and metabolically) when exposed to antimicrobial drugs resulting in the antimicrobial drug becoming clinically ineffective, and persistence of the infections. Compared to susceptible microorganisms of the same species, antimicrobial resistant microbes (un-susceptible microbes) can multiply and persist in the presence of increased levels of a given antimicrobial drug.

In this dissertation, the words “veterinary antimicrobial(s)” refer to antimicrobial(s) of veterinary importance. In line with the WHO definition of an antimicrobial [1], this dissertation is limited to the use of antibacterial antimicrobials by veterinary professionals and cattle producers.

Medically important antimicrobial classes

Medically important antimicrobials are antimicrobial classes used in humans and in non-human medical settings such as in food-producing animals and categorized by WHO as critically important, highly important or important for human medicine [2]. Because of the need to prevent potential adverse public health consequences of use of medically important antimicrobials in food-producing animals, the World health Assembly adopted the global action plan on AMR. This plan seeks to contain AMR using multifaceted measures such as reduction in unnecessary AMU both in humans and animals [2]. The WHO guidelines [2, 3] recommend the following in food-producing animals (1) overall reduction in use of all medically important antimicrobials, (2) complete restriction of use of all medically important antimicrobials for growth promotion, (3) complete restriction of use of all medically important antimicrobials for prevention of undiagnosed infectious diseases, (4) antimicrobials classified as critically important for human medicine should be used for control of the spread of a clinically diagnosed infectious disease identified within a group of food-producing animals (metaphylaxis), (5) antimicrobials classified as highest priority critically important for human medicine should not be used for treatment of food-producing animals with a clinically diagnosed infectious disease. However, to maintain animal health and to promote animal welfare, veterinary professionals can make exceptions to some of the WHO recommendations based on C/S test results showing that the selected antimicrobial must inevitably be used due to lack of any other alternative [2, 3].

Critically important antimicrobials for human medicine

In June 2017, an updated WHO "ranking of medically important antimicrobials for risk management of AMR due to non-human AMU" was published. In that updated classification, the WHO ranked antimicrobials as critically important, highly important and important to human medicine [1]. Based on this ranking, critically important antimicrobial classes include: Aminoglycosides e.g. gentamycin, Ansamycins e.g. rifampicin, carbapenems and other penems e.g. meropenem, cephalosporins (3rd, 4th, and 5th generation) e.g. ceftriaxone, cefepime, and ceftaroline, glycopeptides e.g. vancomycin, glycylcyclines e.g. tigecycline, lipopeptides e.g. daptomycin, macrolides and ketolides e.g. erythromycin, and telithromycin, monobactams e.g. aztreonam, oxazolidinones e.g. linezolid, penicillins (natural, aminopenicillins, and antipseudomonal) e.g. ampicillin, phosphonic acid derivatives e.g. Fosfomycin, polymyxins e.g. colistin, quinolones e.g. ciprofloxacin, drugs solely used for treatment of tuberculosis or other mycobacterial diseases e.g. isoniazid. Highly important antimicrobial classes include amidinopenicillins e.g. mecillinam, amphenicols e.g. chloramphenicol, cephalosporins (1st and 2nd generation) and cephamycins e.g. cefazolin, lincosamides e.g. clindamycin, penicillins (anti-staphylococcal) e.g. oxacillin, pseudomonic acids e.g. mupirocin, Riminofenazines e.g. clofazimine, steroid antibacterials e.g. fusidic acid, streptogramins e.g. quinupristin/dalfopristin, sulfonamides, dihydrofolate reductase inhibitors and combinations e.g. sulfamethoxazole, trimethoprim, sulfones e.g. dapsone, tetracyclines e.g. chlortetracycline. Important antimicrobial classes include: aminocyclitols e.g. spectinomycin, cyclic polypeptides e.g. bacitracin, nitrofurantoins e.g. nitrofurantoin, nitroimidazoles e.g. metronidazole, pleuromutilins e.g.

retapamulin. Among the critically important antimicrobials, quinolones, third, fourth and fifth generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins are categorized as highest priority critically important antimicrobials while other critically important antimicrobials were subclassified as high priority critically important antimicrobials [1].

The problem of antimicrobial resistance

Antimicrobials are a non-renewable resource that are endangered by AMR development [4] and AMR is now considered a one health issue whose containment requires a multidisciplinary effort from all actors in the one health arena [5-7]. Compared to antimicrobial susceptible infections, AMR infections have been found to have worse clinical outcomes (more septicemia, longer hospitalizations) [8]. Antimicrobial use as well as abuse of antimicrobials in human medicine, veterinary medicine, and environmental sectors, spread of resistant bacteria and resistance determinants within and between humans, animals and the environment, drive AMR [9]. In other words, in addition to prudent and non-prudent AMU in human and veterinary medicine, animal agriculture, waste and environmental contamination from pharmaceutical industries, application of untreated manure in crop production are other sources of AMR [6, 10-12]. Also use of poor quality antimicrobials (inadequate amounts of active agent(s), ineffective release, occurrence of impurities and degradation of active compounds) in food animals especially in low-and middle income countries is believed to be contributing to the problem of AMR by exposing microbes to low levels (subtherapeutic levels) of active antimicrobials and subsequently selecting for resistance [13]. Additionally, there is evidence that use of non-antibiotic antimicrobial agents e.g. biocides (disinfectants, antiseptics and preservatives), and heavy metals (zinc and copper) as growth promoters and therapeutic agents for some animals also induce/select for AMR [14-16]. Specifically, use of zinc oxide as a growth promoter in livestock has been associated with the emergence of Livestock-Associated MRSA [17, 18].

Researchers have shown through metagenomic analysis of ancient samples that AMR is ancient and occurs naturally [19]. Also, a study that evaluated the efficacy of 21 antimicrobials (both old and new) against ~ 500 spore-forming soil bacteria found MDR in all sampled bacteria with each bacterium resistant to 7-8 antimicrobials, suggested that MDR could be naturally occurring in most microbes [20, 21]. However, non-judicious use of antimicrobials is known to select for AMR. Wildlife species including migrating species such as birds have been found to harbor antimicrobial resistant microorganisms and are thought to be exposed to antimicrobial resistant organisms through inadequately treated animal and human waste products (exposure to antimicrobial resistant bacteria reservoirs such as contaminated soil, water or crops) [22, 23].

Antimicrobial resistance mechanisms include: bacterial production of enzymes that inactivate antimicrobial drugs e.g. beta-lactamases that inactivate beta lactam antimicrobials), removal of antimicrobials through efflux pumps, modification of antimicrobial binding sites (target sites) such that the antimicrobial fails to bind to its target on the bacteria, antimicrobial bypass mechanisms such as modification of bacterial cell surface to prevent entry by the antimicrobial agent [20, 24, 25]. A study conducted at a US tertiary university referral hospital found MDR in 19 out of 70 isolates obtained from dogs in the Intensive Care Unit [26]. That study also found that MDR was observed in samples taken after 48 hours of hospitalization, suggesting that length of hospitalization may be associated with infections with AMR organisms. Although public concerns about AMR is widespread, a UK study that compared public views regarding drivers of AMR to expert views regarding drivers of AMR found that the public did not fully understand the multifaceted nature of AMR causation [27]. In that study, it was found that 192/405 (47.4%) of study participants believed that overuse/misuse of antimicrobials in humans was a major driver of AMR while 66/405 (16.3%) respondents believed that misuse of antimicrobials in animal health was a major driver of AMR. In the U.S., there is no published study that has evaluated public views about key contributing factors to AMR. A study comparing current public views regarding drivers of AMR with the views of AMR/AMU experts would prove useful.

The burden of AMR in the United States

According to the Centers for Disease Control and Prevention (CDC), at least 2 million people become infected with AMR bacteria annually in the U.S. and at least 23,000 human deaths occur annually directly from AMR bacterial infections [28]. More than 400,000 AMR-related illnesses in the U.S. are attributed to drug-resistant non-typhoidal *Salmonella* and *Campylobacter* [8]. Additionally, as of 2013, the CDC estimated that *Campylobacter* AMR increased from 13% in 1997 to almost 25% in 2011 while about 5% of non-typhoidal *Salmonella* tested by CDC were resistant to five or more antimicrobials [28]. Both *Campylobacter* and non-typhoidal *Salmonella* are zoonotic. Currently in the US, the national Antimicrobial Resistance Monitoring System (NARMS) is charged with the duty of monitoring AMR among foodborne pathogens from humans, retail meats and animals [8].

Mechanisms of action of antimicrobial drugs and selection for AMR

Generally, the mechanisms of action of antimicrobials include: prevention of microbial DNA or RNA synthesis; blockade of nucleic acid synthesis by prevention of folate synthesis; destruction of bacterial cell wall/membrane; and prevention of bacterial protein synthesis by interfering with ribosome function [24]. All use of antimicrobials whether for therapeutic purpose, prophylactic use, metaphylactic use, judicious or non-judicious exerts selection pressure on microbes that can result in AMR [29, 30]. However, some researchers [31] state that although sub-optimal AMU in hospitals, in the community, and in agriculture may be drivers of AMR, there is no evidence showing the extent to which these perceived drivers contribute to the development, emergence and spread of AMR. A review of the impact of AMU in lactating and non-lactating cows in the US concluded that although AMU in adult dairy cows and other food producing-animals contributes to AMR, there was no widespread emergence of AMR among pathogens isolated from dairy cattle [32]. Another review found that there is scientific evidence that AMU in farms contributes to AMR [33].

Evidence of and methods of transfer of AMR between animals and humans

Although the direction of transfer of pathogens between animals and humans may not have been proven empirically, review studies provided scientific evidence that MDR organisms are shared between companion animals and humans. For example, researchers have reported transfer of Methicillin-resistant Staphylococcus aureus (MRSA) between companion animals and their owners and MRSA isolated from a dog was found to be related to a human epidemic MRSA cluster [34-37]. The organisms originating from companion animals that may directly or indirectly cause disease or colonize humans include: MRSA, methicillin-resistant *Staphylococcus pseudointermedius*, *Staphylococcus intermedius*, Vancomycin-Resistant Enterococci (VRE), Extended Spectrum Beta Lactamases (ESBL) or Carbapenemase-producing Enterobacteriaceae and gram-negative bacteria [34, 38-40]. Strains of MRSA that predominate humans have been found in companion animals while people working with MRSA colonized or infected horses reportedly acquired zoonotic infections while high rates of colonization with MRSA have been reported in veterinary personnel from different countries [41]. Also, evidence of transmission of MRSA from a horse to a young girl in the Netherlands is documented [42] and a review study [18] provided evidence of transmission of livestock associated MRSA to humans.

The perceived public health impacts of AMU in food animals on AMR in human pathogens have generated prolonged controversial, and on-going debate [17]. Marshall and Levy provide evidence showing that animal-to-human spread of AMR from food animals may occur directly through human contact with colonized or infected food animals especially among veterinarians, farm workers, slaughterhouse workers or indirectly through the food chain, water and manure application for crop production [30]. The horizontal gene transfer of genetic elements e.g. plasmids through conjugation (bacterial mating), increases the direct and indirect animal-to-human spread of AMR [30]. However, a systematic review [43] found no concrete evidence of the direction of transfer of AMR between animals and humans. Other investigators assert that AMR pathogens disseminate from animals to people and vice-versa through environmental pathways such as via foodstuffs, animal wastes, and water sources [44]. Additionally, a review by Nordstrom and others found that *E.coli* isolates from human urinary tract infection (UTI) cases were genetically related to *E. coli* isolates from food animals and retail meat, and that a case-control study found that occurrence of MDR UTIs in women was associated with consumption of chicken and pork [45]. This review suggested that retail meats, especially poultry, were important reservoirs for human exposure to antimicrobial resistant *E. coli* with infection of humans occurring through ingestion of the uro-pathogenic *E. coli* and its transfer from the hosts gastrointestinal tract to the urinary tract through ascending infections. A study of flies captured using revenge sticky tapes from cattle farms in Georgia showed that flies could be effective mechanical vectors of antimicrobial resistant *Salmonella* and antimicrobial resistant genes on cattle farms [46]. In that Georgia study, *Salmonella* resistant to tetracycline, b-lactams, and streptomycin were isolated.

Antimicrobial use in veterinary medicine and the scarcity of data

A lot of studies on veterinary AMU have been conducted in Europe, where AMU is reported to vary substantially between countries [47]. However, data on AMU in North America and particularly in the U.S. is generally scanty, suggesting a need for more in-depth research in the area of AMU in the U.S., both in companion and in food animals. This long-standing gap of lack of AMU data in the U.S. animal industry makes identifying AMR drivers in U.S. difficult [8]. Additionally, species-specific AMU data in US agricultural settings is not available [8]. Such data is crucial for the identification of AMR drivers in livestock production. A review article concluded that more AMU data related to on-farm management practices and species-specific quantities of AMU are needed in the US so that AMR trends can be better understood for targeted interventions to reduce AMR and protection of public health [8].

A 2001/2002 survey conducted in 113 dairy herds in Pennsylvania found that only 50% of the surveyed farms kept antibiotic treatment records, only 21% had written plans for treatment of sick animals, 32% sought veterinarian's advice prior to initiating animal antibiotic treatments and in 93% of the farms, antimicrobial treatments were done by the farmer/manager or designated herdsman [48]. In that survey, producers mostly used beta lactams and tetracyclines, and records from 33 farms showed that antimicrobials were mainly used to treat enteritis and pneumonia in calves, and foot rot in cattle. A 2000/2001 survey of conventional and organic dairy farms in the US found that ceftiofur was the most commonly used antimicrobial in both farming types. In that survey, antimicrobials were used in heifer calves in the majority of conventional farms (74.7%) and in a few organic herds (21.9%) [49]. In Washington state, it was found that veterinarians most commonly prescribed beta lactam antimicrobials [50]. Also, at the Ohio State University Veterinary Medical Center, it was found that beta lactams were the most used antimicrobial class in dogs [51]. A study conducted at a veterinary teaching hospital in Italy, found that broad-spectrum antimicrobials such as penicillins with beta-lactamase inhibitors, first-generation cephalosporins, and fluoroquinolones were the most prescribed [52]. In that Italian study, use of C/S testing to decide choice of antimicrobial was conducted in only 5% of cases. A dairy CAFO in New York state was found to use approximately 493 kg of antibiotics (79 kg penicillin, 16.5 Kg lincosamide, 8 kg aminogylcosides,7.7kg sulfamides,3.4 kg cephalosporin, 2 kg macrolides, 0.7 kg amphenicols, 0.1 kg fluoroquinolones and 376 kg ionophores [53].

Classes of antimicrobials used seem to vary by geographic region. A 2003/2005 survey conducted in Washington State found that penicillin, ceftiofur, and oxytetracycline were the most commonly cited drugs used for treatment by dairy producers [54]. In the Washington state survey, 37% of dairy producers believed that antimicrobials that worked well in the past were no longer effective in the treatment of the same conditions. That survey identified areas of improvement in dairy production in that state to be: reducing the use of medicated milk replacer; increasing veterinarian involvement in AMU decisions; implementing treatment protocols; enhancing biosecurity and ensuring optimal cow and calf immunity. This Washington study concluded that further research was needed to identify and test management practices that would lead to improved antimicrobial stewardship.

In Wisconsin, a survey of conventional and organic dairy producers found that among conventional dairy producers, penicillin was most used for dry cow therapy and cephapirin was mostly used to treat clinical mastitis while organic dairy producers reportedly used non-antimicrobial agents for disease treatment and prevention [55]. That survey of conventional and organic dairy producers concluded that two-thirds of antimicrobials used at the farm level were for dry cow therapy; penicillin, streptomycin, and cephapirin were the antimicrobials most commonly used for dry cow therapy while cephapirin, pirlimycin, and amoxicillin were the most commonly used for treatment of clinical mastitis. A study of AMU in Canadian dairy farms found geographic variations in commonly used classes [56]. Dairy herds in Ontario mainly used third generation cephalosporins (ceftiofur) compared to Quebec. Alberta dairy herds used tetracyclines the most compared to Maritimes. A study of AMU in 24 beef farms in Ontario found that among injectable antimicrobials, oxytetracycline, penicillin, macrolides, florfenicol, and spectinomycin were the most commonly used, while monensin, tylosin, lasalocid, tetracyclines were commonly used in feed [57]. Lincomycin-spectinomycin, chlortetracycline, and oxytetracycline were commonly used in water. This Ontario beef study found that extra-label use of lincomycin-spectinomycin and tiamulin was prevalent. However, this study did not report if the extra-label use was under veterinary oversight and guidance.

A cross-sectional survey of antimicrobial prescribing patterns in UK small animal veterinary practice found that clinicians in non-referral hospitals were more likely to prescribe an incorrect dose of antimicrobials compared to those in referral hospitals; clinicians who used pharmaceutical companies as sources of information were more likely to prescribe an incorrect dose compared to those who did not; an association was found between prescribing unlicensed antimicrobials and the position of the clinician in practice [58]. That study found that locums were more likely to prescribe unlicensed antimicrobials compared to practice partners. A study that evaluated antimicrobial prescription patterns in 8 mixed veterinary practices in Switzerland found that clinicians prescribed penicillins and cephalosporins most frequently (37% of treatments), followed by aminoglycosides (18 %), tetracyclines (14%), and sulphonamides (11%) respectively [59]. This swiss study concluded that most prescriptions in the study practices adhered with prudent use guidelines.

In Australia, Hardefeldt et al suggest that labeling of antimicrobials could be a potential contributor to inappropriate AMU by veterinarians. These authors asserted that some specified doses on antimicrobial drug labels in Australia are inappropriate in light of currently available drug dosage recommendations [60]. No research on appropriateness of veterinary antimicrobial labelling in the U.S. was found in the reviewed literature. Although national estimates of AMU based on sales data may be available, there is currently no reliable data on AMU in the US that is publicly available. This has been the case for many years [61].

An online survey conducted in Finland in 2016 found that of 715 dairy farms, 558 (78%) commonly used selective dry cow therapy, 95/715 (13.3%) used blanket dry cow therapy while 62/715 (8.7%) did not use dry cow therapy at all [62]. There are no documented studies reporting use of dry cow therapy in Tennessee. A study conducted among Ohio Bovine veterinarians reported that the surveyed veterinarians mentioned that producers used antimicrobials without prior veterinary consultation and suggested that veterinarians should encourage producers to seek more veterinary consultation or a treatment protocol approved by a herd veterinarian before treating animals with antimicrobials [63].

Data on antimicrobial usage in many countries is generally scarce because many countries do not collect such data [64]. Although the FDA annually publishes national data on sales and distribution for all antimicrobial drugs approved for use in food-producing animals [65], such data at state or county level is lacking. Studies quantifying on-farm veterinary antimicrobial use in the US are scarce and yet detailed data on antimicrobial consumption could be useful in detecting inappropriate use [66]. Quantities of antimicrobial drugs consumed could be measured in terms of pharmaceutical firm turnover, treatment costs, weight (total weight or dose equivalent, treatment doses (daily dose and prescribed daily dose, or number of items or packages sold [67]. Although prices and costs may not be good indicators due to price changes with time. Use of records of items purchased and translating them into weight of active drug would give a better indicator of quantities of AMU consumed on-farm [67].

Antimicrobial stewardship: Its role in containing AMR

Antimicrobial stewardship (AMS) is a multi-faceted (multi-dimensional) term that describes integrated and multi-disciplinary approaches that are intended to maintain clinical efficacy of antimicrobials through optimization of drug use, choice, route of administration, duration of treatment, and dosage rates while minimizing AMR development and minimizing adverse drug effects [68, 69]. Other scholars have defined AMS as "a coherent set of actions which promote using antimicrobials responsibly" [70]. Although AMS is being championed as a means to minimize AMR development, a recent systematic review of studies evaluating the effectiveness of antimicrobial stewardship programs (ASPs) in human hospitals found no solid evidence of the effectiveness of ASPs in reducing AMR [71].

The goal of an ASP is to preserve the currently available antimicrobials for future generations. Antimicrobial stewardship involves all stakeholders (in human, animal, and environmental health) responsible in some way or another for AMU [72]. The key elements of AMS include: use of practice guidelines (in-practice guidelines, local, national and international guidelines); dosage considerations (knowledge of pharmacokinetic and pharmacodynamic aspects of antimicrobial treatment and knowledge of factors affecting antimicrobial treatment), clinical microbiology data (use of diagnostic microbiology e.g. C/S, point-of-care diagnostics), AMR and AMU surveillance (knowledge of critical resistance problems and understanding AMR and AMU locally, nationally and internationally); infection control practices (development and use of local, national and international infection control policies and procedures); alternatives to antimicrobials (use of vaccines and immunostimulants); national and international regulations (knowledge and compliance with set standards); owner/producer compliance (owner education and compliance assessment, educational materials); continued education to ensure AMU best use practices; acceptance of responsibility for AMR as a potential effect of AMU [72].

Generally, the three approaches that have been recommended for limiting AMR include preventing disease occurrence, reducing overall AMU and improved AMU [29]. To mitigate the development of AMR in the environment, Bengtsson-Palme and others [73] suggest: avoiding the creation of settings that select for, mobilize and allow persistence of AMR genes in bacterial communities; reduction of AMR spread routes; and limiting the selection pressure for AMR pathogens through prudent AMU. In the Netherlands, one study that examined variation in AMU in dairy farmer groups and the effects of external factors on AMU at herd level found large variations in AMU between herds. This study also found that increasing AMU awareness was an important factor in reducing AMU and variation in AMU among herds [74]. This study concluded that the main reason for AMU among the dairy farmers studied was maintenance and restoration of cow udder health. To reduce antimicrobial use in food animals, some authors have suggested imposition of user fees and regulatory caps on use of veterinary antimicrobial drugs [75]. It has also been suggested that behavioral interventions in farmers such as educational campaigns or increased veterinary support could lead to rational AMU among farmers [76].

Ensuring prudent use (judicious AMU) is a key strategy in containing AMR [77]. The world organization for animal health (OIE) Terrestrial Code defines prudent AMU as comprising a series of practical measures and recommendations which confer benefits to animal and public health while preserving and maintaining the therapeutic efficacy of antimicrobials while the WHO defines prudent AMU as AMU which maximizes therapeutic effect while minimizing the development of AMR [78]. To promote judicious AMU, Michigan State University and University of Minnesota, with support from the CDC, developed an on-line suite of educational materials on AMR targeting veterinary medical students [79]. Additionally, the Association of Public and Land Grant Universities (APLU) and the Association of American Veterinary Medical colleges (AAVMC) recognize the need to better educate veterinarians on AMS/AMR and to that end have developed a national strategy to contain AMR [80] . Fanning and others suggested a holistic education of future veterinarians on AMR and AMU given that most veterinary curricula are crowded with no modules specifically dedicated to antimicrobial use [81]. However, in Australia, a study found that compared to older graduates, veterinarians who graduated after 2011 had lower odds of compliance with AMU guidelines [82]. Additionally, an Australian study of factors that influence effective AMS in veterinary practices found that lack of AMS governance structures, client expectations, competition among practices, cost of C/S testing, lack of access to continued education and training resources were barriers to effective AMS. They found concern for the role of veterinary AMU on the development of AMR in humans and willingness to change prescribing behaviors were enablers of AMS [83].

Drivers of AMU in human health

Non-prescription AMU in humans is common worldwide [84] and overuse and inappropriate AMU in humans are known to drive the occurrence of AMR [28, 85, 86]. In developing countries, poverty and poverty-related factors, self-medication, non-compliance, and advertising pressures drive inappropriate use of antimicrobials [87]. Also, pressure from patients influences physicians to prescribe antimicrobials [86, 88, 89]. Some approaches used by patients to exert pressure on the doctor to prescribe antimicrobials include: direct request, portraying severity of illness, reporting a possible diagnosis to the doctor, reporting previous positive experience with an antimicrobial [88].

In an Irish study of general practitioners, patients reportedly requested for antimicrobials from general practitioners and in some situations, specified to the doctor the treatment required [86]. In an Australian study, general practitioners felt pressured to prescribe antimicrobials by their patients with upper respiratory tract infections (URTI) and reported that 10-30% of their patients with URTI demanded antimicrobials [90]. Other than patient demand and pressure, other factors influencing antimicrobial prescription by physicians include severity of illness, uncertainty of diagnosis, duration of infections, availability and supply of antimicrobials, fear of losing patients, and pharmaceutical company marketing activities [89]. However, a qualitative study conducted in Ireland found that medical general practitioners believed over use and mis-use of antimicrobials by veterinarians and in agriculture was part of the problem contributing to AMR [86].

Sources of information and drivers of antimicrobial use among veterinarians

Peer reviewed literature, textbooks or drug hand books were identified as the most important sources of antimicrobial information for veterinarians at one US veterinary teaching hospital [91]. A survey conducted in the UK small animal veterinary practices found that pharmaceutical company representatives were considered an important source of AMU information for 70% of survey respondents, veterinary science degree course notes (46.3%), the

Veterinary Medicines Directorate (22.2%), the British Small Animal Veterinary Association (BSAVA) formulary (14.8%), practice policy (14.3%), and scientific journals (8.0%) [58]. Among veterinarians in Europe, prescribing behavior was strongly influenced by sensitivity tests, veterinarians own experience, ease of administration and the risk of AMR developing [92]. Factors other than clinical evidence and scientific knowledge such as social norms have been shown to influence antimicrobial use among veterinarians [93]. In Ireland, non-clinical factors such as professional stress and non-pharmacological issues such as the veterinarian's experience, cost of antimicrobial, farmer's ability to administer the antimicrobial influenced the veterinarian's choice of antimicrobial [94]. In a UK study, perceived efficacy and perceived owner compliance, and clinician's experience were some of the factors that influenced veterinarian's choice of antimicrobials [93]. Although dairy veterinarians in New Zealand considered technical reasons when prescribing antimicrobials, non-technical factors such as client feedback about perceived efficacy and perceptions of cost/benefit did influence veterinarians prescribing of antimicrobials [95]. Among UK pig veterinary surgeons, external pressures (pressure from clients, legislation and public perception) were identified as strong influencers of antimicrobial prescribing [96]. In the Netherlands, financial dependency on clients, risk avoidance, lack of farmers adherence to veterinary advice, public health interests, personal beliefs regarding the veterinary contribution to AMR reportedly influenced antimicrobial prescribing behavior of farm animal veterinarians [97]. In Ontario Canada, dairy veterinarians ranked antimicrobial drug efficacy as the most important factor considered when choosing an antimicrobial for treating dairy animals followed by label indications for dairy cows, and drug withdrawal times [98].

Factors influencing antimicrobial use among cattle producers

In Flanders and the Netherlands, veterinarians perceived insufficient biosecurity measures, insufficient immunity of young animals, and economic considerations of farmers to be important drivers of high antimicrobial use in farm animals [99]. The need for AMU to prevent infectious bovine diseases for economic gain, and reduce the risk of disease transmission is one factor driving AMU among beef producers [64]. In dairy cattle, mastitis is a key disease for which antimicrobials are used [100]. In England and Wales, the most influential source of information on AMU for dairy producers was the producers' own veterinarian while approval of reduced AMU from social referents (other producers, milk buyers, retail consumers) was an important driver towards reduced AMU [101]. In New Zealand, veterinary advice, personal on-farm experience, price (financial consideration), short drug withdrawal period, ease of using an antimicrobial, packaging and syringe design, perceived drug efficacy, were important influencers of AMU among dairy producers [95]. In South Carolina, majority of dairy producers relied on their own experience when deciding to use antimicrobials [102]. In Europe, a qualitative study found that social referents such as herd veterinarians, other producers influenced dairy farmers decision making on the duration of treatment for clinical mastitis [103]. In this qualitative study, it was concluded that veterinarians being positive social referents for farmers would be invaluable in communicating evidence-based information to farmers so as to cause change in AMU for mastitis treatment.

A study conducted among dairy producers in Michigan, Pennsylvania, and Florida found that maintaining and reviewing treatment records was strongly associated with a producer's use of antimicrobials systemically or for intra-mammary use. Farmer's education level and type of cow bedding were significantly associated with systemic AMU [104]. In that study, dairy producers with less than high school education were 1.7 times likely to use antimicrobials systemically compared to those with other education levels. While the odds of systemic AMU in dairy farms that used a mattress with straw, sawdust or wood shavings, and those that used sand were 0.5 times the odds of systemic AMU in dairy farms with other cow bedding types. This study concluded that attitudes and beliefs of dairy farmers may influence antimicrobial therapeutic choices for clinical mastitis. A Danish study of dairy farmers found that high somatic cell counts and high milk yield were associated with high probability of AMU for udder health management [105]. This Danish study concluded that determinants of AMU varied among dairy farms, and that improved udder health and prudent AMU would be achieved through farm-specific interventions that factor in how dairy farmers decide which animals to treat with antimicrobials. A French study found the dairy farming system (type of dairy operation) had very little influence on the farmers AMU. All organic dairy farmers practiced selective treatment of their dairy herds [106]. A 2007/2008 survey of Tennessee beef producers regarding AMU found that herd size, participation in Beef Quality Assurance and master beef certification programs, quarantining of newly purchased cattle, use of written instructions for animal treatment and observation of drug withdrawal periods were strongly associated with higher AMU [107]. However, it is possible that over time, AMU practices could have changed in Tennessee such that these factors may not be currently associated with higher AMU.

Alternatives to antimicrobials

Alternatives to antimicrobials have been defined as non-compound approaches (non-classic antibacterial compounds) that target bacteria or approaches that target the host in the treatment of bacterial infections [108]. Vaccines are an important alternative to antimicrobials in that vaccines can reduce the prevalence of AMR by reducing the need for AMU [24, 109]. Use of probiotics to improve animal health is also suggested as an alternative to AMU [110]. A study conducted in the U.S. among dairy producers in Michigan and Ohio, found that alternative antimicrobial therapies (with little documented clinical efficacy) were used by both organic and conventional producers; with garlic, aloe Vera, and other herbal remedies being used by majority of organic dairy producers [111]. In that study among dairy farmers, the authors suggested that more research on antimicrobial alternatives needed to be conducted, that treatment protocols needed to be applied widely in the farms, and recommended farm personnel education and training on diagnostic criteria for initiation of AMU. A 2015 French study that analyzed dairy producer's choice of antimicrobials and alternative medicine for mastitis treatment found that whereas producers are more willing to try alternative antimicrobial therapies for mastitis treatment, veterinarians and farm advisors poorly supported use of alternative antimicrobial therapies because of lack of scientific evidence for their efficacy [106]. In France, dairy farmers use aromatherapy, essential oils, homeopathy, phytotherapy as alternative therapies for mastitis. That 2015 French study recommended an evaluation of use of alternative therapies for mastitis therapy in different countries.

Use of culture and sensitivity test results

In a New Zealand study, dairy producers perceived the use of culture and sensitivity/susceptibility (C/S) testing to be of limited value because producers believed C/S results did not affect what antimicrobial was prescribed by the veterinarian [95]. In a survey of European veterinarians, 37.8% of practitioners reported to frequently use C/S before starting antimicrobial treatment while 44.3% only undertook AST when prompted by poor response or complicated clinical cases [92]. In that European survey, cheaper and rapid sensitivity testing were identified as factors that would encourage use of C/S testing by veterinarians. In

Washington state, cost was identified as a barrier to conducting C/S testing to guide veterinarians in antimicrobial therapy [50]. Implementation of national pet insurance schemes that cover the costs of C/S testing have been suggested as a method to increase use of C/S test results [72]. However national pet health insurance schemes are unavailable in most countries. A veterinary expert opinion study conducted in 3 European countries found that C/S testing was rarely used for selecting antimicrobials and the time lag (long waiting time) between C/S testing and obtaining the results was a reason for the rare use of C/S [112]. In that veterinary expert opinion study, C/S was also perceived to not be helpful in clinical decision making (or on the selection of the antimicrobial for clinical use). This finding from the European study resonates well with the opinions of the New Zealand dairy farmers where dairy producers perceived C/S testing to be of limited use because producers believed C/S results did not affect what antimicrobial was prescribed by the veterinarian [95].

Farmers knowledge of AMR

Dairy producers in New Zealand were reported to have limited knowledge or concern about AMR [95]. Similarly, dairy producers in south Carolina were reported to be unaware of the significance of AMR [102]. In a European survey of pig producers, producers generally perceived their AMU to be lower than that of their peers and these farmers were generally less concerned (less worried) about AMR and more concerned about financial and legal issues surrounding their production [113]. A survey conducted in four European countries found that survey respondents were neutral regarding the risks associated with AMU and AMR (the risks associated with AMU were rated by farmers to be moderate) suggesting a need for more farmer awareness about AMU and public health risks of AMR [114]. A survey conducted in Germany found that compared to respondents from the general public (non-pig farmers, non-health professionals), pig farmers had much better knowledge of AMR [115]. The authors of that Germany survey suggested that when addressing interventions to contain AMR, farmers should at least be treated as semi-professionals (instead of regarding them as lay people).

Knowledge of AMU/AMR among consumers and general public

A 2016 survey of public acceptance of AMU in Canada (where AMU for growth promotion, prophylaxis and therapeutic use was allowed) and Germany (where AMU was more limited) found disparities in individuals willingness to consume animal products from antimicrobial treated animals [116]. The findings of that survey suggested that there was a low understanding amongst the public (study population) of how antimicrobials are used in animal production and of the benefits of antimicrobials in animal production. Findings from a cross-sectoral survey of physicians, veterinarians, farmers and the general public found that respondents from the general public had lower basic knowledge of AMR compared to pig farmers [115].

A qualitative study conducted in Denmark reported the unintended outcome of increased medical and public health focus on AMR with increased public criticism of farmers [117]. This research study found that pig farmers and their families (children, spouses, relatives) experience stigmatization in society because of their use of antimicrobials since they are perceived to be carriers of resistant bacteria such as MRSA [117]. This stigmatization of Danish pig farmers and their families is associated with increased public concern about AMR linked to conventional pig farming in that country. To prevent introduction to hospitals, and to prevent nosocomial infections, Cuny and others suggested that farmers and veterinarians with livestock contacts should be screened at hospital admittance for MRSA colonization [18]. Health care facilities in countries where Livestock Associated-MRSA is reportedly endemic, take precautionary measures when caring for persons in contact with pigs [118]. There is no documented evidence of stigmatization of US livestock producers associated with their use of antimicrobials. However, there is a possibility that such stigmatization of farmers (associated with AMU and carriage of AMR bacteria) may get infused into the US public as concerns about AMR occurrence and non-judicious AMU in livestock production increases.

The impact of AMU regulations on animal health and welfare

There have been various reports of the effect/impact of the ban of AGPs in Europe. One report states that in Denmark, Finland, Norway, and Sweden, the ban of antimicrobial growth promoters led to significantly decreased AMU and reduced AMR in enterococci previously resistant to antimicrobials used for growth promotion [119]. While others state that although the ban on antimicrobials for growth promotion in Denmark led to decreased total AMU, resistance in key zoonotic bacteria had not reduced [120]. In the Netherlands, a 56% reduction in antimicrobial use in farm animals was realized between 2007 and 2012 due compulsory and voluntary efforts by stakeholders within the livestock sector [121]. One systematic review has shown that interventions that restrict AMU in food-producing animals are associated with a reduction in the occurrence of AMR in those animals [122]. A Dutch study found that farmers in the Netherlands quickly adopted selective dry cow therapy and abandoned blanket dry cow therapy when preventive AMU in animal husbandry was prohibited in 2013 [123].

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CHAPTER 2

Antimicrobial use practices of veterinary clinicians at a veterinary teaching hospital in the United States

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Abstract

Indiscriminate antimicrobial use (AMU) is a factor contributing to antimicrobial resistance (AMR). The objectives of this study were to (1) identify factors influencing AMU practices of veterinary clinicians at The University of Tennessee Veterinary Medical Center (UTVMC), (2) analyze the clinicians' preferential choices of antimicrobials, and (3) evaluate their perceptions, opinions, and concerns regarding AMU and AMR. A total of 121 clinicians were surveyed. Among the 62 respondents, culture and susceptibility test results and pressure from clients were the most and least important factors in their antimicrobial prescription decision-making, respectively. Compared to clinicians who obtained their veterinary degree from 1970–1999, those who graduated from 2000–2009 and 2010–2016 were 3.96 ($P = 0.034$) and

5.39 (P = 0.01) times less concerned about AMR, respectively. There is a critical need to increase awareness about judicious AMU practices among clinicians, increase emphasis about AMR in the present veterinary curriculum, and implement antimicrobial stewardship program (AMS) in this institution. Educational activities in combination with awareness campaigns and the stewardship programs could be used to improve AMU practices at this hospital. More client education on AMR is needed.

Key words

Antimicrobial resistance; antimicrobial stewardship; ordinal logistic regression; questionnaire; survey.

Introduction

Antimicrobial drugs in veterinary practice are primarily prescribed for the purposes of maintaining or improving animal health and increasing productivity [1]. However, the emergence and spread of antimicrobial resistant microorganisms is eroding the value of antimicrobial drugs [2, 3]. Although antimicrobial resistance (AMR) is an ancient phenomenon [4, 5], indiscriminate antimicrobial use (AMU) is an important risk factor for the development of AMR [6]. The increase in the prevalence of microorganisms resistant to antimicrobials, both in veterinary and human medicine, is now widely attributed to AMU [7, 8].

Shedding of drug resistant microorganisms by animals can directly (through contact) or indirectly lead to human infections/colonization by commensal bacteria [1, 9, 10]. These bacteria carry transferable resistance genes across species through multiple pathways like food, water, fomites, sludge and manure applications to food crop soils [1, 11-13], as well as household environments with pets carrying resistant bacteria and other environments contaminated with pet feces [14]. Multi-drug resistant infections exert a huge burden on veterinary medical care [15] and pose public health risks [16, 17].

To reduce indiscriminate use and to improve AMU practices, veterinary practices are encouraged to develop and implement antimicrobial stewardship (AMS) programs. Such stewardship programs include effective infection control, bacteriologic culture and antimicrobial susceptibility testing, and the use of individual practice guidelines for AMS [18, 19]. According to the American Veterinary Medical Association [20] and the U.S. Food and Drug Administration [21], veterinarians in the U.S. are required to direct AMU only within the context of a valid veterinarian-client-patient-relationship (VCPR) to ensure judicious use. In the context of VCPR, the veterinarian can write a prescription or dispense prescription drugs only when all of the following five requirements are observed (1) the veterinarian assumes the responsibility of providing health care for the patient and the client agrees to follow the veterinarian's instructions, (2) the veterinarian is sufficiently knowledgeable of the patient to initiate care and is well acquainted with the keeping and care provided to the patient either through patient evaluation or through timely visits to the operation where the patient is managed, (3) the veterinarian is available for follow-up evaluations or has planned for emergency health coverage, continuing veterinary care and treatment, (4) the veterinarian provides oversight of treatment, compliance and outcome, and (5) patient records are well kept. The VCPR can be applied to individual animals as well as a group or groups of animals within an operation (production system).

Research conducted from May 2008 to May 2009 at a veterinary teaching hospital in the northeastern U.S. suggests clinicians are frequently prescribing antimicrobials without proper documentation in medical records or without indicating their use [22]. In a 2014 survey, veterinarians in North Carolina State University veterinary teaching hospital believed the veterinary practice over-prescribed antimicrobials, were concerned about AMR, and supported the idea of restricting the use of certain antimicrobial classes in companion animals [23]. Prior to the present study, the factors that influenced AMU practices of veterinary clinicians at University of Tennessee Veterinary Medical Center (UTVMC) were unknown. Similarly, their perceptions, opinions, and concerns about AMU, AMS, and AMR were undocumented. Additionally, the association between the effort allocation to veterinary clinical practice and the frequency of antimicrobial prescriptions for therapeutic treatment of infectious diseases had not been explored. This study contributes to the wider knowledge of AMU by providing insights into the AMU practices of clinicians at a veterinary teaching hospital.

The objectives of this study were to (1) identify factors influencing AMU practices of veterinary clinicians at the UTVMC, (2) analyze the clinicians' preferential choices of antimicrobials, and (3) evaluate their perceptions, opinions, and concerns regarding AMU, AMS, and AMR. These findings will be beneficial in improving AMS programs and educational training on judicious AMU. Ultimately, these efforts could prolong the efficacy of current antimicrobials and reduce the burden of AMR within veterinary medicine and public health.

Materials and methods

Study design and administration of survey

A questionnaire (see appendix 1) was developed and validated by four professionals with expertise in survey design and the University of Tennessee Knoxville Institutional Review Board for the Protection of Human Subjects in Research approved the study (Protocol number: UTK IRB-16- 103 02956-XP). A survey software (Qualtrics software, Provo, UT) housed the 36-questions questionnaire, which were adapted for computer, tablet, and cell phone responses.

These questions targeted the respondent's demographics and their antimicrobial prescription practices, perceptions, opinions, and concerns about AMU, AMS, and AMR. The anonymize function in the software was optimized, so responses were not attached to any personal identifiers. The questionnaire was pre-tested among four veterinary clinicians at UTVMC and their comments were used to improve questionnaire clarity.

Targeted demographic information included gender, the nature of the clinical position (faculty versus house officers), the primary type of patients seen (small animal, food animal, equine, etc.), where the veterinary degree was obtained (U.S. versus non-U.S.), and year of graduation from veterinary school/total number of years in clinical practice from time of graduation. Biological age of respondents was not included because year of graduation and number of years in clinical practice were considered to be more clinically relevant to the research question. This demographic information were our explanatory variables of interest. Our two outcomes of interest were (1) the frequency of antimicrobial prescription and (2) the degree of concern about antimicrobial resistant infections. Most of the survey questions were closed-ended while a few were free-text (open questions). Three-point scales and ordinal Likert scales were used to capture participant responses to most of the closed-ended survey questions relating to perceptions about AMU practices and AMR. Regarding antimicrobial class preference based on clinician's frequency of prescription, participants were asked to rank medically important classes of antimicrobials on a five-point Likert scale ranging from a strong dislike (never prescribed) to a strong preference (always prescribed).

During departmental meetings approximately a week before the study's start date, eligible participants (all faculty members with clinical appointments, residents, and interns at UTVMC) were notified of the upcoming survey in an effort to increase response rate.

Subsequently, a notification email was sent to all potential respondents an hour before the survey went live. Afterwards, all 121 eligible participants received an email invitation about the survey, which was optimized to accept only one response from each respondent. To minimize potential selection bias, the survey was sent to all clinicians at the hospital irrespective of whether their primary clinical duties directly or indirectly involved AMU. The survey remained open for 6 weeks (January 27, 2017 through March 10, 2017). Weekly follow-up email reminders were sent to non-respondents. No incentive was provided to clinicians for participation or completion but a thank you message was sent to all respondents at the end of the study.

Statistical analysis

Descriptive and inferential analyses was completed using commercial statistical software (SAS, version 9.4, SAS Institute Inc, Cary, NC). Descriptive statistics (frequencies and proportions) were used to summarize the data. Side-by-side bar charts and stacked bar charts for responses on the three-point scales and on the Likert scales were created using another commercial software (Tableau software, version 8.2, Seattle, WA). No corrections were made on missing data.

To test for associations between the captured demographic information and the two outcomes of interest, both univariable and multivariable analysis were performed using ordinal logistic regression. The model fit was assessed using the Score Test for the Proportional Odds Assumption, Deviance, and Pearson Goodness-of-Fit Statistics, and a plot of the empirical cumulative logit function. The proportional-odds assumption for the ordinal logistic regression models was evaluated using the Score Test for the Proportional Odds Assumption, and a plot of the empirical cumulative logit function. A plot yielding approximately parallel empirical cumulative logits was indicative of an appropriate proportional odds model. Specifically, ordinal logistic regression was used to investigate the effects of antimicrobial class on clinicians' frequency of prescription and to identify differences in preference between classes of antimicrobials. To validate the data on ranking of classes of antimicrobials based on frequency of prescription, the commonly prescribed antimicrobial drugs captured as free text (generic or trades names) from clinician responses were further grouped into classes as described previously [23, 24]. From these classes, we isolated the medically important antimicrobial classes as grouped by the United States Food and Drug Administration [25]. These medically important classes included: aminoglycosides e.g. gentamicin; cephalosporins e.g. ceftriaxone, cefazolin; fluoroquinolones e.g. ciprofloxacin; lincosamides e.g. clindamycin, lincomycin; macrolides e.g. erythromycin; penicillins e.g. amoxicillin, ampicillin; sulfonamides e.g. sulfadiazine, sulfathiazole; and tetracyclines e.g. doxycycline, oxytetracycline. The United States Food and Drug Administration groups antimicrobials as medically important in line with the World Health Organization's classification of antimicrobials. Preferential ordering of the medically important antimicrobial classes was analyzed based on the main categories of patients seen by clinicians. The preference ordering was assessed based on the relative magnitudes of the parameter estimates from the model. Preferential ordering refers to the order in which antimicrobial classes were preferred from the least preferred to the most preferred. During the modeling, tetracyclines was selected as the reference class and the probability of disliking another class of antimicrobial in comparison to tetracyclines was estimated. Spearman's rank correlation was used to evaluate for correlations and quantify the strength of association between two ranked variables: for example, the proportion of total professional activity dedicated to clinical practice (effort allocation to clinical practice) and the frequency of prescription of antimicrobials for therapeutic purposes; number of years in clinical practice from the time of graduation from veterinary school and year of graduation from veterinary school.

In assessing the clinicians' degree of concern about AMR, a multivariable ordinal logistic regression model was manually fitted using backwards elimination method. Briefly, potential predictors at a $P \leq 0.20$ from the univariable analyses were included in the multivariable model building and variables were dropped if they were either non-significant ($P > 0.05$) or non-confounders. Possible effects of confounding were evaluated by comparing a change in parameter estimates with and without the suspected variables [26, 27]. A predictor variable that caused a ≥ 20% change in another parameter estimate upon removal from the model was considered a confounder and was retained in the final model regardless of its statistical significance [28]. For two predictor variables that were highly correlated (number of years in clinical practice from the time of graduation from veterinary school and year of graduation from veterinary school), only one variable was used in the multivariable model building based on completeness of data or ease in clinical interpretation. Year of graduation was captured as a free text and was later classified into 3 quantiles (1970 – 1999, 2000 – 2009, and 2010 – 2016) as done in a previous study [23]. In the final model, two-way interactions (e.g., year of graduation and clinician's primary patient load) were assessed based on plausibility and standard multiple pairwise comparisons were obtained.

Results

Study site

The UTVMC is the veterinary teaching hospital of UTCVM and the only academic veterinary medical center in the US state of Tennessee. This veterinary college is under the Institute of Agriculture at the University of Tennessee and employs a total of 99 faculty members and 174 staff. There are currently three academic departments at UTCVM namely: biomedical and diagnostic sciences (29 faculty members and 54 Staff), large animal clinical sciences (21 faculty members and 29 Staff) and small animal clinical sciences (49 faculty members and 91 Staff). As of fiscal year, 2017, the average annual large animal caseload (both clinic and ambulatory) was 15,031 patients. The annual small animal case load was estimated to be more than 15,000 patients and the avian caseload was estimated to be 1,500 per year.

Descriptive statistics

Of the 121 invited participants, 62 (51.2%) responded to the survey. Complete responses were provided in most questions except for a few responses that were unanswered. The demographic information of the 62 respondents is presented in **Table 2.1**.

Among the factors that influence the choice of antimicrobial drug(s) for clinical use at UTVMC **(Figure 2.1)**, results from bacteriological culture and antimicrobial susceptibility tests were the most important. Pressure from clients/producers to the clinician to prescribe antimicrobials and the fear of litigation by the client/producer in the event of an undesirable clinical outcome were the two least important factors. Peer-reviewed scientific literature and textbooks/drug handbooks were the most important sources of information on antimicrobial drugs for these clinicians while pharmaceutical company representatives and online resources (e.g., blogs or media searches) were the least important sources of information **(Figure 2.2)**.

Frequency of prescriptions differed among these clinicians. Twenty clinicians (32.3%) prescribed antimicrobials for therapeutic purposes more than five times a week, while 35 of 62 (56.5%) clinicians prescribed antimicrobials for prophylactic purposes (**Figure 2.3**). Of these 35 clinicians, 23 (65.7%) prescribed antimicrobials for pre-operative surgical prophylaxis, 29

(85.3%) for post-operative surgical prophylaxis, and 29 (82.9%) for peri-operative surgical prophylaxis (**Figure 2.4**).

Table 2.1: Demographics of clinicians (n = 62) on an online survey to identify determinants of antimicrobial use practices at the University of Tennessee Veterinary Medical Center, 2017

Variable	**Number (%) of respondents**
Gender	
Female	37 (59.7)
Male	21 (33.9)
Preferred not to report gender	4 (6.5)
Nature Clinical Position	
Faculty members	44 (71)
House officers	17 (27.4)
Not reported	1 (1.6)
Year of graduation from veterinary school	
1970 - 1999	21 (33.9)
2000 - 2009	22 (35.5)
2010 - 2016	19 (30.7)
College where veterinary degree was obtained	
U.S. veterinary school	51 (82.3)
Non-U.S. veterinary school	11 (17.7)
Primary patient load	
Small animal	37 (59.7)
Equine	8 (12.9)
Food animal	7 (11.3)
Others (mixed animal, exotics)	10 (16.1)
Specialty board certification	
Obtained specialty board certification	43 (69.4)
No specialty board certification	19 (30.6)

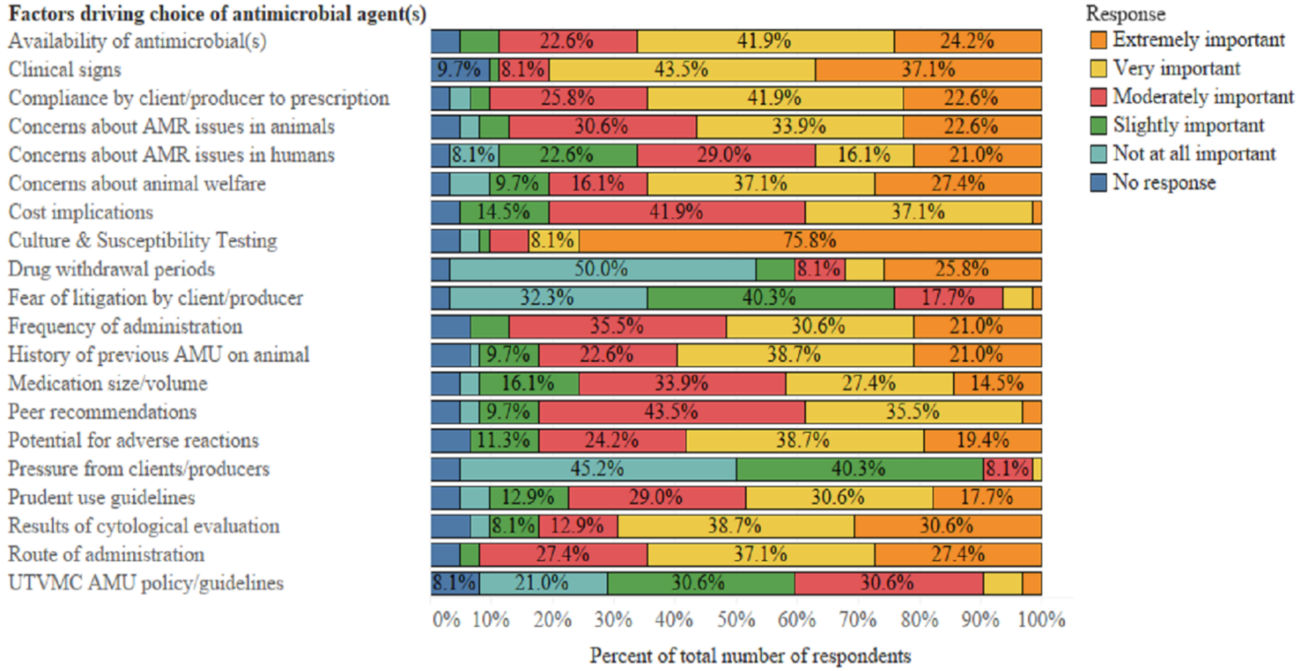

Figure 2.1: Distribution of factors that influence the initiation and the choice of antimicrobials used by clinicians at the University of Tennessee Veterinary Medical Center, 2017 (n = 62).

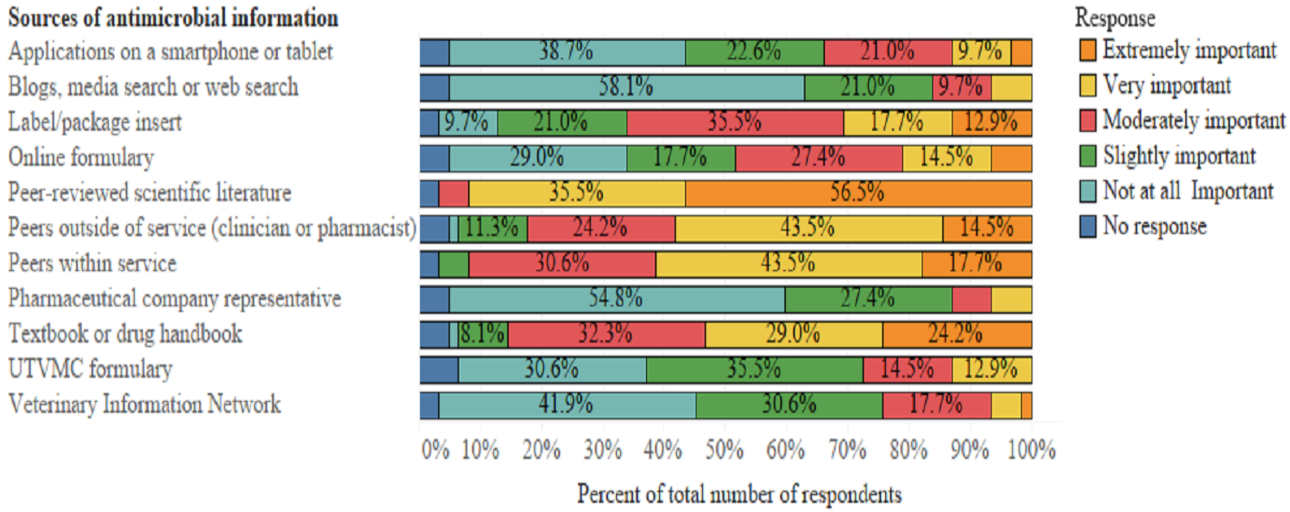

Figure 2.2: Distribution of sources of information influencing the choice of antimicrobials used by clinicians at the University of Tennessee Veterinary Medical Center, 2017 (n = 62).

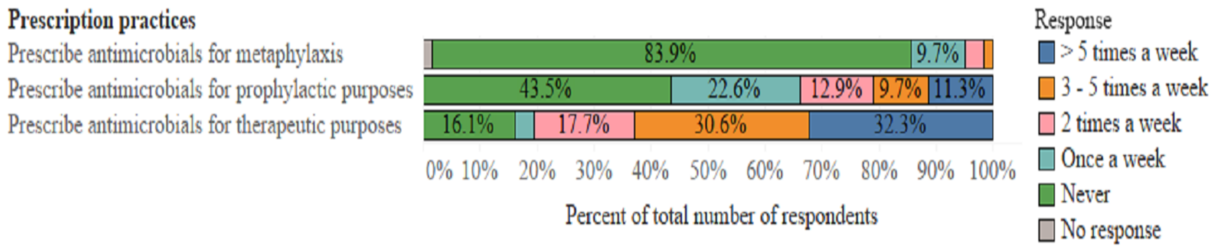

Figure 2.3: Self-reported antimicrobial prescription practices of clinicians at the University of Tennessee Veterinary Medical Center, 2017 (n = 62).

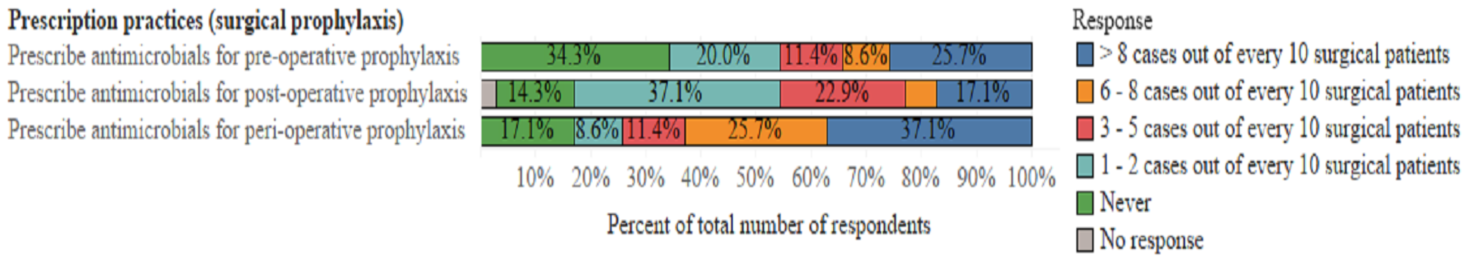

Figure 2.4: Self-reported antimicrobial prescription practices for surgical prophylaxis by clinicians at the University of Tennessee Veterinary Medical Center, 2017 (n = 62).

Clinicians' opinions on AMU practices at UTVMC differed. One clinician (1.6%) believed antimicrobials were prescribed based only on confirmed infections, 21 (33.9%) believed antimicrobials were sometimes prescribed based on no documented evidence of infection. Thirty-eight clinicians (61.3%) believed that antimicrobials were sometimes prescribed for suspected (but not confirmed) infections, and two clinicians (3.2%) were not sure.

As per prescription rate at UTVMC, clinician's opinions also differed. One clinician (1.6%) believed antimicrobials were under-prescribed. While 29 (46.8%) and 32 (51.6%) believed antimicrobials were optimally prescribed and over-prescribed, respectively. Overall, two (3.2%) clinicians believed UTVMC had an AMS program, 51 clinicians (82.3%) were not sure, while nine (14.5%) mentioned that none existed. Within the faculty cohort (n = 44), eight (13.1%) believed there was no AMS program, 34 (55.7%) were not sure, and two (3.3%) mentioned that one existed.

Of the 17 house officers, 16 (26.2%) were not sure if AMS program existed and one individual (1.6%) believed none existed. The respondent who did not disclose the nature of their clinical position was also not sure of the existence of AMS program at UTVMC. Of the nine clinicians who believed no AMS program currently exists, seven (77.8%) mentioned that development and implementation of AMS program in the hospital was necessary while the other two (22.2%) clinicians mentioned the opposite.

Regarding the clinicians' familiarity with Veterinarian Client Patient Relationship (VCPR), three (4.8%) were not familiar at all. While nine clinicians (14.5%) were moderately familiar with VCPR, 17 (27.4%) were very familiar, 33 (53.2%) were extremely familiar. A comparison of the level of familiarity with the VCPR between faculty members and house officers is shown in **Figure 2.5**.

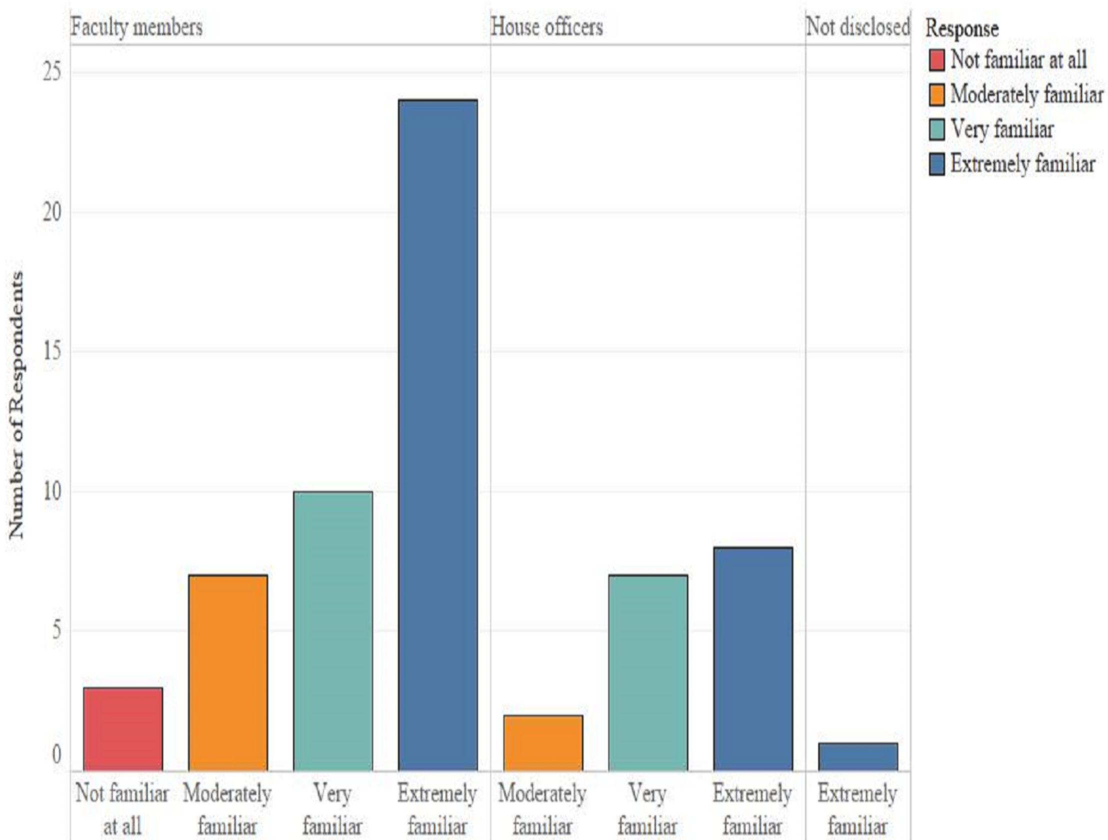

Figure 2.5: Self-reported level of familiarity with Veterinarian Client Patient Relationship by clinicians at the University of Tennessee Veterinary Medical Center, 2017 (n = 62).

Of the 62 respondents, 10 clinicians (16.1%) mentioned that they never utilized VCPR in their antimicrobial prescription practice, three (4.8%) mentioned that they rarely used VCPR, and four (6.5%) sometimes utilized VCPR. Ten clinicians (16.3%) often utilized VCPR, and 35 (56.5%) always utilized VCPR in their antimicrobial prescription practice. A comparison of the use of VCPR in antimicrobial prescription practice of clinicians based on the nature of clinical position is shown in **Figure 2.6**.

The extent to which the Doctor of Veterinary Medicine (or equivalent veterinary degree) training adequately equipped clinicians with knowledge on rational use of antimicrobials varied. For one clinician (1.6%), it was "not at all," three (4.8%) mentioned "a little," 22 (35.5%) responded "somewhat," 28 (45.2%) believed "quite a bit," and eight (12.9%) said "very much." Similarly, the extent to which the present-day veterinary curriculum adequately trains students on rational use of antimicrobials varied. One clinician felt that present-day veterinary medical students do not receive any adequate training on rational use of antimicrobials, nine (14.8%) stated the students received "a little," 28 (45.9%) responded "somewhat," 21 (34.4%) responded "quite a bit," and two (3.3%) responded "very much." Seventeen (27.4%) clinicians had never read the FDA / American Veterinary Medical Association (AVMA) guidelines for judicious use of antimicrobials, 19 (30.7%) rarely did, 20 (32.3%) sometimes did, and six (9.7%) very often read the guidelines.

In rating other veterinarians' concerns about AMR, 18 clinicians (29.1%) believed other veterinarians were slightly concerned about AMR, 36 (58.1%) believed that others were moderately concerned, five (8.1%) believed that others were quite concerned, and three (4.8%) believed others were very concerned.

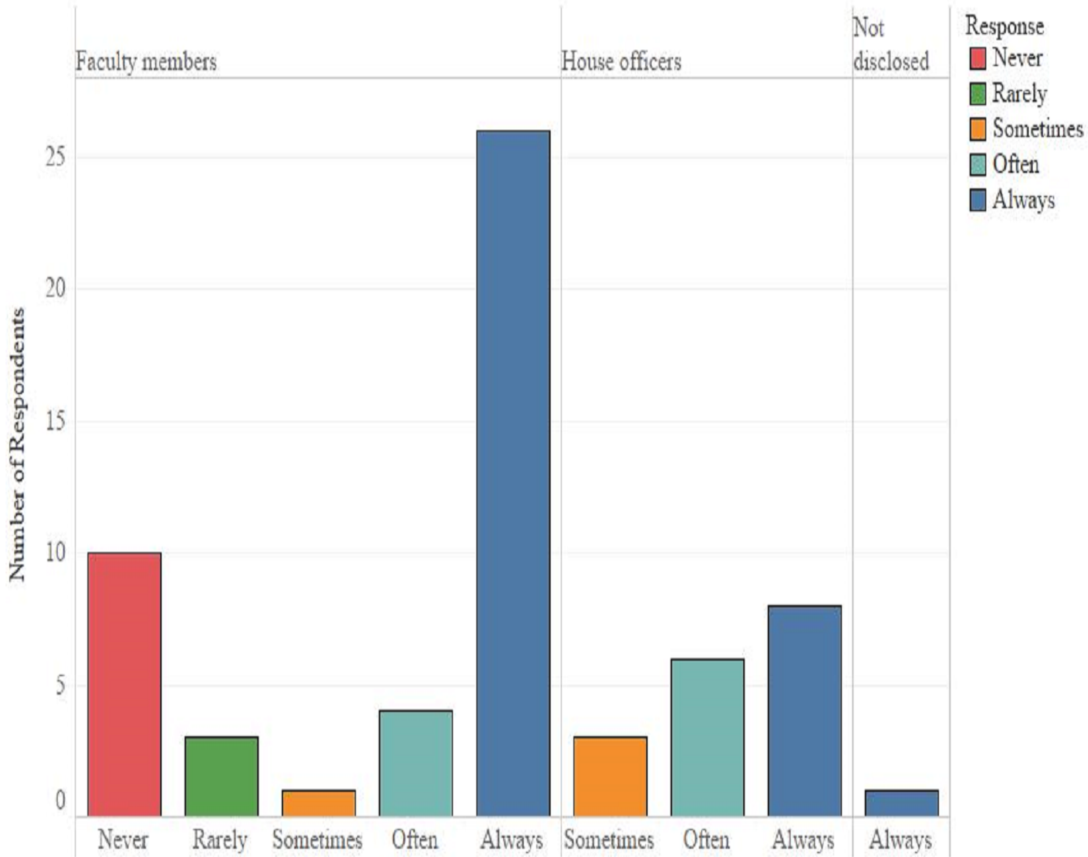

Figure 2.6: Self-reported use of Veterinarian Client Patient Relationship in antimicrobial prescription practice by clinicians at the University of Tennessee Veterinary Medical Center, 2017 (n = 62).

With respect to their clients' concern about AMR, 27 clinicians (43.6%) believed their clients were not concerned, 25 (40.3%) believed they were slightly concerned, eight (12.9%) believed the clients were moderately concerned, and two (3.2%) believed they were quite concerned. Twelve clinicians (19.4%) strongly disagreed with the statement "antimicrobial classes commonly used in human medicine should not be used in veterinary medicine because their use in veterinary medicine selects for AMR in microbes affecting humans." Thirty-two (51.6%) disagreed with this statement, 11 (17.7%) neither disagreed nor agreed, and seven (11.3%) agreed with this statement. For the statement "antimicrobial drug use in veterinary practice may lead to AMR in pathogens affecting humans," one (1.6%) strongly disagreed, 8 (12.9%) disagreed, 17 (27.4%) neither disagreed nor agreed, 24 (38.7%) agreed, and 12 (19.4%) strongly agreed. One respondent (1.6%) was not concerned about antimicrobial resistant infections. Two (3.2%) were slightly concerned; 27 (43.6%) were moderately concerned. Nineteen clinicians (30.7%) were quite concerned, and 13 (21%) were very concerned about antimicrobial-resistant infections.

Preferential ordering of the medically important antimicrobial classes by small animal clinicians

For these results on preferential ordering of the medically important antimicrobial classes by small animal clinicians, a plot of the empirical cumulative logit function yielded approximately parallel empirical cumulative logits which was indicative of an appropriate proportional-odds model. Based on the frequency of prescriptions, the small animal clinicians preferred the following medically important antimicrobial classes in an increasing order: lincosamides, aminoglycosides, macrolides, sulfonamides, fluoroquinolones, tetracyclines, and penicillins/cephalosporins (**Table 2.2**). Compared to the tetracycline, the lincosamides, aminoglycosides, macrolides, and sulfonamide classes were significantly less preferred classes but there were no significant differences in the preference for fluoroquinolones, penicillins, and cephalosporins by small animal clinicians (**Table 2.2**).

Table 2.2: Increasing order of preference of medically important antimicrobial classes based on self-reported frequency of prescription by small animal clinicians at the University of Tennessee Veterinary Medical Center, 2017 (n = 37).

Antimicrobial class†	**Parameter estimate**	**Standard error**	**Odds ratio (95% CI)**	***P* value**
Lincosamides	2.6468	0.4637	14.11 (5.69 – 35.01)	<0.001
Aminoglycosides	2.6050	0.4522	13.53 (5.58 – 32.83)	<0.001
Macrolides	1.8271	0.4518	6.22 (2.56 – 15.07)	<0.001
Sulfonamides	1.7709	0.4411	5.88 (2.48 – 13.95)	<0.001
Fluoroquinolones	0.1857	0.4374	1.20 (0.51 – 2.84)	0.671
Tetracyclines*	—	—	—	—
Penicillins	–0.3091	0.4768	0.73 (0.29 – 1.87)	0.517
Cephalosporins	–0.3086	0.4425	0.73 (0.31 – 1.75)	0.486

*Reference class. †The least preferred class had the highest odds ratio because the probability of disliking a class was modeled.

Univariable analyses

Number of years in clinical practice (clinical experience), year of graduation from veterinary school, and nature of clinical position were the only explanatory demographic variables that were significantly associated with the outcome variable (**Table 2.3**). Compared to clinicians with more years in clinical practice, those with less were significantly less concerned about AMR (OR = 0.95). In other words, that the estimated odds of being less concerned about AMR decreased by 5% for every year in clinical practice. Similarly, compared to clinicians who graduated from 1970–1999, those who graduated from 2000–2009 and 2010–2016 were 2.83 and 4.55 times less concerned about AMR, respectively. However, there was no significant difference observed between graduates of 2000–2009 and those of 2010–2016. House officers were 3 times less concerned about AMR in comparison to faculty members.

Table 2.3: Univariable analyses for associations between various demographic predictors and clinicians' degree of concern about antimicrobial resistant infections at University of Tennessee Veterinary Medical Center, 2017.

Variable	**Category**	**OR (95% CI)**	***P* Value**
Gender	Male vs *Female	1.01 (0.37 – 2.74)	0.307
Number of years in clinical practice	1-year increase	0.95 (0.91 – 0.99)	0.018
Nature of clinical position	House officers vs *Faculty members	3.19 (1.04 – 9.79)	0.043
Year of graduation from veterinary school	††Overall	–	0.040
	2000 – 2009 vs *1970 – 1999	2.83 (0.91 – 8.77)	0.071
	2010 – 2016 vs *1970 – 1999	4.55 (1.35 – 15. 38)	0.015
	2010 – 2016 vs *2000 – 2009	1.61 (0.49 – 5.25)	0.431
Where veterinary degree was obtained	U.S. vs *Non-U.S.	1.79 (0.54 – 5.94)	0.343
Specialty board certification	No vs *Yes	2.84 (0.98 – 8.19)	0.054
Primary patient load	††Overall	–	0.164
	Food animal vs *Small animal	4.14 (0.82 – 21)	0.086
	Equine vs *Small animal	2.34 (0.55 – 9.97)	0.251
	Food animal vs *Others†	1.36 (0.2 – 9.16)	0.755
	Food animal vs *Equine	1.77 (0.24 – 12.91)	0.573
	Others† vs *Equine	1.31 (0.22 – 7.77)	0.768
	Others† vs *Small animal	3.06 (0.77 – 11.88)	0.107

†A combination of mixed animal and exotics. *Reference category.
††Overall = overall effect of predictor on outcome variable.

There was no significant correlation between proportion of total professional activity dedicated to clinical practice (effort allocation to clinical practice) and frequency of prescription of antimicrobials for therapeutic treatment of infectious diseases (r = 0.20211, P = 0.1152). Likewise, there was no significant correlation between period of graduation from veterinary school and frequency of prescription of antimicrobials for therapeutic treatment of infectious diseases (r = 0.1654, P = 0.1989). However, number of years in clinical practice and year of graduation from veterinary school were highly correlated (r = 0.915, P < 0.001).

Multivariable analyses

In the multivariable cumulative logit model, year of graduation from veterinary school was significantly associated (P = 0.025) with clinicians' degree of concern about AMR, after controlling for clinicians' primary patient load which was a confounder in the model (**Table 2.4**). The Score test for the Proportional Odds Assumption (P = 0.132), Deviance (P = 0.278) and Pearson (P = 0.286) Goodness-of-Fit Statistics indicated that the model fit the data very well. Compared to clinicians who obtained their veterinary degree from 1970–1999, those who graduated from 2000–2009 and 2010–2016 were 3.96 (P = 0.034) and 5.39 (P = 0.01) times less concerned about AMR, respectively.

Table 2.4: Cumulative logit model of multivariable analyses of factors associated with clinicians' degree of concern about antimicrobial resistant infections at the University of Tennessee Veterinary Medical Center, 2017.

Variable	Category	OR (95% CI)	*P* Value
Year of graduation from veterinary school	2000 – 2009 vs *1970 – 1999	3.69 (1.104 – 12.33)	0.034
	2010 – 2016 vs *1970 – 1999	5.39 (1.49 – 19. 51)	0.010
	2010 – 2016 vs *2000 – 2009	1.46 (0.44 – 4.87)	0.537
Primary patient load	Food animal vs *Small animal	3.32 (0.64 – 17.25)	0.153
	Equine vs *Small animal	3.9 (0.83 – 18.36)	0.085
	Others† vs *Food animal	1.14 (0.16 – 8.22)	0.894
	Equine vs *Food animal	1.18 (0.15 – 9.44)	0.879
	Equine vs *Others†	1.03 (0.16 – 6.49)	0.977
	Others† vs *Small animal	3.8 (0.91 – 15.80)	0.067

†A combination of mixed animal and exotics; *Reference category.

Discussion

In the present study, we have shown that controlling for UTVMC clinicians' primary patient load, clinicians' concern about AMR decreased among those who graduated after 1999 compared to those that had been in clinical practice for longer. There are two possible explanations for this finding. Firstly, clinicians who graduated from 1970-1999 could have been more experienced and had received greater exposure and awareness about the risks associated with AMR than those who graduated after 1999. Alternatively, the result perhaps reflects an inadequate emphasis on the judicious use of antimicrobial drugs in the veterinary curriculum over the recent years. The latter may be true because teaching of AMR and antimicrobial pharmacology in most veterinary schools has been described as inadequate [3]. In fact, most clinicians in the present study expressed less enthusiasm about the adequacy of training on rational AMU practices received by present day veterinary students. Before a generalized conclusion can be made from the observed results, further evaluation of the tested associations is needed from other veterinary teaching hospitals as well as from primary care veterinary hospitals. In the interim, educational interventions, such as an increased educational emphasis about AMS approaches for veterinary students and continuing professional development for practicing veterinarians aimed at promoting prudent AMU by veterinary clinicians at all levels of clinical experience, would be helpful in modifying prescription behaviors and practices of clinicians. Also, in this study, we found that many clinicians believed their clients were either not concerned about AMR, or were slightly concerned, suggesting a need for more client education on AMR.

The use of bacteriological culture and antimicrobial susceptibility test results, along with other Good Stewardship Practices (GSP), is very important in the practice of evidence-based antimicrobial therapy [3, 18, 29]. Based on predisposition for choice of and source of information for antimicrobial drugs, clinicians in the present study utilized evidence-based approach in their prescription practices. Firstly, 47 clinicians (75.8%) reported results from bacteriological culture and susceptibility tests to be an extremely important factor in deciding their choice of antimicrobial. This is consistent with the findings of other studies, [7, 23] where veterinarians rated bacteriologic culture and antimicrobial susceptibility among the most important factors in clinical decision-making. Next, cultural measures of uncertainty avoidance and wide power distance between the clinician and client/producer may influence antimicrobial prescribing practices [30, 31]. Clinicians with high uncertainty avoidance would probably prescribe antimicrobials in the event of undesirable clinical outcomes. Likewise, fear of litigation by the client/producer could influence the clinician to yield to client's requests on AMU. However, these factors were not identified as major drivers in AMU practice in the present study. Pressure from clients or producers to the clinician to prescribe antimicrobials was not at all important to over 45% of the clinicians in the present study. Similarly, fear of litigation by the client or producer was not an important factor. Evidently, power distance (the extent to which power is distributed between the clinician and the client or producer based on their hierarchical distance in the society) is narrow in the UTVMC. Thus, uncertainty avoidance may not be a very influential factor in prescription decision-making in this hospital. Furthermore, aggressive marketing by pharmaceutical companies is believed to influence clinicians' information about antimicrobials. In a survey of small animal veterinarians in the UK, 331 clinicians (70%) ranked pharmaceutical companies as an important source of information on antimicrobial drugs [32]. However, among the 62 clinicians in the present study, 55% rated pharmaceutical company representatives as "not at all important" but over 56% rated peer-reviewed literature as “extremely important” sources of information for antimicrobial products. A survey at another U.S. veterinary teaching hospital identified peer-reviewed literature as an important source of antimicrobial information utilized by most clinicians in determining their choice of antimicrobial [23]. But, in a survey of all companion animal veterinarians in Australia, 260 clinicians (36%) reported using peer-reviewed literature as a source of information on antimicrobials [33]. Possibly, compared to veterinarians in general care hospitals, those in referral hospitals rely more on peer-reviewed literature for their sources of antimicrobial information. In summary, it is reassuring that clinicians in the present study utilize evidence-based approach in their prescription practices, an attitude that would improve success of an AMS program.

To promote judicious AMU practices, FDA and AVMA developed guidelines for judicious antimicrobials by veterinary clinicians. However, the uptake of these AMU guidelines among the clinicians at UTVMC appears low. Although a few clinicians were either not at all familiar with or never used VCPR, these clinicians had clinical duties that did not directly involve antimicrobial prescription. Nevertheless, this observation does not justify a non-judicious AMU practice. Only six clinicians (9.7%) read very often the FDA/AVMA guidelines for judicious use of antimicrobials while the rest either never read or infrequently read the guidelines. Apparently, little awareness exists among these clinicians about the existing guidelines for judicious use of antimicrobials. A recent survey of U.S. veterinarians [34] found that 218 of 247 (88%) clinicians were unaware of the available guidelines for judicious AMU practices. However, implementation of AMU guidelines led to a significant decrease in antimicrobial prescription rates in some human pediatric emergency departments [35] and compliance with AMU guidelines may have led to a reduction in overall AMU at a veterinary teaching hospital [19]. Therefore, more awareness and compliance is needed about the available

AMU guidelines for veterinary clinicians. Furthermore, only nine clinicians (14.52%) knew that UTVMC does not have an AMS program currently. Others were either uncertain or believed that an AMS program existed. These disparities might be due to variations in knowledge and awareness among clinicians about what constitutes an AMS program, suggesting a need for more training and awareness on AMS and GSP.

Antimicrobial stewardship programs involve multifaceted approaches that aim to sustain the efficacy of antimicrobial drugs, while minimizing the emergence of AMR [18]. Clinician preference for certain antimicrobials is justified in certain situations e.g. based on knowledge of drug toxicity such as aminoglycoside toxicity; when the characteristics of the infecting bacteria at a given infection site are known; when knowledge of the usual susceptibility profile of the suspected pathogens is available; when the cost of treatment is an issue; and when observation of AMU regulations is required [36]. Also, a clinician may prefer a certain antimicrobial when based on his or her judgment, culture and susceptibility testing shows that it is the only treatment option [37]. Frequent use of preferred antimicrobial classes will lead to prolonged exposure of bacteria to these drugs and subsequently select for resistance. In the present study, β-lactams, were the most preferred antimicrobial classes by small animal clinicians. Recent studies of veterinary antimicrobial prescribing practices in the U.S. also showed that β-lactams are the most commonly prescribed antimicrobials by veterinarians [38, 39]. The antimicrobial preference ordering for food animal, equine and other clinicians was not reported because of the few respondents in these categories which did not allow for meaningful analysis. Similarly, our study did not evaluate the preference for specific drugs within an antimicrobial class. Future studies could benefit from evaluating clinicians' preference for specific drugs within antimicrobial classes. Such scrutiny could provide additional details about prudent AMU. Implementation of

AMS strategies [16], such as de-escalation (reduction in the spectrum of antimicrobials used through the discontinuation of antimicrobials or switching to a narrow-spectrum antimicrobial) and antimicrobial cycling (rotational use of two or more antimicrobial classes on a specified time scale) could minimize likely buildup of AMR to the most preferred classes at this hospital. Additionally, non-judicious AMU for surgical prophylaxis may exert selection pressure leading to AMR. In routine surgical practice, antimicrobials may be given prophylactically: pre-operatively, peri-operatively or post-operatively, often based on the judgment of the surgeon. These AMU for surgical prophylaxis is especially important when surgeries are performed either in suboptimal conditions, such as in farm animal practice, [40] or when the surgical procedure is classified as contaminated [41]. Surgical prophylaxis is not recommended for neutering and routine uncomplicated dental procedures [33]. In the present study, most clinicians used antimicrobials for surgical prophylaxis in more than half of their surgical cases. Although we did not ascertain the types of surgical cases for which antimicrobials were used, we contend that an AMS program at this hospital would provide guidance on AMU for surgical prophylaxis. There is a need to develop and implement an AMS program at UTVMC based on the findings of the knowledge gaps or current AMU practice at this hospital. Through training, antimicrobial prescribers are more likely to accept and implement AMS after benefits are evident; this approach reduces their non-judicious AMU practices [3]. In the absence of an AMS program and training programs, AMR challenge could be evident in this hospital. Also, it would be useful to explore the AMU practices among other primary and tertiary veterinary hospitals in the U.S. A nationwide survey would provide details on the feasibilities of reducing AMR burden at a national scale.

A 2004/2005 observational study of Norwegian general medical practitioners found that antimicrobial prescribing rates of physicians significantly increased with increased number of consultations [42]. Findings from this Norwegian study suggested that busy physicians may rely on antimicrobials in presence of diagnostic uncertainty, as the consultation duration may be too short to conduct a proper clinical investigation. At the design of this present study, we had hypothesized that busy veterinary clinicians with less effort allocation to clinical practice and more effort allocation to other non-clinical duties would perhaps play safe by prescribing broad-spectrum antimicrobials as a timesaving strategy in the face of diagnostic uncertainties. However, effort allocation to clinical practice was not significantly correlated with frequency of prescription of antimicrobials at UTVMC. Possibly, the difference in these observations could be from the nature of patients seen or the expertise level of the clinicians. We contend that the findings of this study cannot be extrapolated to first opinion (primary care) veterinary practices because clinicians in primary care may have different AMU practices than those in tertiary hospitals that are mostly comprised of specialists in their fields. An evaluation of the association between effort allocation and frequency of antimicrobial prescription at other veterinary schools and in primary care veterinary hospitals would be useful in providing a better justification for this disparity.

There is a growing perception among veterinarians that non-judicious AMU practices occur in veterinary practice. In this study, 21 clinicians (33.9%) mentioned that antimicrobials were sometimes prescribed based on no documented evidence of infection, while 38 (61.3%) mentioned that antimicrobials were sometimes prescribed for suspected (but not confirmed) infections. A recent retrospective study [22] from a veterinary school showed similar findings: 38% of antimicrobial prescription did not have documented evidence of infection, while 45% of antimicrobial prescriptions at that hospital were for suspected infections. In the present study, 32 clinicians (51.6%) believed that antimicrobials were over-prescribed. Clinicians in another U.S. teaching hospital [23] also held a similar view that antimicrobials were overprescribed. Therefore, it is necessary to conduct a targeted study evaluating actual prescription records in these hospitals to validate or dispute the perceived non-judicious AMU practices.

Communicating the importance of the survey along with sending reminders to respondents through diverse media has been suggested to improve response rates [43]. Response rate in the present study was higher than other surveys among veterinarians in the U.S. and elsewhere [23, 34, 38, 43, 44]. Attending departmental and weekly clinical rounds meetings before the survey as well as sending out weekly email reminders to participants during the survey duration could have contributed to the observed high response rate of 51.2%.

Although bias was not assessed, results of this study could have been influenced by response and or non-response bias. Social desirability bias (which is a form of response bias) and non-response bias can be issues in any survey [45]. Possibly, the clinicians provided answers that they deemed socially acceptable (social desirability bias) rather than their true opinions, perceptions and practices. Alternatively, the survey answers of the respondents could have differed from those of non-respondents. Non-responder analysis was not performed because it would breach the confidentiality and anonymity of the study. Furthermore, results of this study may be more reflective of opinion and perceptions of small animal clinicians than other clinicians because of the over representation of small animal clinicians in the study. However, this observation is a true representation of the clinician demographics in this hospital and could not have been improved by any other method.

Conclusions

After controlling for UTVMC clinicians' primary patient load, clinicians' concern about AMR decreased among those who graduated after 1999 compared to those that have been in clinical practice for longer. Most clinicians utilize evidence-based approach in their choice of antimicrobials but are unaware or underutilize the FDA/AVMA guidelines for judicious use of antimicrobials. Some practices and perceptions are suggestive of non-judicious AMU practices. Therefore, there is a critical need to increase awareness about judicious AMU practices among clinicians, increase emphasis about AMR in the present veterinary curriculum, and implement AMS program in this institution. Educational activities in combination with awareness campaigns and the stewardship programs could be used to improve AMU practices of veterinary clinicians at this hospital. Also, more client education on AMR is needed. Prospectively, evaluation of AMU practices across other veterinary hospitals in the U.S is necessary to provide details on the feasibility of reducing AMR burden at a national scale.

Competing Interests

The authors declare that they have no financial or personal relationships which may have inappropriately influenced them in writing this article.

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CHAPTER 3

Drivers of antimicrobial use practices among Tennessee beef cattle producers

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Abstract

Background

In recent years, there has been an increased awareness of antimicrobial resistance in both animals and humans, which has triggered concerns over non-judicious antimicrobial use. In the United States, antimicrobial use in food-producing animals for growth promotion or improved feed efficiency is perceived as non-judicious. To facilitate judicious antimicrobial use, the United States Food and Drug Administration implemented the Veterinary Feed Directive, effective from January 1, 2017. Interventions, such as the VFD, designed to ensure the judicious use of

antimicrobials among cattle producers may be more effective if the factors that inform and influence producer AMU practices are addressed. The specific objectives of this study were to determine the following among Tennessee beef cattle producers: (1) the most common drivers for using antimicrobials, (2) the perceived alternatives to antimicrobials, (3) the knowledge and perceptions regarding antimicrobial resistance, and (4) the preferred avenues for receiving information on prudent antimicrobial use. A total of 5 focus group meetings with beef producers were conducted in East, Middle, and West Tennessee. Each focus group was video recorded and thematic analysis was performed using NVivo.

Results

The factors that producers considered to drive antimicrobial use were the type of cattle operation, disease and animal welfare, economic factors, veterinarian consultation, producer's experience and peer support, Veterinary Feed Directive, and perceived drug efficacy. Vaccination, proper nutrition, and other good management practices were considered alternatives to antimicrobial use. To encourage vaccine use among small producers, participants suggested packaging vaccines into smaller quantities. Antimicrobial resistance was perceived to be a problem affecting animal and public health. Participants suggested additional education for cattle producers on the prudent use of antimicrobials as a measure for improving antimicrobial use. The veterinarian, producer associations and meetings, and county extension agents emerged as trusted avenues for channeling information on prudent antimicrobial use to cattle producers.

Conclusions

Several factors drive antimicrobial use among cattle producers in Tennessee. Participants generally perceived their antimicrobial use to be discreet and used only when necessary. More awareness of drivers for the development of antimicrobial resistance and continuing education on prudent antimicrobial use is needed for Tennessee beef producers.

Keywords

Qualitative study, focus group discussions, antimicrobial use, antimicrobial resistance, veterinary feed directive, Tennessee-beef cattle producers

Background

In recent years, there has been an increased awareness of antimicrobial resistance (AMR) in both human and veterinary medicine. This increased awareness has triggered concerns over non-judicious antimicrobial use (AMU) in animals, especially due to the perceived risk associated with the zoonotic transfer of resistant pathogens from animals to humans [1]. Although there is currently no robust evidence concerning the impact of AMU in food animals on AMR in human pathogens, some studies suggest evidence of AMR transmission from food animals to humans, while other studies do not support such transmission [2-4]. This lack of strong evidence has led to an on-going controversial debate on the public health impacts of AMU in food animals [2, 5].

Recent studies have shown that indiscriminate use of antimicrobials for both therapeutic and non-therapeutic purposes in animals leads to propagation and shedding of substantial amounts of AMR microorganisms [6, 7]. Furthermore, antimicrobial treatment failure in swine herds was found to be associated with the use of multiple antimicrobial drugs [8]. Despite the controversies around the public health impacts of AMU in animals, it is necessary that judicious practices are widely adopted by all sectors within the animal agriculture food production system in order to prolong the efficacy of current antimicrobial agents [9].

The World Health Organization (WHO) recommended complete restriction of AMU for growth promotion and disease prevention in food-producing animals to preserve the efficacy of medically important antimicrobials [10]. Judicious approaches to AMU in animals have been supported and instituted in many countries based on the precautionary principle [6, 11]. The precautionary principle is a guiding tenet of public health which recommends adoption of preventive measures in the face of uncertainty and exploring various alternatives to potential threats to public health [12].

In the U.S., AMU in food-producing animals for growth promotion or improved feed efficiency is perceived as non-judicious and use for disease management has minimal veterinary oversight due to lack of food animal veterinarians in some areas [13]. To facilitate the judicious use of medically important antimicrobials in food producing animals, the FDA implemented the Veterinary Feed Directive (VFD), effective from January 1, 2017, authorizing the use of medically important antimicrobials in feed and water for therapeutic purposes under the supervision of a licensed veterinarian. Interventions, such as the VFD, designed to ensure the judicious use of antimicrobials among cattle producers may be more effective if the factors that inform and influence producer AMU practices are addressed. Producers consistently base their decisions and actions on a complex system of core values and knowledge. A review by Garfoth suggested that producers do what makes sense to them in the circumstances of their farms, families, and businesses [14]. Behavioral change communication can be effective in educating the farming public about the dangers of non-judicious AMU if the producers' knowledge, attitudes, skills, and aspirations about AMU and AMR are considered [15].

Studies conducted on United Kingdom pig farmers and pig veterinary surgeons identified economic factors, issues surrounding farming systems, management, agricultural factors, and external pressures as key drivers affecting AMU [1, 16]. Among New Zealand dairy producers, veterinary advice and the producer's personal on-farm experience were identified as primary drivers of AMU [15]. However, prior to this study, the drivers of AMU by U.S. cattle producers were not documented. A 2007 quantitative survey of Tennessee (TN) beef cattle producers found that higher AMU was associated with herd size > 50, participation in beef quality assurance or master beef producer certification programs, quarantining of newly purchased animals, use of written instructions to treat disease, and observation of withdrawal times [17]. Nevertheless, this 2007 survey did not use qualitative methods to identify drivers of AMU among beef producers.

The purpose of this study was to identify and document the factors driving AMU, alternatives, knowledge, and perceptions towards AMU among Tennessee beef cattle producers. The specific objectives of this study were to determine the following: (1) the most common drivers for using antimicrobials, (2) the perceived alternatives to antimicrobials, (3) the knowledge and perceptions regarding AMR, and (4) the appropriate avenues for receiving information on prudent AMU. These findings will optimize the efforts of targeted campaigns to apply nationwide stewardship of AMU. These efforts could, in the long run, lead to responsible AMU and the reduction in selection pressures from non-judicious use that drive AMR.

Materials and methods

Focus group design, structure, and procedure

We conducted a total of five beef producer focus groups in East TN, Middle TN, and West TN in June 2017. Overall, 39 producers participated in the focus group discussions. These regions were chosen based on the demographic density of the Tennessee beef cattle population [18]. For recruitment, the leadership of the Tennessee Cattlemen's Association (TCA) invited members (via e-mail) with experience in different cattle production systems and from different geographical areas to represent a range of beef producers in TN. All the four authors attended each focus group. Each focus group comprised of 5 - 9 producers (participants) recruited from a purposive sampling technique and lasted approximately 90 minutes. An informed consent form giving an overview of the study was provided to all participants, and a signed consent was obtained before their participation in the focus group discussion. Participants could opt out of the discussion at any time, and a meal was provided to each participant as an incentive.

A semi-structured interview guide which was modified after the first focus group was utilized (see appendix 2). The modified interview guide (appendix 2B) consisted of 11 open-ended questions. To maintain anonymity, each participant was assigned an identity number, which was used throughout the discussion. Participants announced these numbers before speaking and were identified by these numbers for any follow-up questions. All the focus group discussions were moderated by one of the researchers (EBS) with a background in the behavioral sciences. As described previously, the moderator's role and responsibility was to give guidance to the discussion and to allow free discussion to develop, while ensuring that all areas in the topic guide were addressed [19, 20]. Three members of the research team (JEE, MC, and CCO) took hand written notes of any key points, provided clarifications to questions, and asked follow-up questions when necessary. At the end of each focus group meeting and before the next focus group discussion, the research team held a debriefing session to allow for discussion of emerging themes and for comparison between focus groups [21]. Data saturation was reached during the fifth focus group discussion. These video-recorded focus group discussions were held either at local restaurants or at county extension centers. Recorded video from each focus group was transcribed verbatim by a professional transcription service provider for thematic analysis.

Data analysis

The transcribed discussions were analyzed using data analysis software (NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 11, 2017). A recursive six-phase approach (familiarization with the data, generation of initial codes, search for themes, review of themes, definition and naming of themes, and report production) to thematic analysis was performed as described previously [22]. In a brief description of the recursive approach, each member of the team read all transcripts from the focus groups to be familiarized with the data. To visualize patterns in the data, the primary author (JEE) performed a cluster analysis (in NVivo) by grouping focus groups that shared similar words. Jaccard's coefficient, a statistic that measures similarity between groups by determining the percent of word similarity between groups, was used to assess the degree of similarity for each pair of focus groups. The primary author (JEE) developed a master project with initial nodes identified through consensus at the debriefing meetings and distributed the same to the other authors for individual coding. During the thematic analysis, each author was at liberty to use either the already prescribed coding frame in the master project (theoretical/deductive approach) or to create new nodes independent of the prescribed coding frame (the inductive approach). Thus, each author either added nodes to the master themes or created new themes. After the individual coding, the primary author (JEE) imported the other team members' coded data into the master project and checked if the themes from the individual coding were related to the coded extracts and all the data transcripts.

To ascertain the degree of agreement in the data coding, inter-rater reliability testing was performed in NVivo using percent agreement (JEE, MC, EBS, and CCO). The entire team met twice to review and harmonize the results of the independent coding. Disagreements at the first review and harmonization meeting related to definition and naming of themes were resolved at the second review and harmonization meeting. These themes were refined to identify sub-themes and to ensure that each theme is meaningful and clear but distinct from other themes [16]. Sub-themes that were linked by a common subject area or which related to an overall topic were grouped together, given a unique theme title, and considered as major themes. A thematic map was constructed to review the relationships between minor themes and major themes.

Results

Focus group participant characteristics

A total of 39 beef producers, 1 female and 38 male, from a wide range of beef cattle production systems in Tennessee participated in the 5 focus groups. Participants' perceived ages ranged from late twenties to early seventies. The reported herd size per producer ranged from approximately 20 to 225 cattle (**Table 3.1**).

The degree of similarity between focus group pairs (Jaccard's similarity index) ranged from 27% to 33%. This Jaccard's similarity index showed there was diversity among participants in the different focus groups. Percent agreement (in coding) between each pair of coders was >75 %.

Objective 1: Drivers of antimicrobial use practices

The major themes identified as drivers of AMU were: a) type of operation; b) disease and animal welfare; c) economic factors; d) veterinarian consultation; e) producer's experience and peer support; f) VFD; e) perceived drug efficacy (**Figure 3.1)**. A detailed presentation of these factors accompanied by excerpts from the focus group transcripts is given below.

Table 3.1: Focus group participant characteristics

Focus group	Geographic region (location)	Number of participants (n)	Herd size range	Gender of participants	Cattle operation type (number of participants)
1	Johnson City, East Tennessee	9	40 - 80	All male	Cow-calf operation (n = 2)
					Cow-calf and backgrounding (n = 2)
					Stocker (n = 2)
					Backgrounding and finishing (n = 1)
					Cow-calf and stocker operation (n = 2)
2	Dickson county, middle Tennessee	9	40 - 135	All male	Cow-calf producer (n = 3)
					Cow-calf producer and commercial stocker (n = 1)
					Seed stock producer (n = 1)
					Stocker (n = 1)
					Brood cow producer (n = 1)
					Seed-stock and brood cow producer (n = 1)
					Seed-stock and replacement bull, heifers (n =1)
3	McNairy county, west Tennessee	8	30 - 200	All male	Black angus operation (n = 1)
					Angus seed-stock operation (n = 2)
					Seed stock operation (n = 2)
					Cow-calf operation (n = 2)
					Cow-calf operation and angus seed stock (n = 1)
4	Jefferson county, East Tennessee	8	20 - 200	All male	Cow-calf operation (n = 6)
					Stocker (n = 1)
					Cow-calf and backgrounding operation (n = 1)
5	Athens, McMinn county, East Tennessee	5	30 - 225	Male	Cow-calf (n = 2)
					Cow-calf and backgrounding operation (n = 1
					Brood cow and backgrounding operation (n = 1)
				Female	Cow-calf and backgrounding (n = 1)

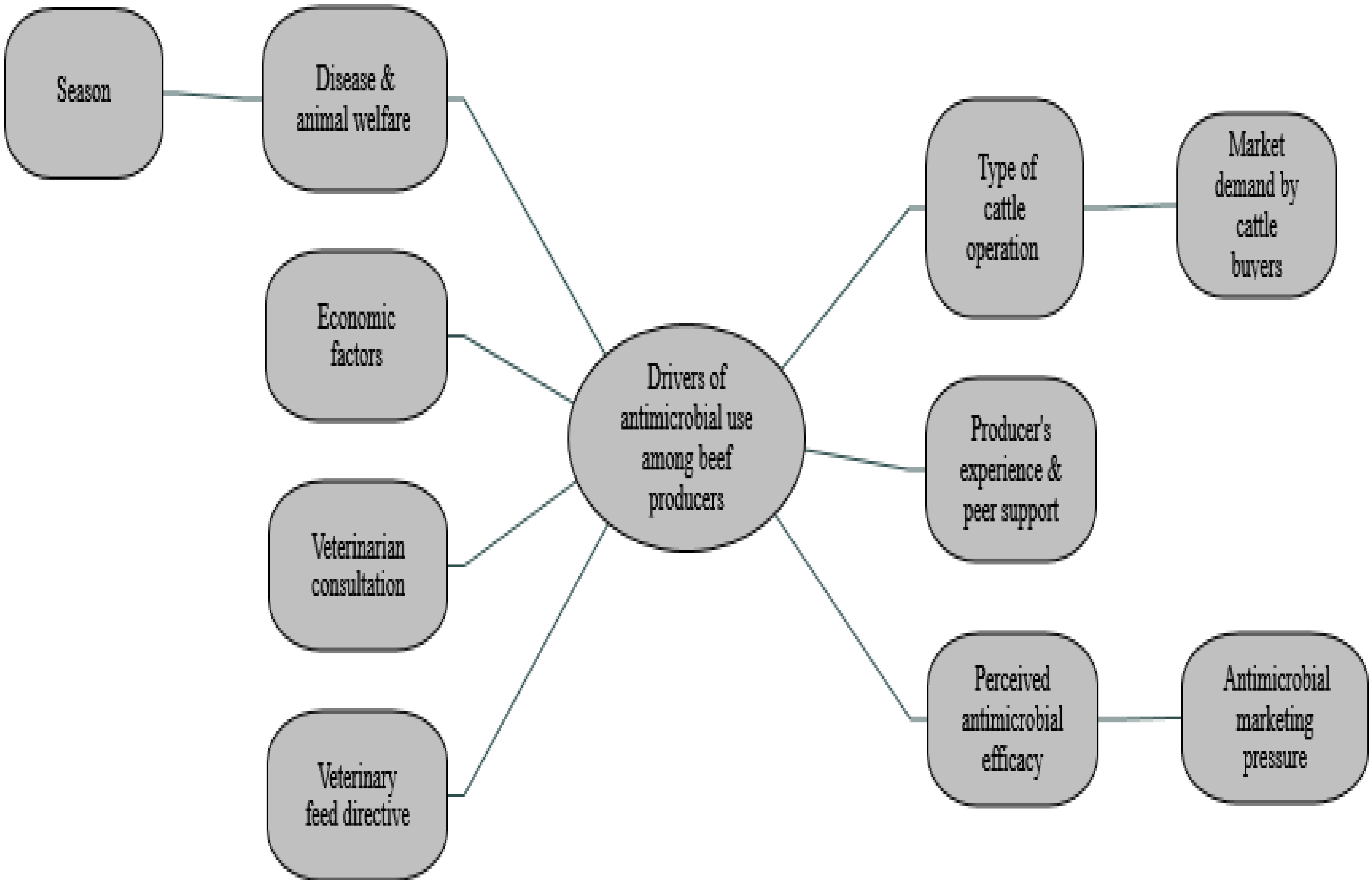

Figure 3.1: A thematic map showing drivers of antimicrobial use among beef producers in Tennessee, 2017.

1a. Type of cattle operation (management factors)

The type of operation was associated with the degree of AMU. Stocker cattle operations use more antimicrobials due to stress and potential sickness associated with stocker operations compared to cow-calf operations. Additionally, compared to producers with open herds, those with closed herds require and use less antimicrobials in their operations.

> *…a lot of the cattle that we see not just in this county but surrounding counties, 85 to 90 percent of the cattle are mismanaged cattle. So, if it was left up to the mamma cow, cow-calf operators to take better care and management of their cattle, it would help No. 2 and No. 9's larger backgrounder or stocker operators, not just on antibiotic cost but health and letting them turn cattle over faster to ship or do whatever… [No. 1, focus group 1]. …And with the stocker cattle, used a lot more antibiotics because the cattle required it because of the stress and potential sickness and a lot of the diseases that we go through the cattle…But with the cow-calf operation, unless it's warranted by some medical condition, they don't get it… [No. 3, focus group 4].*

1ai: Market demand by cattle buyers: Along with the routine use of antimicrobials associated with a specific type of cattle operation, consumer requests encourage increased AMU. Some buyers request that cattle breeders treat their cattle with antimicrobial drugs prior to shipping. This prophylactic treatment is aimed at reducing the risk of infection during transit from the breeder to the buyer.

> *…we bring in cattle – I would say quite weekly but almost biweekly from other places. And we sell across the country and ship stuff out. Antibiotics is second nature to us. We have to have that. A lot of people out in California we sell cattle to, they mainly buy young calf and resell it. They want that calf to have draxxin before it gets on the truck,*

because they don't know how long it's gonna take to get them from our ranch in Tennessee to California. They might stop at ten other ranches to water and this and that. And they want a shot of draxxin just for those ten days so that calf don't pick up anything or get sick on day three and have a seven-day haul to get to where they're going. I agree with a closed herd, which with my operation, we can't do that… [No. 8, focus group 3].

1b. Disease and animal welfare

In order to maintain the welfare of their cattle, producers tend to use antimicrobials for disease management in their herds. The presence of early signs of disease was considered to commence AMU because producers feel they have a responsibility to protect the lives of cattle under their care.

…We use it as needed sometimes – foot problems. They can step on something, stab or a thorn or something in their foot. And we use antibiotics for that. If a calf in the wintertime acts like he's getting pneumonia or something like that, we see the early signs – whether it be a cow, calf or whatever, we give that… [No. 7, focus group 2].

…If I see early symptoms, I'll treat early and try to head things off rather than let it get full blown, otherwise, it's grass and hay, protein and mineral… [No. 3, focus group 2].

…As far as what's important when deciding to use the antibiotics, they key factor comes down to economics and the animal welfare. I think cattlemen are very strong proponents of animal welfare because if the animal is not being treated properly or is not healthy, we're not making money off of them. And that's what we have to make sure of at the end of the day… [No. 3, focus group 4].

1bi: Season: Antimicrobial use for disease management tends be influenced by season (weather/climate). Wintertime use of antimicrobials was mentioned in focus group 1 for the management of interdigital phlegmon and focus group 2 in suspected cases of respiratory disease. However, participants from focus group 4 stated that antimicrobials were mainly required from spring through fall for the management of anaplasmosis and infectious bovine keratoconjunctivitis.

> *…. Antibiotics depends on the weather. Spring or whether it's fall …. have an issue where you need some antibiotics… [No. 8, focus group 4].*
>
> *…I do use some feed grain antibiotics when I have train wrecks … in September and October. You are going to have some sick cows during what we call dead-cow month October/November… Occasionally, there's some feed through antibiotics that goes through those wrecks… [No. 2, focus group 4].*

1c. Economic factors

The need to obtain economical gain from a healthy herd was an important driver of AMU among producers. The producers frequently stated that they use antimicrobials to maintain a healthy and productive herd for sustainable economic gain. They were defensive and frequently asserted that antimicrobials are only used when necessary and not indiscriminately, as perceived by policy makers, consumers, and the public.

> *… I think it comes down once again to economics…that economic threshold... But as a producer, you have to look at it from an economic standpoint is it worth it to give the antibiotic? Is it worth it to pay the vet bill at this point? Or am I going to try something that's worked in the past?... [No. 3, focus group 4].*

1d. Veterinarian consultation

Although access to emergency veterinary care was mentioned to be difficult in some areas, a section of participants from areas with active food animal veterinarians (McMinn county, Jefferson county) considered veterinarian consultation an important influencer of AMU. Producers with a good relationship with their veterinarians consulted them on AMU issues.

> *…. I just work close with my veterinarian. He goes off label or whatever you're trying to treat at the time. I just stay with that…. [No. 6, focus group 5].*
>
> *…I'll say consultation with a veterinarian is one factor… [No. 3, focus group 4].*

However, for those with limited access to food animal veterinarians, veterinarian consultation was not an influencer of AMU.

> *…We don't have a veterinarian we regularly work with. What [we do] is just visual appraisal if we have sick animals… [No. 7, focus group 4].*

Some producers in East TN, Middle TN, and West TN decried the lack of food animal veterinarians in their areas.

> *… [It is] more difficult [to access a food animal veterinarian] than it was a few years ago. Most of them [veterinarians] going to be cat and dog vets. They won't treat the cattle... [No. 6, focus group 2].*

1e. Producer's experience and peer support

The participants frequently stated that they rely on their own experience, knowledge, and judgment when deciding to use antimicrobials in their cattle and tapped into the AMU experiences of their peers (other producers). However, in situations that are difficult to handle, they consult the veterinarians. There was a shared belief among participants that peers are easy to access given that some areas do not have food animal veterinarians.

> *…I think for most of us, we're relying on our own experience and our own knowledge. If it's something that I've seen before and I know how to treat it, I'm going to treat it like I*

treated it before…whatever has been successful. If it happens to be something that I have a question about, I can text one of the vets I was talking about… [No. 4, focus group 2].

…. experience and not necessarily my experience but experience of producers that've done the same thing I'm doing a lot longer than I have. I find a lot of times they know – nothing against the veterinarians, the producers deal with this every day. In a lot of cases, they know more about it than the veterinarian does and will offer some more solid advice of what to use, when to use it, that kind of thing but still consulting with the veterinarian in doing the right thing… [No. 3, focus group 4].

…What I pick up on is when I start having wrecks, I just pick up the phone and call somebody else who does the same thing…He's doing the same thing I'm doing week in and week out…You get on the phone. You start calling. Hey, what's working? What medicine are you using?... [No. 2, focus group 1].

1e. Veterinary Feed Directive

Throughout all the focus groups, it was common for participants to state that the restriction of in-feed antimicrobial products at sub-therapeutic concentrations and for prophylactic indications by way of the VFD has led to increased occurrence of disease in herds and increased mortalities. Examples of those diseases are infectious bovine keratoconjunctivitis, anaplasmosis, and interdigital phlegmon in calves.

…There is increase in injectable because we're having a lot more pinkeye, a lot more foot rot. Even in our weaned calves this year, we have foot rot we never had before, never... [No. 3, focus group 5].

1g. Perceived drug efficacy

Antimicrobials perceived to be more efficacious are often chosen in preference to those perceived to be less efficacious. In the event of treatment failure, producers switch from apparently less effective antimicrobial to a "more effective" one sometimes based on their own observation or on the advice of a veterinarian or their peer group.

> *…And the medicines – I don't know about anybody else, but I've used every medicine that's new and old and come out. And the truth of the matter is one week this might work. The next week, this one don't work. We have a veterinarian come through all the time that wants you to switch. ... Sometimes when you switch, it's a disaster. I've used everything that's come out… To me it seems like the medicines aren't strong enough, if anything. They're not working. We had Draxxin come out a few years ago. I mean, it worked great. Now you just as well shoot farm water at them with a dart gun. That's what we found out. They just wouldn't respond to it.… [No. 2, focus group 1].*

1gi: Marketing pressure from veterinary pharmaceutical companies: Marketing from drug companies tend to shape producers' perception of antimicrobial efficacy, as well as antimicrobial choice. Producers expressed the marketing techniques to be persuasive and aggressive.

> *…I don't know about anybody else here, but there's nothing no worse than to look up a driveway and see the Pfizer man coming up the driveway. If they're like me, they go try to hide because it's gonna drive you crazy. Their product's always the best and always this and always that. Most of the time, we wanna get it done. We wanna feed. We wanna make sure the cattle's healthy... [No. 2, focus group 1].*

Objective 2: Alternatives to antimicrobials

The commonly mentioned alternatives to antimicrobials used by focus group participants generally included proper animal nutrition, use of good management practices, use of vaccines, and immunostimulants. The excerpts that support these alternatives are provided below.

2a. Proper animal nutrition

Maintaining cattle on good ration, good pasture, and clean fresh water were suggested as prerequisites to a healthy productive animal. Adequate mineral and vitamin supplementation was also considered important in raising healthy animals to abrogate the need antimicrobials.

…We use good minerals, good feed… [No. 5, focus group 5].

…You've got to keep your cattle in a good body score. They can't be too fat, definitely not too skinny. It's just like No. 7 said, we have good grass, good mineral program and a good vaccination program – not antibiotics, your viral vaccines… [No. 3, focus group 5].

2b. Good management practices

Good management practices, such as on-farm biosecurity/infection control programs, vector control (tick control), rotational grazing, proper sanitation and hygiene, stress management, provision of good cow comfort through proper housing, and routine deworming of the herd, were suggested as preventive measures to limit AMU. Participants who maintained closed herd operation types stated that a closed herd operation system helped them in preventing disease introduction from other farms and minimized AMU on their farms. However, those with open herds practice isolation of newly introduced animals from other farms to prevent disease introduction and minimize the need for AMU.

…You do everything management wise to prevent the need for it [need for antimicrobials], whether it be sanitation, nutrition, daily removal of stress from the

animal's life – in your case, trying to keep out infectors from them. We do everything within our power management wise. And it's a whole program, not just one step… [No.7, focus group 3].

… We don't have a closed herd. Definitely, [we] see the benefits to a closed herd… And we're doing that in picking new animals along the way. …We isolate a period of time and vaccinate as soon as we get those animals to see if we'll have any disease and sickness and keep that from being a threat to rest of the herd… [No. 5, focus group 4].

2c. Vaccination and immunostimulants

Vaccination and use of immunostimulants, such as zelnate®, were frequently mentioned as alternatives to AMU. Also, immunostimulants are used to boost the animals' immune response to infection.

…we use vaccines … [No. 5, focus group 5].

…we have good grass, good mineral program, and a good vaccination program – not antibiotics, your viral vaccines… [No. 3, focus group 5].

…And to go along with vaccinations, the cattle have to be prepared to respond to those vaccines. You can't give vaccines to sick calves or calves that are not prepared to respond and expect them to respond because it won't work… [No. 4, focus group 2].

… We put ours on a good health protocol. They're run through… twice a year for vaccines, worming … You've got to have a healthy animal for your vaccines to work. If you don't have a healthy animal to start with, they're not going to work… [No. 6, focus group 2].

Objective 3: Knowledge of AMR and perceptions regarding AMR

Generally, many participants were well informed regarding AMR and perceived it to be a threat to both animal and public health. Participants suggested several measures for containing AMR. A detailed presentation of participants' knowledge of and perceptions regarding AMR is given below.

3a. Knowledge of AMR

Although many participants had a fair understanding of AMR, it was clear from the discussions that some were uninformed regarding AMR. Some participants associated AMR with prolonged use of the same antimicrobials in the farm. A section of producers believed AMR in cattle pathogens does not exist.

> *…Has anybody seen when you give them some antibiotic and they don't respond? Most of them respond. So, they're not resistant to it… I think most people here are not convinced that there is animal antibiotic resistance …. I do believe there's human just because of the abuse of antibiotics… [No. 3, focus group 5].*

3b. Perceptions regarding AMR emergence

A section of participants perceived AMR emergence to be a problem challenging animal and public health. It was voiced that AMR could be occurring in Tennessee cattle pathogens.

> *…Unless the medicines are changed, then my opinion the bugs or whatever you want to use as a scientific name, are getting resistant because it's not doing the same thing. I can't tell you that [because] I don't know if they're weakening the medicine… [No. 2, focus group 1].*

The role played by AMU in livestock on the emergence of AMR was generally disputed by participants. Although some producers thought that other producers could be indiscriminately using antimicrobials and contributing to selection pressure associated with non-prudent use, the focus group participants generally perceived their AMU practices to be prudent. Concerns about over-use in cattle production were generally regarded as unfounded and not evidence-based.

…Use the same antibiotic for everything – some [cattle producers] do that. They've only got one bottle, they'll just give them a dose it… [Unidentified participant, focus group 5].

…As mentioned [we use antimicrobials only as needed], just as needed to treat animals that – whether it's his foot or respiratory illness or cow or calf needs, something like that but only as needed and usually the least potent thing to do the job… [No. 4, focus group 2.

Participants frequently mentioned non-judicious use of antimicrobials in human health (and not in livestock) as the key driver of AMR in pathogens affecting humans.

… There's been misuse on the human side… [No. 7, focus group 4]. …the humans are taking a lot more than the cattle are taking… [No. 2, focus group 2].

…I think they take in what has happened in the human side and try to say that's happening in the beef side, and it's not. The human side, ya know, I got a sniffle. I go get a shot. They give me a Z-Pack. And we don't do the animals like that. They don't get five rounds of antibiotics a year like some people do… [No. 3, focus group 5].

3c. Proposed solutions to AMR

The focus group participants suggested a wide range of measures for containing AMR. A brief description of measures suggested by the participants is given below.

3c. i Restricted use of medically important antimicrobials

Restriction of the use of medically important antimicrobials in food animals was strongly supported and was perceived to be an important measure for prolonging the efficacy of medically/critically important antimicrobials. Participants suggested that medically important antimicrobials should be reserved for use in humans.

…I'm pretty concerned about the superbugs you hear about in hospitals and the new bugs that are out there that don't respond to any antibiotic. I think it's a pretty big concern for all of us how we're going to treat some of this in the future. I think there are some common sense approaches we can take, especially some of the types of antibiotics we use that are not necessarily used on the human side. I hope we can identify those and not just restrict all antibiotics because I think there are some that are important to us that aren't used on the human side… [No. 7, focus group 4].

… I think avoiding medically important antibiotics for humans in animal production as much as possible [is important]. [We should] use those antibiotics that are not used for human medicine as much as we can … [No. 3, focus group 4].

3c. ii Use of sound research

More investment in research on AMR and AMU by federal agencies and development of novel antimicrobial drugs by the pharmaceutical industry was suggested. Additionally, it was suggested that scientific evidence of the link between AMU in livestock and development of AMR in animal and human pathogens should be provided to producers. Such evidence whether pictorial or in video format would trigger behavioral change towards maintenance and adoption of prudent AMU by producers. It was suggested that wide consultations with producers before enacting and implementing policies on AMU in animal production would be useful for wider acceptance of such policies.

… As far as the results that they get from the research that they do on the certain antibiotic, show the results. They say this does this. This does that. Where's the proof?

Show it to us. Show the farmer what it's doing. Give us the proof. Let us know what it's doing. Show us pictures. Show us what to do… [Unidentified participant, focus group 5].

3c. iii Additional education of producers

Additional education of cattle producers on prudent AMU was frequently suggested by participants to improve AMU in cattle production so that selection pressure from non-judicious use can be reduced. Areas in which additional education for producers is needed include proper management of cattle, farm-level biosecurity to prevent disease, use of antimicrobial cycling/rotation in farms, and encouraging producers to always consult the veterinarians on AMU.

… I believe education [on AMU] is the key to it all… [No. 6, focus group 3].

…Well, I think it would be a good thing to teach us on it [antimicrobial use]. And we'll use that [the acquired knowledge] for our background and start our program… [No. 8, focus group 4].

3c. iv Promoting vaccination of animals

The need to promote vaccine use among producers for those diseases that are vaccine-preventable was frequently mentioned as a measure for reducing AMU and minimizing AMR selection pressure. Packaging of vaccines into smaller quantities was suggested to cater for producers with small herd sizes because the currently available livestock vaccines are mainly packaged in large quantities. Such large quantities that may be ultimately wasted are perceived to deter small scale producers from using vaccines.

… I think we could accomplish a lot with proper vaccination programs in the southeast. In Tennessee, we have a lot of part-time producers that just don't know or it's not that

important to them to have the proper vaccine protocols. And that's what leads to the need for all the antibiotics at the doctoring background… [No. 7, focus group 4]

… there's so many producers that …they're not gonna break into a box that says ten doses to vaccinate three calves. That's throwing seven doses away. I'm just not gonna do it. I don't know if we can break this down into smaller doses or something just to get these products[to] more smaller producer[s] … [No. 5, focus group 1].

3c. v Simplified antimicrobial labeling

The current antimicrobial labels and information on the antimicrobial package inserts were perceived to be very technical for producers to comprehend. Thus, participants suggested that antimicrobial drug labels and information in the antimicrobial package insert should be written in non-technical language to make such information easy for producers to comprehend.

…. Sometimes you read those drug labels. I'm not a chemist or biochemist. But maybe get the veterinary college to simulate the information down to a working level …. [No. 6, focus group 5].

... I deal with people every day that try to read those labels and can't understand them – too many big words. I think if they would speak in plain language, say this is for shipping fever, pneumonia, or what this specifically does. That would be a help for people… [No. 5, focus group 5].

3c.vi Miscellaneous measures

Other measures suggested for reducing AMU and containing AMR include the promotion of infection control and biosecurity measures; discouragement of veterinary pharmaceutical companies from aggressive marketing of antimicrobial products; training more food animal veterinarians; training para-professionals, such as veterinary technicians; and incentivizing the producers through subsidies so as to encourage wider adoption of use of vaccines and alternatives to antimicrobials.

> *…Start at the top with the drug producers…. I would ask them to not be marketing at such an aggressive level as to prevention, cure, et cetera, et cetera … [No. 3, focus group 2].*

> *…. encouraging people to use vaccines. I think the best encouragement is if you hit them in the pocketbook. When everything's bringing the same price, whether it's vaccinated or unvaccinated, there's no motivation for producers to vaccinate. But if there's some price differentiation, people will spend the $5.00 to vaccinate. We have to make it justified economically, once again… [No. 3, focus group 4].*

Objective 4: Avenues for receiving information on prudent AMU

Avenues for reaching out to producers on prudent AMU vary by producer's age as well as the geographical region. Although no one medium for receiving information on prudent AMU would work for all producers, the following were identified as viable avenues: email, farm magazines, feed sales persons, peers/other producers, producer meetings, the veterinarian, county extension agents, photographs, videos, and hard copies mailed to their mail boxes.

> *…I love Internet. But I also love hardcopy [as source of information] because [if] I get a magazine, and I won't read it. I'll stick it back in the bookcase. Something might come up, and I'll read it through it and be an article from two years ago. And I can go back and kinda research. I kinda like it both ways… [No. 4, focus group 3].*

However, the veterinarian (for areas with food animal vets), producer associations/meetings, and county extension agents were commonly mentioned as trusted avenues for channeling information on prudent AMU to cattle producers.

… if there's information, I want it from a trusted source and not from somebody that I don't know or somebody just trying to sell something. I trust my vet and other producers who have used products or may know more than I know about it.... [No. 4, focus group 2].

Discussion

A deep understanding of factors influencing producers' decision-making, their beliefs, attitudes, and perceptions is needed as a basis for building effective interventions [14]. Hence, identifying producers' current behavior towards AMU is a critical step towards achieving success in policy interventions that promote judicious AMU among cattle producers. This qualitative study provides a detailed understanding of drivers of AMU among beef cattle producers in TN. Additionally, this study identified the producers' alternatives to antimicrobials, their perceptions regarding AMR, and the appropriate avenues for disseminating information on prudent AMU to these producers. These findings should aid in shaping and optimizing interventions that seek to promote and improve judicious AMU in TN and the entire US. The impact of such interventions on AMU could then be validated when measuring AMU both qualitatively and quantitatively.

Our study shows that the factors driving AMU among beef producers in TN are numerous and in conformity with those identified in other studies elsewhere [1, 23]. Occurrence of disease at farm level, cost-benefit analysis of the treatment of disease, producer's expertise and experience, and producers attitude towards risk, among other factors, have previously been identified as drivers of AMU [23]. Previous European studies have demonstrated that economic factors drive farmers' AMU [1]. Among dairy cattle producers in New Zealand and dairy producers in South Carolina, owner's experience was an important driver of AMU [15, 24]. The

OIE prudent use guidelines discourages the veterinary pharmaceutical industry from directly advertising antimicrobials to food-animal producers [25]. In the present study, producers perceived the veterinary antimicrobial marketing techniques to be persuasive and aggressive. Aggressive marketing of antimicrobials is a known driver of AMU that has led to calls for banning pharmaceutical industry and drug retailers from advertising antimicrobials [26]. Several findings of our study are in keeping with findings of these previous studies.

The VFD was identified as a key factor that is driving increased use of injectable antimicrobial agents by producers and decreased use of in-feed antimicrobials, since it became effective on January 1, 2017. This is an important finding that needs to be further validated. It is necessary to conduct a targeted country-wide evaluation of the impact of the VFD on the use of injectable antimicrobials in the US. In Denmark, where the use of antimicrobials for growth promotion (AGP) has been banned, the reported impacts of the ban are conflicting. In one study, the ban reportedly led to a reduced total AMU and increased therapeutic use of antimicrobials due to significant increase in health problems in Danish pigs [27]. However, in another study [28] that evaluated changes in AMU and productivity in the Danish pig industry, long term swine productivity was not affected by the ban on AGP use.

Optimal housing and hygiene practices, climate control, feed, and water quality are known to be prerequisites for reduction of AMU in farm animals [29]. In the present study, there was strong appreciation of good management practices and vaccination as alternative approaches to reduce AMU. The WHO action plan to combat AMR has identified vaccination as an alternative to AMU and part of the solution to AMR [30]. The producers' suggestion for promotion of vaccinations as an alternative to antimicrobials is in line with the WHO action plan to combat AMR. Use of vaccines eliminates the need for antimicrobial therapy and indirectly combats AMR, reducing AMU through indirect protection provided by herd immunity [31]. Countries, such as Denmark, have already taken steps to promote the use of vaccines and to discourage use of antimicrobials, especially critically important antimicrobials (CIAs). Denmark, since 2013, is applying differentiated taxes (0% on vaccines, 0.8% on narrow-spectrum penicillins and other veterinary medicines, 5.5% on other veterinary antimicrobials, and 10.8% on CIAs) on antimicrobials to promote the use of vaccines by farmers [23, 32]. The participants in this study suggested that vaccines should be packaged in smaller quantities to encourage small producers to use vaccines, and incentives should be provided to farmers to encourage the adoption of alternatives to antimicrobials. Further evaluation of the potential benefits of these suggestions would be useful in providing a better justification for their adoption.

A previous study suggested that farmers should be provided with clear evidence of the consequences of non-judicious use of veterinary antimicrobials and the need to reduce AMU [33]. Dissemination of existing knowledge to producers about best practices to reduce AMU while at the same time not compromising animal health and production has been suggested to convince producers of the feasibility of production with less AMU [33]. In the present study, the participants suggested that producers should be provided with scientific evidence that shows how the use of AMU in food animals contributes to AMR. Although many participants had a fair understanding of AMR, others appeared not to be conversant with AMR, with some participants stating that such resistance in cattle pathogens did not exist. These findings suggest a need for more awareness among producers of what constitutes and drives the development of AMR. If producers don’t believe there is AMR in veterinary pathogens, then they are likely to maintain those practices that would select for resistance.

The WHO has suggested restriction of critically important antimicrobials for use in food animals [34]. In this study, some participants were positive about restriction of medically important antimicrobials for use only in humans and suggested that such restriction will be significant in preserving the efficacy of medically important antimicrobials. With more awareness, cattle producers are likely to embrace such AMU restrictions as recommended by WHO.

The participants in this study called for more sound research and development of new antimicrobials. This suggestion echoes well with calls by various actors for industry to develop novel antimicrobials [30, 35]. The participants suggested antimicrobial drug labelling should be made easy for producers to comprehend and should be written in non-technical language. This is an important suggestion that needs to be considered by pharmaceutical companies. In the day-to-day running of farms, it is the farmers themselves and their farm staff who make ultimate diagnostic and antimicrobial treatment decisions for their animals, sometimes under veterinarians' guidance [15]. The authors contend that simplified drug labels (with non-technical language) might actually reduce the complexity that would cause inaccurate dosage determination by producers. Accurate dosage determination is important for prudent use.

In a UK study, farmers perceived themselves as prudent antimicrobial users [1]. In our study, participants generally perceived their use of antimicrobials to be prudent (responsible and within sound reason) and concerns about antimicrobial misuse/over-use in cattle production to be unfounded and not evidence-based. Such perceptions could likely hinder behavioral change towards prudent AMU. Behavioral change communication to educate the farming public about the dangers of uncontrolled AMU would likely be a challenge, since most producers perceive their practices to prudent. Researchers in Europe found that when producers do not see the need to change behavior, long-established on-farm practices are difficult to change [36]. Possibly, quantification of on-farm AMU and benchmarking (comparing a farm's AMU practices against the practices in one or more peer farms with the objective of identifying the best AMU practices for improved use) best practices could cause producers to critically reflect on their current AMU practices. Nevertheless, campaign efforts targeting behavioral change on AMU among TN producers should focus on encouraging producers to continue benchmarking AMU practices from peers.

In the present study, the veterinarian (for areas with food animal vets), producer associations/meetings, and county extension agents emerged as trusted avenues for channeling information on prudent AMU to cattle producers. In the Netherlands, administration of veterinary antimicrobials restricted to veterinarians only and farmers are only permitted to administer antimicrobials to their animals in specified cases without the physical intervention of the veterinarian [37]. However in the U.S., most antimicrobial treatments in farms are administered by non-technical farm personnel (producers and farm employees) [38, 39]. In the present study, veterinarian's prescription was an important driver of AMU only in areas with active food animal veterinarians and training of more food animal veterinarians was suggested due to the shortage of food animal veterinarians in the U.S. Some producers in East TN (Johnson City focus group) and Middle TN (Dickson County focus group) decried the lack of food animal veterinarians in their areas. This lack of food animal veterinarians in some counties in Tennessee could be a key barrier to judicious use of antimicrobials. Also, training of veterinary nurse practitioners and para-veterinarians was suggested to fill the gap of lacking food animal veterinarians. More access to food animal veterinarians could play a key role in stimulating change towards prudent AMU among producers. Although encouraging behavioral change among producers is necessary intervention for promoting prudent AMU and managing AMR, the lack of food animal veterinarians in some counties make it difficult to implement this intervention. Training of food animal para-professionals and licensed veterinary technicians might be worth exploring (although it might emerge as a contentious issue in the veterinary community).

In human medicine, integration of behavioral change messages into routine health care has been suggested as a measure for improving AMU practices [21]. Because the veterinarians, producer associations/meetings, and county extension agents are the trusted avenues for reaching out to producers, targeted behavioral change messages towards prudent AMU could be integrated into routine farm visits and veterinary/agricultural extension programs. The use of behavioral techniques such as motivational interviewing informed by assessing producers' readiness for change could be useful [40]. Producer meetings/associations could be used to identify AMU training needs and raise more awareness about AMR and prudent AMU among producers. European researchers suggested that AMU behavioral change among producers can be realized if farmers are offered a sense of ownership of the recommendations for judicious AMU [41]. It would be beneficial to conduct studies exploring objectified, reproducible, and transparent methods for quantifying on-farm AMU in the U.S., since such measures could create awareness and stimulate behavioral change towards prudent AMU.

Like any other focus group study, our findings may have been biased by the presence of dominant participants, such that the results may reflect the opinions of the dominant participants, rather than that of the group. However, such bias was minimized by having a moderator in the research team with a behavioral/social science background, skilled in moderating such meetings. Selection bias resulting from purposive sampling may also inevitably be an issue. However, purposive sampling of participants allowed for inclusion of beef producers with experience in different beef cattle production systems and from different geographical areas to represent a range of beef cattle producers in TN. Cluster analysis of the focus groups (Jaccard's similarity index, ranging from 27% to 33%) suggested that there was great diversity of opinions among participants in the different focus groups. The issue of AMU in farm animals is emotive given the current debate in the media that is shaping the public/consumer perceptions of AMU in food producing animals. Because producers are aware of concerns about non-judicious AMU in animal production, social desirability bias could also be an issue in this study. The producers might have given socially desirable responses. To assess how the factors identified in this study represent the opinions of all beef producers in the state, a quantitative study built on preliminary findings of this study was conducted and findings presented in a separate paper.

Conclusions

This study provides insight into the several factors that drive the use of antimicrobials among cattle producers in TN. Participants generally perceived their use of antimicrobials to be discreet. However, what the producers perceive as prudent AMU may not necessarily be prudent use. As a result of this study, campaign efforts targeting behavioral change on AMU among producers should focus on encouraging producers to continue benchmarking AMU practices from peers. Benchmarking best practices could perhaps cause producers to critically reflect on their current AMU practices. To reduce the burden of AMR, more awareness of what constitutes and drives the development of AMR, and additional education on prudent use of antimicrobials is needed for beef producers. Training on prudent AMU is likely to be well received by producers if the information comes from their veterinarians, county extension officers, or trusted fellow producers. The trainings should utilize published evidence of the consequences of non-judicious use of veterinary antimicrobials and the need to improve judicious AMU in livestock. Perhaps such training may cause reflection on current practices and would trigger acceptance of messages that aim at behavioral change towards prudent AMU.

List of abbreviations

AMU: Antimicrobial use

AMR: Antimicrobial resistance

CIAs: Critically Important Antimicrobials

OIE: World Organization for Animal Health

VFD: Veterinary Feed Directive

WHO: World Health Organization

Declarations

Ethical approval and consent to participate

The study was reviewed and approved by the University of Tennessee Institutional Review Board (IRB NUMBER: UTK IRB-17-03702-XP). A signed informed consent was obtained from each participant before the focus group discussions commenced.

Consent for publication

The authors declare that the manuscript does not contain any personally identifiable information and all personal data were anonymized.

Availability of data and material

All data (focus group transcripts) pertaining to the manuscript can be obtained from the corresponding author upon reasonable request.

Additional files

Appendix 2A: The first focus group interview guide (.docx).

Appendix 2B: The modified focus group interview guide (.docx).

Appendix 4: Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist.

Competing interests

The investigators declare that they have no competing interests.

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Authors Contributions

The primary author (JEE) was involved in study design and execution, data management, data analysis and interpretation, and preparation of the manuscript draft. MC, EBS, and CCO were involved in study design and execution, data analysis, and interpretation, as well as editing the manuscript. All authors read and approved the final manuscript.

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CHAPTER 4

Drivers of antimicrobial use practices among Tennessee dairy cattle producers

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This chapter is a manuscript that was submitted to the journal: Veterinary Medicine International in September 2018. My contributions to this paper included gathering and review of literature; design and execution of the study; data preparation, both the qualitative and quantitative data analysis; interpretation of results; formulation of discussion topics; drafting and editing of the manuscript.

Abstract

Non-judicious antimicrobial use (AMU) and inadequate antimicrobial stewardship are known modifiable factors driving the occurrence of antimicrobial resistance (AMR). A mixed methods approach using a combination of focus groups and survey questionnaires was used to explore the AMU practices of Tennessee (TN) dairy cattle producers. Specifically, the objectives of the study were to determine the following: (1) the most common drivers for using antimicrobials, (2) perceived alternatives to antimicrobials, (3) knowledge of and perceptions regarding AMR, (4) and the appropriate avenues for receiving information on prudent AMU.

Two focus groups were conducted, one in July 2017 and the other in March 2018. The questionnaire was simultaneously made available to participants both in print form and online from January 26, 2018 through May 11, 2018. Twenty-three dairy producers participated in the focus groups and 45 responded to the survey. Eight (18.6%) producers never used bacterial culture and sensitivity testing (C/S) to select antimicrobials, more than half (25 producers (58.1%)) sometimes used C/S, four (9.3%) used C/S about half the time, five (11.6%) most of the time, and one (2.3%) always used C/S. The most common drivers for using antimicrobials were disease and animal welfare, pathogen surveillance, economic factors, veterinarian recommendation, producer's experience and judgment, drug attributes, and the Veterinary Feed Directive. Good management practices, vaccination, use of immunomodulatory products, and use of appropriate technology for early disease detection were considered alternatives to AMU. Four (9.1%) dairy producers were very concerned about AMR, 27 (61.4%) moderately concerned, and 10 (22.7%) were not concerned about AMR. The veterinarian was considered to be a trusted source of information on prudent AMU. Use of C/S test results for antimicrobial selection is widespread among TN dairy producers. More awareness about C/S and continuing training on prudent AMU is needed.

Key words

Mixed methods study, antimicrobial use, antimicrobial resistance

Introduction

Antimicrobial resistance (AMR) is now recognized as a major global health problem [1, 2]. Non-judicious antimicrobial use (AMU) and inadequate antimicrobial stewardship (AMS) are known modifiable factors driving the occurrence of AMR [3]. The public health threat of AMR has led to increased societal pressure to limit AMU in food animals [4].

To prevent potential public health consequences of AMR, many countries have instituted measures to reduce and minimize AMU in food animals [3]. These measures are based on the precautionary principle, since there is currently no robust evidence on the public health impacts of AMU in food animals on AMR in human pathogens [3]. The precautionary principle of public health recommends the adoption of preventive measures in the face of uncertainty and exploring various alternatives to potential threats to public health [5]. Recent systematic reviews showed that although some primary studies suggested evidence of AMR transmission from and between food animals and humans, a large proportion did not provide evidence supporting such transmission [6-8]. Recent studies have shown that indiscriminate use of antimicrobials for both therapeutic and non-therapeutic purposes in animals leads to propagation and shedding of substantial amounts of AMR microorganisms [3, 9].

The World Health Organization (WHO) recommends complete restriction of AMU in food animals for growth promotion and for disease prevention, as well as a reduction in the overall use of medically important antimicrobials in food animals [1]. Beginning January 1, 2017, the United States Food and Drug Administration (FDA) implemented the Veterinary Feed Directive (VFD), aimed at facilitating the judicious use of medically important antimicrobials in food producing animals. The VFD authorizes the use of medically important antimicrobials in feed and water for therapeutic purposes, under the supervision of a licensed veterinarian. For policy interventions such as the VFD to be effective, factors that inform and influence or drive producer behavior in relation to AMU need to be addressed because producers consistently base their decisions and actions on a complex system of core values and knowledge.

Previous studies among dairy farmers identified veterinary advice, the producer's personal on-farm experience, disease occurrence, animal welfare, and the drug withdrawal period as primary factors driving choice and use of antimicrobials [10-12]. To date, however, there has been very limited investigation into the drivers of AMU practices of cattle producers in the United States. No previous study to our knowledge has explored the drivers of AMU among Tennessee (TN) dairy cattle producers.

In this study, our aim was to use a combination of focus groups and survey questionnaires to explore the AMU practices of TN dairy cattle producers. Specifically, the objectives of the study were to determine the following: (1) the most common drivers for using antimicrobials, (2) perceived alternatives to antimicrobials, (3) knowledge of and perceptions regarding AMR, and (4) the appropriate avenues and formats for receiving information on prudent AMU. These findings should optimize the efforts under which targeted campaigns for nationwide AMS are applied in US dairy production.

Materials and methods

Study design

This was a mixed methods study using a combination of focus groups and survey questionnaires. To aid in the triangulation between the qualitative and quantitative data, preliminary findings from one focus group were used in the development of the survey questionnaire. The University of Tennessee Institutional Review Board for the Protection of Human Subjects in Research reviewed and approved both the qualitative (Protocol number: UTK IRB-17-03702-XP) and the quantitative (Protocol number: UTK IRB-17- 03884-XP) parts of this study.

Qualitative methodology

Focus group design, structure, and procedure

We conducted two dairy producer focus groups in middle TN and east TN in July 2017 and March 2018, respectively. The middle TN focus group (focus group 1) was conducted with dairy producers attending an annual dairy producer meeting. Fourteen people attended this annual dairy producer meeting (12 of whom actively participated in the discussions). Participants in the east TN focus group (focus group 2) were recruited from dairy producers attending a master dairy training meeting. Of the approximately 35 producers who attended this master dairy training session, 11 volunteered to participate. Each focus group meeting lasted approximately 60 minutes. Each participant was given an informed consent form with an overview of the study and a signed consent was obtained before participating in the focus group discussion. Participants could opt out of the focus groups at any time. A meal was provided to all invited participants irrespective of their active participation.

We used a semi-structured interview guide consisting of 11 open-ended questions designed to address the study objectives (See Appendix 2B). We assigned each participant an identity number to maintain anonymity. These identity numbers were used throughout the discussion and participants announced these numbers before speaking. The two focus groups were moderated by one of the authors (EBS). Three members of the research team (JEE, MC, and CCO) took hand written notes of any key points, provided clarifications to questions, and asked follow-up questions when necessary. Each focus group discussion was video-recorded and later transcribed verbatim by a professional transcription service provider for thematic analysis.

Data analysis

We analyzed the transcripts using a data analysis software (NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 12, 2017). Thematic analysis was performed using a recursive six-phase approach (familiarization with the data, generation of initial codes, search for themes, review of themes, definition and naming of themes, and report production) as described previously [13]. To familiarize themselves with the data, each member of the team (JEE, MC, EBS, and CCO) read both transcripts. The percent of word similarity between the 2 focus groups was assessed using Jaccard's coefficient. A master project with the two transcripts uploaded was developed by the primary author (JEE) and distributed to the other authors for individual coding. An inductive approach was used to develop a coding frame (each author created independent nodes). Upon completion of the individual coding, the primary author (JEE) imported the other team members' coded data into the master project and examined if the themes from the individual coding were related to the coded extracts in all the data transcripts. The degree of agreement in the data coding among the coders (JEE, MC, EBS, and CCO) was determined in NVivo using percent agreement. Results of the independent coding was reviewed and harmonized by the research team.

Quantitative methodology

Study design and administration of survey

A survey questionnaire consisting of a section for dairy producers and another for beef producers was developed and evaluated by two professionals with expertise in AMU to ensure all critical issues were identified and covered (See file S2 in the supplementary materials for the survey questionnaire). Dairy producers completed only the dairy section of the questionnaire. Preliminary findings from focus group 1 were used in the development of the questionnaire. The

56 survey questions targeted the producer's demographics and their AMU practices, factors driving producer's choice of antimicrobials, and perceptions, opinions, and concerns about AMU and AMR in cattle production.

The targeted producer demographic information included age, sex (male versus female), level of education, herd size, whether raised on a livestock farm or not, and number of years in cattle farming. This demographic information was our explanatory variables of interest. Our main outcome of interest was the producers' degree of concern about antimicrobial resistant infections in cattle. Also, the association between level of education and producer's perception of antimicrobial label instructions was of interest. Three-point scales and ordinal Likert scales were used to capture participant responses to questions related to AMU practices, factors driving choice of antimicrobials, and perceptions, opinions and concerns about AMU and AMR in cattle production.

The questionnaire was simultaneously made available to participants both in print form and online. Participants who completed the print survey were requested not to complete the online survey and vice versa in the informed consent statement. The on-line version of the survey was housed in a survey software (Qualtrics software, Provo, UT) and was adapted for computer, tablets, and cell phone responses. The anonymize function in the Qualtrics software was optimized, so responses were not attached to any personal identifiers. During an annual dairy producer meeting in January 2018, producers were notified about the online survey option in order to increase the response rate. Subsequently, an email invitation to take the survey was sent out to all the 87 dairy producers on the University of Tennessee Animal Science department email list. The printed questionnaire was distributed to producers attending dairy producer meetings and master dairy training meetings across TN. Completed printed questionnaires were returned to the investigators or mailed to the last author.

Both the printed survey and online survey remained open from January 26, 2018, through May 11, 2018. Participation in the survey was voluntary and the survey targeted all dairy producers in the state (the estimated number of dairy producers in TN as of 2017 was 300) [14]. To further increase the response rate, follow-up email reminders were sent to non-respondents of the online survey every two weeks. All participants were invited to participate in a $10 gift card raffle taken at the end of the survey and the winners were randomly selected. Eligibility to participate in the raffle was not contingent upon survey completion.

Statistical analysis

A commercial statistical software (SAS, version 9.4, SAS Institute Inc, Cary, NC) was used to complete descriptive and univariable inferential analyses. Descriptive statistics (frequencies and proportions) were used to summarize the data. Responses on the Likert scales were visualized using stacked bar charts created in another commercial software (Tableau software, version 8.2, Seattle, WA). No corrections were made to missing data.

Univariable analyses (ordinal models with PROC LOGISTIC) were performed to test for associations between the captured demographic information and producers' degree of concern about antimicrobial resistant infections in cattle (our primary outcome of interest). Model fit was assessed using the score test for the proportional odds assumption, deviance, and Pearson goodness-of-fit statistics. Also, binary logistic regression was used to test the association between level of education and producer's perception of antimicrobial label instructions. For the univariable analysis, level of education was reclassified into two categories, high school/vocational or $\geq$ college, while herd size was reclassified into $\leq$ 150 or $\geq$ 150 dairy cattle.

The 95% confidence intervals were used to test significant associations. Values of $P < 0.05$ were considered statistically significant. Multivariable analyses were not performed because meaningful multivariable analysis was deemed to be untenable based on findings from the univariable analyses.

Results

Focus group participant characteristics

A total of 23 dairy producers actively participated in the two focus groups. Focus group 1 had one female and 11 male participants, while focus group 2 had two females and nine male participants. The reported milking herd size per producer ranged from approximately 40 to 1,100 dairy cattle. There was no participant that self-identified as an organic dairy producer.

The responses from the 2 focus groups were 31.2% similar (Jaccard's similarity index = 0.312). This Jaccard's similarity index provided evidence that there was diversity among participants. Percent agreement (in coding) between each pair of coders was > 80%.

Survey participant characteristics and self-reported AMU practices

Of the estimated 300 dairy cattle producers in the state, a total of 45 participated in the survey. Overall, the estimated survey response rate was 15%. Majority of respondents provided complete responses for most questions, except for a few cases where some respondents left some questions unanswered. Of the 45 dairy participants, 40 completed the print survey, while only five completed the online version. Thirty-nine (39) provided their gender: 31 males and seven females. One of these respondents preferred not to report their gender. The demographic information of the survey respondents is presented in **Table 4.1**. Majority of the participants mentioned that they kept up-to-date written records on antimicrobial purchases and did not practice extra-label AMU (**Table 4.2**).

Table 4.1. Demographics of Tennessee dairy producers surveyed concerning antimicrobial use practices, 2017

Variable	Number (%) of respondents
Gender	**n = 39**
Female	7 (18.)
Male	31 (79.5)
Preferred not to report gender	1 (2.6)
Age group (years)	**n = 37**
20 – 29	2 (5.4)
30 – 39	6 (16.2)
40 – 49	8 (21.6)
50 – 59	13 (35.1)
60 – 69	8 (21.6)
Education level	**n = 37**
High school	16 (43.2)
Vocational	2 (5.4)
College	18 (48.7)
Professional	1 (2.7)
Years in dairy cattle production	**n = 38**
< 5	1 (2.6)
6 – 10	6 (15.8)
16 – 20	1 (2.6)
21 – 25	4 (10.5)
26 – 30	4 (10.5)
> 30	22 (57.9)
Herd size	**n = 37**
1 – 49	2 (5.4)
50 – 99	8 (21.6)
100 – 149	7 (18.9)
150 – 199	5 (13.5)
200 – 299	7 (18.9)
300 – 399	3 (8.1)
400 – 499	1 (2.7)
500+	4 (10.8)
Raised on a cattle farm	**n = 39**
Yes	2 (5.1)
No	37 (94.9)

Table 4.2: Survey results showing the practices of Tennessee dairy producers related to antimicrobial use, 2018

Practice	Number of participants (percentage)		
	Yes	**Not sure**	**No**
Farm keeps up-to-date written records of antimicrobial drug purchases (n = 40)	23 (57.5)	5 (12.5)	12 (30)
Farm keeps written records of medicated feeds purchased in the framework of VFD (n = 40)	20 (50)	3 (7.5)	17 (42.5)
Farm keeps up-to-date written records of antimicrobial drugs used to treat animals (n = 40)	28 (70)	4 (10)	8 (20)
Cattle on the farm are sometimes treated with antimicrobials at dosages higher than the label provision (n = 40)	9 (22.5)	1 (2.5)	30 (75)
Farm practices extra-label AMU (n = 38)	7 (18.4)	2 (5.3)	29 (76.3)
Farm has written protocols for treating sick animals with antimicrobials (n = 38)	17 (44.7)	3 (7.9)	18 (47.4)

Objective 1: Drivers of AMU practices

For producers who responded to the survey questionnaire, the rating of the level of importance of factors influencing Tennessee dairy producers' choice of antimicrobials before (**Figure 4.1**) and after **(Figure 4.2)** the VFD-final rule became effective on January 1, 2017, were not significantly different. Noticeably, of the 42 producers who rated the level of importance of factors influencing their antimicrobial choice before the VFD, clinical signs and symptoms of disease were rated very important by 54.8% and extremely important by 16.7%. Drug withdrawal times were rated as an extremely important influencer of producers' choice of antimicrobials by 26.2% of the 42 respondents (before the VFD became effective), and culture and susceptibility tests were rated extremely important by 21.4% of respondents **(Figure 4.1)**.

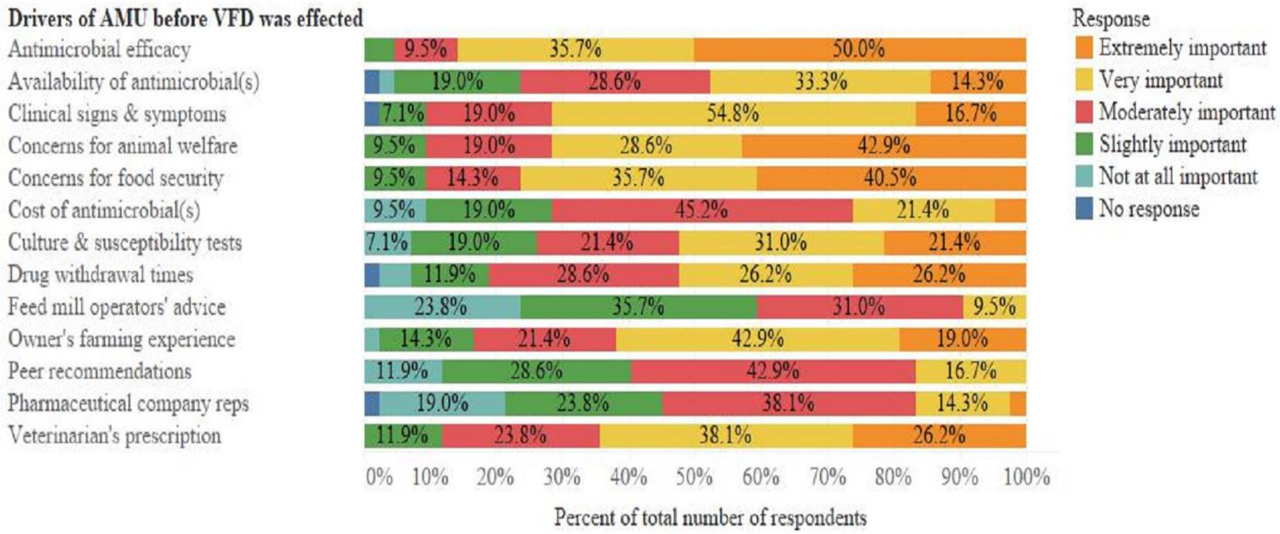

Figure 4.1: Level of importance of factors influencing Tennessee dairy producers' (n = 42) choice of antimicrobials before the veterinary feed directive-final rule became effective on January 1, 2017.

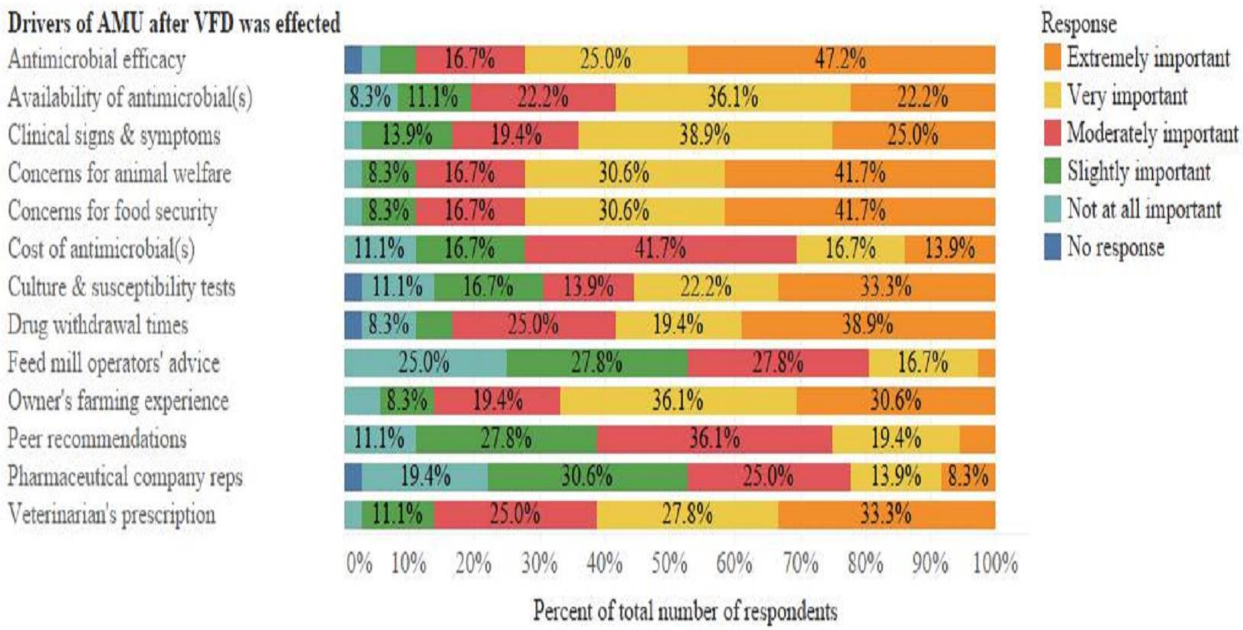

Figure 4.2: Level of importance of factors influencing Tennessee dairy producers' (n = 36) choice of antimicrobials after the Veterinary Feed Directive-final rule became effective on January 1, 2017.

Clinical signs and symptoms of disease were rated extremely important influencer of producers' choice of antimicrobials by 25% of the 36 respondents (after the VFD became effective), veterinarian's prescription was rated extremely important by 33.3% of the 36 respondents, and culture and susceptibility tests were rated extremely important by 33.3% of respondents **(Figure 4.2)**. Figures 1 and 2 provide details of how questionnaire respondents rated the level of importance of factors influencing producers' choice of antimicrobials before and after the VFD-final rule became effective on January 1, 2017.

The major themes identified as drivers of AMU in the focus groups were: a) disease and animal welfare; b) pathogen surveillance; c) economic factors; d) veterinarian recommendation; e) producer's experience, and judgment; f) drug attributes; and g) the VFD. A detailed presentation of these themes from the focus groups and other survey findings salient to this objective are given below.

1a. Disease and animal welfare

The decision to use antimicrobials by dairy farmers was influenced by the presence of early signs of disease, such as high rectal temperatures, droopy ears, and teary eyes. Mastitis was commonly mentioned as the reason for using antimicrobials. Producers believed it was their duty to ensure the welfare of their cattle through treatment with antimicrobials.

> *… if she's running a temperature, we try to get drugs in her pretty quick. … [No. 8, focus group 2].*
>
> *… We treat all of our sick cows with antibiotics. We like to use some tetracycline in our calves to combat lots of things … [No. 3, focus group 2].*

Among survey respondents, mastitis (n = 21), respiratory infections/pneumonia (n = 4), and lameness/hoof problems (n = 2) were mentioned as the most common diseases/conditions for which antimicrobials were used. Other diseases/conditions mentioned by survey respondents included enteric problems/scours (n = 1) and infectious bovine keratoconjunctivitis (n = 1). The most commonly used antimicrobial drugs mentioned by the survey participants belonged to cephalosporins (n = 13), tetracyclines (n = 7), penicillins (n = 3), and amphenicols (n = 1) antimicrobial classes. Ceftiofur (n = 10), cephapirin (n = 3), long acting oxytetracycline preparations (n = 5), and florfenicol (n = 1) were the most commonly mentioned individual antimicrobials used. These individual antimicrobials were often mentioned using their proprietary names.

1b. Pathogen surveillance

A section of focus group respondents self-reported that they used culture and sensitivity test results for on-farm pathogen surveillance. This use of culture and sensitivity testing influenced AMU in some dairy farms and reportedly led to reduced AMU.

> *…We recently started plating mastitis cows. That's been a big deal whether or not because before we would just treat anybody who got mastitis. And now we actually not 100 percent know the bug. But we know what group it's in. So that's kind of cut down on our antibiotic use as far as mastitis goes… [No.12, focus group 1].*
>
> *…I've sent cultures[samples] off to university. Nine times out of ten, it's a form of e-coli. And he'll [the veterinarian] give you the drugs to take care of it… Once that's stopped to kill that bacteria, these drugs [do] not work no more… [No.4, focus group 2]*

On the other hand, eight producers (18.2%) who completed the questionnaire reported they never used bacterial cultures to determine cause of disease in their farms, more than half of the survey participants (26 (59.1%)) reported that they sometimes used bacterial cultures to determine causes of disease in their farms, 10 (9.1%) reportedly used bacterial cultures for disease detection half of the time, and six (13.6%) used bacterial cultures for disease detection most of the time. Regarding the use of bacterial culture and sensitivity testing (C/S) in selection of antimicrobials, eight (18.6%) participants reported that they never used C/S, more than half (25 (58.1%)) reported that they sometimes used C/S to select antimicrobials, four (9.3%) used C/S about half of the time, five (11.6%) most of the time, and one (2.33%) always used C/S.

1c. Economic factors

In the focus groups, the economic value of the animal was commonly mentioned to be an important driver of AMU. Animals perceived to be worth treating with antimicrobials were treated, while those perceived not worth treatment were culled and replaced by healthy stock.

> *… We started looking at cattle a lot closer. If she's actually worth the treatment? Or is it better just to [inaudible] and ship them down the road? I have kind of stressed that real hard amongst the employees. Before you treat, come to us; let's see is she worth it?... [No.5, focus group 1].*
>
> *… Really, the history of the cow. If that cow is worth putting antibiotics in, calling the vet or whatever – we've sent some to slaughter because of her history. She's just not [worth treating] – and her genetics, too – she's carrying a good heifer cow or whatever, we look at that also… [No.9, focus group 2].*

Among survey questionnaire respondents, four (10%) strongly agreed with the statement "profitability of your operation is an important factor influencing your decision to use antibiotics on your cattle," 20 (50%) agreed with this statement, 10 (25%) neither disagreed nor agreed, four (10%) disagreed, and two producers (5%) strongly disagreed.

1ci. Lactation stage and the dry period: The stage of lactation (early lactation or late lactation) as well as the dry period influenced AMU practices of dairy producers.

…I mean, stage of lactation is probably first [determinant of antimicrobial use] … [No.10, focus group 1].

… [Animals are treated with antimicrobials] depending on dry cow or freshing cow or just depending on what stage of lactation they've come through… [No.6, focus group 2].

Some focus group participants reported using blanket dry cow therapy (intramammary antimicrobials are administered to all quarters of all cows in the farm at the end of lactation) at their farms to minimize the economic losses associated with intramammary infections, while others indicated that they do not use blanket dry cow therapy, but rather utilized selective dry cow therapy (cows receive antimicrobial treatment at the end of lactation only based on evaluation of the infection status of the cow or quarter. Only cows infected in one or more quarters are treated with intramammary antimicrobials in all quarters at dry off). In focus group 2, cessation of blanket dry cow therapy was associated with an increase in somatic cell counts.

…One thing that hasn't been mentioned is dry cow therapy, which is pretty much blanket treatment at our farms. [No.12, focus group 1].

…I was told by someone else to not [do] blanket dry treatment because I'm seasonal. So, I have to do [selective dry cow] treatment… [No.6, focus group 1].

…This is the first year that I didn't do that [blanket dry cow therapy]. And I've had more somatic cell count problems than I've ever had… [No.6, focus group 2].

1d. Veterinarian recommendation

For some producers with access to a veterinarian, veterinary recommendations influenced their AMU. However, others mentioned that the veterinarians they consulted had limited knowledge of dairy cattle restrictions. Cost was an additional barrier to seeking veterinary assistance.

…. We follow veterinarian recommendations as well.…. [No. 5, focus group 1].

… We have access to a group of veterinarians about an hour, 45 minutes away. They deal mainly with beef cattle on the large animal side. They know very little about dairy produce restrictions and that sort of thing. Like somebody said earlier, they ask me what we should use? When you get the bill, it kind of hurts your feelings.... [No.13, focus group 1].

1e. Producer's experience and judgment

Most producers mentioned that they relied on their own experience, knowledge, and judgment when deciding to use antimicrobials in their cattle. This helped them reduce costs, such as veterinary fees, and helped them handle emergency cases in the event the veterinarian delayed. Furthermore, because producers are used to working with cattle on a daily basis, some dairy farmers believed they knew more about food animal issues compared to some veterinarians not used to working with food animals.

… Our vet lives over an hour away. So, if you have something that's an emergency, you still have to wait for him. In my experience, what happened with us was I just learned to do everything myself. So, they sort of worked their self out of a job. … [No. 12, focus group 1].

1f. Drug attributes

Perceived efficacy of the antimicrobial medicines, cost of antimicrobials, and the antimicrobial drug withdrawal times were mentioned as key factors influencing choice of antimicrobial drugs. Drugs perceived to be highly efficacious were preferred, while drugs with short withdrawal times were also preferred. It was mentioned that because some antimicrobials are very expensive, producers preferred highly efficacious products to avoid the additional costs of repeat treatments associated with treatment failure.

> *… Most important is an antibiotic that we use actually take care of the problem with one – not necessarily the same dose but one round of antibiotics. The problem's gone, and it doesn't return. If you go one round of antibiotics and the cow is fine and she's straightened up, and then two weeks later, she's got to get it again, that's not a good result from your antibiotics. We want one round to make sure it's all done; that problem's over with… [No.6, focus group 1].*

Among questionnaire respondents, fifteen (37.5%) agreed with the statement "Aggressive marketing of antibiotics by pharmaceutical companies greatly influences producers' use of antibiotics," 19 (47.5%) neither disagreed nor agreed with this statement, five (12.5%) disagreed, and one (2.5%) strongly disagreed with this statement. However, in the focus group discussions, marketing pressure from veterinary pharmaceutical company representatives was not identified as a driver of AMU.

1g. The VFD

The VFD was believed to be driving the increase in the therapeutic use of antimicrobials, especially in calves, because it has restricted access to in-feed antimicrobials for disease prevention. Producers gave an example of Aureo S 700®, an in-feed antimicrobial preparation that was previously easily accessible to producers and now is restricted to use by or on the order of a licensed veterinarian. This restricted access to in-feed antimicrobials by federal law was reported to be leading to increased use of injectable antimicrobials by producers.

…We used it [aureomycin S 700] during winter stress times when it would get really cold. We would use it as a preventative thing. So, now [with the VFD] we doctor with something else once they get sick rather than preventing it. Using that prevents having to use something stronger. If you put something there and prevent pneumonia, that's better than having it come back with whatever, you know, LA-200 or whatever else you're going to use… [No. 13, focus group 1].

For the questionnaire respondents, seven (17.5%) strongly agreed with the statement "The VFD would lead to increased use of injectable antibiotics by producers," 11 (27.5%) agreed with this statement, 18 (45%) neither disagreed nor agreed, and four producers (10%) disagreed.

Objective 2: Alternatives to antimicrobials

Most of the dairy producers' alternatives to antimicrobials were geared towards mastitis prevention and control. The focus group participants considered: a) good management practices; b) use of vaccines, and immunostimulants; and c) early disease detection as their alternatives to antimicrobials. The excerpts that support these perceived alternatives are provided below.

2a. Good management practices

The husbandry practices considered alternatives to AMU included proper animal nutrition, proper housing, and infection control measures. Specifically, good milking parlor management, clean cow facilities, and good udder health management were reported to be alternatives to AMU. Examples of good udder health management practices mentioned include the use of teat dips, teat sprays, and teat sealants.

…I agree with managing your facilities properly. All your milking equipment and housing and whatever plays a big part in it… [No.13, focus group 1].

…we use teat sealant[s]… [No.9, focus group 2].

2b. Vaccines and use of immunomodulatory products

Vaccinations and use of immunomodulatory products, such as pegbovigrastim (Imrestor®), were frequently mentioned as an alternative to antimicrobials. It was mentioned that immunomodulatory products are used in fresh cows to minimize AMU.

> *… Well, I started using it [Imrestor®] temporarily just because it's supposed to help these cows, you know, fresh cows and keep the drug use down.… [No.11, focus group 1].*

2c. Use of appropriate technology for early disease detection

Early disease detection using appropriate technology, such as rumination monitors, was considered important in minimizing and reducing AMU.

> *… we have a monitoring system that monitors rumination as well as activity. So, when her rumination goes down, you know something's wrong. And maybe you can prevent it or treat it before it gets bad… [No.12, focus group 1].*

Additional training for dairy producers on infection prevention and control was supported by many survey respondents. Two participants (5.1%) strongly agreed that infection prevention and control measures (farm-level biosecurity and vaccination) would reduce AMU in dairy operations, 17 respondents (43.6%) agreed, 17 (43.6%) neither disagreed nor agreed, and three (7.7%) strongly disagreed.

Objective 3: Knowledge of AMR, and perceptions regarding AMR

Many focus group participants as well as survey participants were familiar with AMR. The salient findings for our third objective are presented below in detail under the themes: a) knowledge of AMR; b) perceptions regarding AMR emergence; and c) proposed solutions to AMR.

3a. Knowledge of AMR

Some focus group participants demonstrated their knowledge of AMR and believed there was "some amount" of AMR occurring in food animal pathogens. Also, the repeated treatment of animals with antimicrobials was mentioned in the discussions.

> *…As far as antibiotic resistance, there is some out there. I don't think it's gone completely from food animals… [No.5, focus group 1].*
>
> *…There'd be 25-30 percent chance of a repeat [treatment of animals with antimicrobials] … [No.6, focus group 1].*

The extent to which survey questionnaire respondents were familiar with AMR varied among the 43 respondents to this question. One producer (2.3%) reported to be extremely familiar with AMR, 12 (27.9%) very familiar, 21 (48.8%) moderately familiar, six (14%) slightly familiar, and three (7%) were not familiar at all. In rating their degree of concern about AMR, four (9.1%) reported they were very concerned about AMR, 27 (61.4%) moderately concerned, 10 (22.7%) reported that they were not concerned about AMR, and three producers (6.8%) did not rate their degree of concern about AMR because they were unfamiliar with the meaning of AMR.

One dairy producer (2.5%) strongly agreed with the statement "Some antibiotics you use on your cattle have become ineffective (there is resistance to antibiotics used in cattle)," 17 (42.5%) agreed with this statement, 16 (40%) neither disagreed nor agreed, five (12.5%) disagreed, and one (2.5%) strongly disagreed. For the statement "Antibiotic drugs work less effectively than in the past," one (2.5%) strongly agreed, 10 (25%) agreed, 20 (50%) neither disagreed nor agreed, 7 (17.5%) disagreed, and two (5%) strongly disagreed. Producer's gender (male vs female; $P = 0.699$), herd size ($P = 0.447$), education level ($P = 0.524$, age ($P = 0.508$), and number of years in cattle farming (P = 0.535), were not significantly associated with producer's degree of concern about AMR. Based on these findings, no meaningful multivariable analyses could be performed.

3b. Perceptions regarding AMR emergence

Participants attributed the emergence and occurrence of AMR to the over-use and prolonged use of the same antimicrobials without rotating and the lack of new antimicrobials. The problem of AMR in human pathogens was attributed to antimicrobial over-use in humans and not in livestock.

> *… [Antimicrobial resistance bites you] eventually if you overuse and use the same thing [antimicrobial] too long. It's the same as pesticides. They only work for so long. Hopefully you can get enough variety to where you can switch from one to another and maintain both… [No.11, focus group 2].*

> *…As humans, we do a lot of stuff that probably amplifies that. Everybody's antibacterial nowadays. You can't sneeze without being doused in it almost… [No.5, focus group 1].*

Some participants believed that the human health risks associated with AMU in food animals are not evidence-based and generally perceived their AMU practices to be prudent.

> *…We realize that there's some amount of resistance to antibiotics. But a lot of the population that has these fears of resistance that aren't science based. And they're the ones that tend to drive regulation with non-science-based opinions on antibiotic resistance. If something is science based and real, hey, I'm all for doing it. Because some people in town think that antibiotics in cows cause them to have resistance and there's no science behind it, I think that's a real problem… [No. 6, focus group 1].*

The producers believed the public was misinformed about how and why antimicrobials are used in food animals, and the producers associated the misinformation with a lack of consumer education and milk marketing with buzzwords such as “antibiotic free.”

> *…I think part of the problem with the public is our milk marketing. This jug of milk says antibiotic and hormone free and this one does not. So, they assume that that one has antibiotics in it, which falls into antibiotics in milk and all this antibiotic resistance and stuff like that when no milk has antibiotics in it. But they just don’t know that. They’re just not educated… [No. 12, focus group 1].*

3c. Proposed solutions to AMR

The participants suggested: i) improving antimicrobial drug labels; ii) additional producer training on prudent AMU; and iii) development of diagnostic tools for rapid on-farm detection of AMR and on-farm antimicrobial sensitivity testing as measures for improving AMU and containing AMR. A brief description of the suggested measures is given below.

3c. i Improving antimicrobial drug labels

It was suggested that the dosage rates indicated on antimicrobial drug labels need to be changed to reflect the appropriate dosage rates because current antimicrobial drug labels may not reflect the appropriate drug dosage rates.

> *… The [antimicrobial] labels need to be labeled for appropriate doses instead of what appropriate doses were 40 years ago. All that information needs to be there on the label, so we know what the appropriate dose is, what the appropriate withdrawal is and what the appropriate bug or disease it’s going to take care of in a very concise, easy to read, easy to understand label. That would be a most important change… [No.6, focus group 1].*

Also, producers perceived the current antimicrobial labels and information on the antimicrobial package inserts to be very technical and difficult to comprehend and suggested that antimicrobial drug labels and package inserts should be written in non-technical language to make such information easier for producers to understand. To cater to non-English speaking farm employees (Hispanic/Latino farm workers), it was suggested that antimicrobial drug labels be written in both English and Spanish.

Among survey questionnaire respondents, 13 (33.3%) found antimicrobial labels difficult to understand and interpret, whereas 26 (66.7%) found these labels easy to understand and interpret. Education level was not significantly associated with producer's perception of difficulty to comprehend antimicrobial label instructions (OR = 2.24; 95% CI = 0.563, 8.91; P = 0.253). Of the 39 survey participants who responded to the question on the preferred language for antimicrobial label instructions, only three (8%) preferred these labels to be in both English and Spanish, whereas 36 (92%) preferred antimicrobial drug labels to be in English.

3c. ii Additional training on prudent AMU

Participants suggested that more training for dairy producers on prudent AMU was needed for improving AMU in cattle production. However, continuing professional education for medical practitioners on prudent AMU was suggested in order to reduce non-judicious AMU in humans.

> *…I'd like to know more information about it [antimicrobial use]. I'd like to be able to treat the animal one time and get it taken care of. It requires some advanced training. And it's hard to get that sometimes…. [No. 5, focus group 2].*
>
> *…I have a statement about the human side of it. They need to educate doctors that prescribe all of these liquid antibiotics to children for earaches and everything else when*

they're not earaches and different things. And I think that's what causes resistance in humans… [unidentified participant, focus group 2].

Additional training for dairy producers on prudent AMU practices was supported by many survey respondents. Four producers (10%) strongly agreed that producers required additional training on prudent AMU, 10 (25%) agreed, 15 (37.5%) neither disagreed nor agreed, nine (22.5%) disagreed, and two (5%) strongly disagreed.

3c.iii Development of diagnostic tools for rapid on-farm detection of AMR and on-farm antimicrobial sensitivity testing.

It was suggested in the focus groups that producers should be able to test cows on-farm for AMR and antimicrobial susceptibility. Such on-farm diagnostics would properly orient antimicrobial therapy and guide the implementation of appropriate on-farm isolation measures.

… [We should be] able to test the cows on the farm – your own antibiotic and your own somatic cell. We had a product that we were getting from RapiDEC for somatic cells. For some reason they took it off the market… Products like that can help us on the farm… [No. 1, focus group 1].

Objective 4: Avenues for receiving information on AMU

In the focus groups, participants identified the following as viable avenues for receiving information on prudent AMU: the veterinarian, email, dairy publications, and producer meetings. The producers considered the veterinarian (for areas with food animal vets) to be a trusted source of information on prudent AMU.

…Our vet has a meeting once a year where he will bring in sponsors that will be reps of his companies mail list. It's generally whenever we have a question, we call and ask. He's our source of information… [No. 3, focus group 2].

Regarding avenues/formats for receiving information on prudent AMU, no single medium was most preferred by survey questionnaire respondents. The most commonly mentioned avenues for receiving information on prudent AMU included brochures (n = 8), educational seminars (n = 6), and a producers' handbook on prudent AMU (n = 4). These formats for receiving information were chosen individually or in combination with others, such as AMU flowcharts for the barn, videos on prudent AMU, and laminated posters.

Discussion

The Jaccard's similarity index and the survey participant demographics showed that there was diversity of opinions among participants in the present study. Our study utilizes the strength of a mixed methods research design (a combination of qualitative and quantitative methods) to extend the knowledge of AMU in dairy production by highlighting the diversity and complexity of factors driving AMU among dairy producers in TN. Additionally, we identified the dairy producers' alternatives to antimicrobials, their perceptions regarding AMR, and the appropriate avenues and formats for disseminating information on prudent AMU to these producers. Gussmann *et al*, suggested that campaign efforts that target improvements in AMU among farmers need to take into account farmers' usual AMU practices in order to motivate farmers to adopt control measures that facilitate prudent AMU [4]. Therefore, our findings should aid in optimizing the efforts under which targeted campaigns for nationwide AMS are applied in US dairy production.

A previous survey by the U.S Department of Agriculture (USDA) found that producers on almost all the sampled dairy operations (99.7%) reported having at least one case of mastitis during 2013 and antimicrobials were administered to mastitic cows on 96.9% of dairy operations [15]. In the present study, mastitis was the most commonly mentioned disease for which antimicrobials were used. This is not surprising because mastitis is known to be the most frequent disease of dairy cows [16]. To minimize AMU, TN dairy producers should be encouraged to strengthen their herd health measures for mastitis prevention and control.

Use of written protocols for treating sick animals with antimicrobials could reduce treatment errors, since most of antimicrobial treatments in farms are often administered by non-technical farm personnel (the farmer or farm employees) [17, 18]. In the present study, many questionnaire respondents mentioned that their farms did not have written protocols for treating sick animals with antimicrobials. This finding suggests a need for TN veterinarians and dairy extension agents to emphasize and encourage the development and use of written AMU protocols.

In the present study, a section of the focus group participants self-reported their use of C/S test results for on-farm pathogen surveillance. Similarly, many producers who completed the questionnaire self-reported their use of C/S to determine the causes of disease in their farms and to select antimicrobials for farm use. In addition, more than half of the survey questionnaire respondents rated C/S as either a very important or extremely important factor influencing their choice of antimicrobials, before or after the VFD-final rule became effective on January 1, 2017. These findings generally suggest that, although not universally practiced, use of C/S test results for on-farm pathogen surveillance and for antimicrobial selection is a widespread and common practice among TN dairy farmers. Producers not utilizing C/S could be constrained by either cost or lack of awareness about the benefits of C/S. These findings are also in contrast to those of a previous New Zealand study, where C/S testing is perceived to be not useful because it did not influence what antimicrobial the veterinarian prescribed and, hence, is not widely used by dairy producers [10]. Possibly, use C/S test results is widespread and common among TN dairy producers because its economic value is appreciated by many producers.

Our findings show that profitability of the dairy operation (economic gain) was a key factor influencing the decisions of many producers to use antibiotics. In their dairies, cows perceived to be economically less valuable were culled, rather than treated. Additionally, the focus groups identified the lactation stage as a factor driving AMU by dairy producers. This association between lactation stage and AMU could be due to high milk yield at peak lactation and changes in immune function at early lactation. The pregnancy status of the cow (in-calf or open) during the lactation period may also be a factor that producers consider when deciding to use antimicrobials. It is possible that these producers treat high milk yielding cows with antimicrobials in case of udder health problems to maintain high economic performance. A Danish study found that high milk yield was associated with a higher probability of both lactational and dry-off antimicrobial treatment of dairy cows [4]. High milk production is a known risk factor for occurrence and recurrence of clinical mastitis, whose occurrence drives AMU [4, 19, 20]. Changes in immune function and non-specific host defense mechanisms is reported to be associated with high incidence of clinical mastitis in early lactation [19]. To minimize the economic losses associated with intramammary infections, a section of focus group participants mentioned using dry cow therapy as a blanket antimicrobial treatment at their farms to control the risk of new intramammary infections during the dry period. This practice of blanket dry cow therapy is concerning and suggests a need for veterinarians and dairy extension agents to encourage TN dairy producers to avoid blanket dry cow therapy and adopt selective dry cow therapy to minimize unnecessary AMU. Although still a common practice in the US, blanket dry cow therapy is now illegal in several European countries to avoid selection for AMR [4, 21, 22]. Similarly, previous studies have shown that blanket dry cow therapy may not be an optimal approach to dry cow therapy when compared to selective dry cow therapy, and dry cow therapy does not compromise animal welfare and productivity and is economically more beneficial compared to blanket dry cow therapy [22-25]. A policy shift towards banning blanket dry cow therapy in TN and the entire US may be worth exploring.

Our findings showed that veterinarian recommendations and peer recommendations generally influence AMU practices of dairy producers. Additionally, we identified the veterinarian, producer meetings, and educational seminars (along with other avenues) to be viable ways for reaching out to producers. Similar to other research [12], our findings suggest that veterinarians and peers could act as agents of change towards prudent AMU among dairy producers. Policy interventions towards prudent AMU should channel AMU-related behavioral change messages to dairy producers through veterinarians (where possible) and other producers (peers) using the identified avenues/formats. Furthermore, targeted behavioral change messages towards prudent AMU practices should be integrated into routine veterinary farm visits and master dairy training programs. Behavioral techniques, such as motivational interviewing informed by assessing producers' readiness for change, could be used [26]. Producer meetings/associations and educational seminars for producers should be used to identify AMU training needs and raise more awareness about AMR and prudent AMU among dairy producers.

The VFD was mentioned to have limited access to preventive in-feed antimicrobials (e.g. Aureo S 700®), and as a result, is believed to be driving increased use of injectable antimicrobial agents. Aureo S 700® contains 3 antimicrobials (aureomycin, chlortetracycline, and sulfamethazine) and is indicated for the use of weight gain maintenance and the management of stressful conditions in calves. We did not ascertain, in the present study, if the increased use of injectable antimicrobial agents was for prophylactic and/or therapeutic purposes. We suggest a nation-wide investigation of the impact of the VFD on the use of injectable antimicrobials among US dairy producers be conducted.

A previous study conducted in the United States showed that AMU among plain (members of Amish or Mennonite religious communities) dairy farmers is minimal due to the more frequent use of natural remedies for mastitis treatment [27]. In contrast to the plain dairy farmers who frequently use natural therapies, our focus group participants considered good management practices, use of vaccines, and immunostimulants, and early disease detection as their alternatives to antimicrobials. There was no mention of alternative forms of treatment, such as phytotherapy, aromatherapy, homeopathy, and use of essential oils and other forms of natural therapy. Also, this finding is in contrast to findings from a 2015 study conducted in France, where some farmers use alternative treatments, such as aromatherapy, phytotherapy, and homeopathy, for the management of mastitis [28]. First, the differences observed could be reflective of cultural differences between TN dairy farmers and plain/French dairy farmers. Second, it is possible that the natural therapies used elsewhere for mastitis are not popular among TN dairy producers because of the current lack of scientific evidence for their efficacy.

Although 12 survey participants reported to be very familiar with AMR, a considerably large number (21) were moderately familiar, while others were either slightly familiar or not familiar at all. Similarly, it is concerning that 10 (22.73%) reported they were not concerned about AMR, and 3 producers (6.82%) did not rate their degree of concern about AMR because they were not familiar with what AMR meant. These findings suggest a need for more sensitization of producers on AMR and AMU.

Researchers in Australia suggested that veterinary antimicrobial drug labels need regular updating to reflect the appropriate dosage rates for treatment of common veterinary pathogens [29]. To improve AMU, our focus group participants suggested that antimicrobial dosage rates indicated on certain antimicrobial drug labels need to be changed to reflect the appropriate dosage rates. A targeted study evaluating the appropriateness of dosage rates indicated on drug labels for currently used veterinary antimicrobials in the US is necessary to validate or dispute this finding. A previous study conducted in South Carolina reported that the dairy industry often relies on Hispanic labor, and the language barrier was a challenge when dealing with non-English speaking farm employees [12]. In the present study, a section of focus group participants suggested that antimicrobial drug labels should be in both English and Spanish to cater for non-English speaking farm employees (Hispanic/Latino farm workers), and only three (7.69% [3/39]) producers who responded to the questionnaire preferred antimicrobial drug labels to be in both English and Spanish. Possibly, these three questionnaire respondents who preferred antimicrobial drug labels to be in both English and Spanish utilize Hispanic labor in their dairy farms. Additionally, a section of focus group participants and many dairy producers (33.33%, (13/39)) who completed the questionnaire perceived the current antimicrobial labels and information on the antimicrobial package inserts to be very technical and difficult to comprehend. Our findings showed that producers' education levels were not significantly associated with producers' perceptions of difficulty to comprehend antimicrobial label instructions, perhaps due to the few survey respondents. There is need to conduct a country-wide investigation of this perception that current antimicrobial labels and information on the antimicrobial package inserts are very technical and difficult for producers to comprehend. Friedman *et al*, based on their South Carolina study, recommend that all farm health resources and interventions should be bilingual (in English and Spanish) and in an easy-to-understand language to cater to the growing population of Hispanic/Latino farm employees [12]. As suggested by the producers during the focus group discussions, we contend that there is a need for US veterinary pharmaceutical companies to consider labeling antimicrobial drugs in both English and Spanish and in non-technical language for easier comprehension.

Social desirability bias can be an issue in both focus groups and survey studies. Our focus groups and survey participants could have given socially desirable responses, thus introducing bias to our findings. However, socially desirable responses, if any, could be very minimal, since both focus groups and survey respondents were assured that the data collected was anonymized and participation was voluntary. Additionally, the survey questionnaire (both paper and online) was self-administered. Thus, participants are likely to have given their true opinions, perceptions, and practices. It is common for studies utilizing focus groups to be biased by the presence of dominant participants. However, in the present study, such bias could be very minimal, if any, because our focus groups were moderated by one of the authors (EBS) with a background in the behavioral/social sciences and wide experience in moderating such meetings.

Conclusions

Use of culture and sensitivity test results for on-farm pathogen surveillance and for antimicrobial selection is a widespread and common practice among TN dairy farmers. There is need for more awareness about C/S to encourage producers not utilizing it to adopt its use. Blanket dry cow therapy is still commonly practiced by some dairy producers in TN. There is need to popularize/promote selective dry cow therapy and its associated benefits among dairy producers in the state. Tennessee dairy producers currently practicing blanket dry cow therapy should be encouraged to adopt selective dry cow therapy and abandon the practice of blanket dry cow therapy. An investigation of the impact of the VFD on the use of injectable antimicrobials among US dairy producers should be conducted. Continuing training on prudent AMU is needed for TN dairy producers.

Ethical approval and consent to participate

The University of Tennessee Knoxville, Institutional Review Board for the Protection of Human Subjects in Research reviewed and approved both the qualitative (Protocol number: UTK IRB-17-03702-XP) and the quantitative (Protocol number: UTK IRB-17- 03884-XP) parts of this study. A signed informed consent was obtained from each participant before the focus group discussions commenced.

Consent for publication

The authors declare that the manuscript does not contain any personally identifiable information and all personal data were anonymized.

Data Availability

Focus group transcripts pertaining to the manuscript can be obtained from the corresponding author upon reasonable request. The survey raw data used to support the findings of this study are included within the supplementary information files.

Supplementary materials

Appendix 2: Semi-structured interview guide.

Appendix 3: Survey questionnaire.

Appendix 4: Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist.

Conflicts of interests

The investigators declare that they have no competing interests.

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Authors Contributions

The primary author (JEE) participated in designing and executing the study, performed both the qualitative and quantitative data analysis, and prepared the manuscript draft. MC, EBS, and CCO participated in study design and execution, performed qualitative data analysis and edited the manuscript. All authors read and approved the final manuscript.

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CHAPTER 5

A survey of antimicrobial use practices of Tennessee beef producers,

2018

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This chapter is a manuscript that will be submitted for publication in PLOS ONE. My contributions to this paper included gathering and review of literature; design and execution of the study; data preparation and analysis; interpretation of results; formulation of discussion topics; drafting and editing of the manuscript.

Abstract

Inappropriate antimicrobial use (AMU) is a key modifiable factor that leads to the development of antimicrobial resistance (AMR). The objectives of this study were to determine the following among Tennessee beef cattle producers: (1) the opinions on factors driving AMU (2) opinions on alternatives to antimicrobials, (3) the knowledge and perceptions regarding AMU and AMR, and (4) the preferred avenues for receiving information on prudent AMU. A survey questionnaire was made available to participants both in print and online from January 26, 2018 through May 11, 2018. The survey questions targeted the producers' demographics and their AMU practices; factors driving producer's choice of antimicrobials; perceptions, opinions and concerns about AMU and AMR in cattle production. Ordinal logistic regression was used to test for associations between the captured demographic information and producers' degree of concern about AMR. Overall, 231 beef producers responded to the survey. More than 60% of the participants mentioned that they kept up-to-date written records on antimicrobial purchases and AMU, whereas 87% did not practice extra-label AMU. Clinical signs were rated as an extremely important influencer of producers' use of antimicrobials by 97 of the 212 respondents and 104 of the 205 respondents before and after the Veterinary Feed Directive became effective, respectively. Controlling for type of cattle operation, age was significantly associated with the producer's degree of concern about AMR (P = 0.022). The commonly mentioned avenues for receiving information on prudent AMU included: brochures, educational seminars, and producers' handbook on prudent AMU. There is a need to promote the use of written antimicrobial treatment protocols among beef producers in Tennessee. Continued training for beef producers on infection prevention and control and prudent AMU is needed.

Introduction

Antimicrobial drugs have been described as a common pool resource with the potential to be depleted over time due to the emergence of antimicrobial resistance (AMR) [1]. In beef production, antimicrobials are important to maintain or improve animal health and increase productivity [2]. Although the development of AMR is a complex multifactorial process [3], inappropriate antimicrobial use (AMU) is a key modifiable factor leading to its development, [4] and as such, AMR is now referred to as a tragedy of the commons [1, 5, 6]. Globally, the use of vaccines as well as other infection prevention and control approaches are viewed as promising alternatives to antimicrobials [7-9]. To facilitate prudent AMU in animal production, an emphasis on the agricultural education of cattle producers on prudent AMU practices is critical

[10]. Furthermore, the whole-of-society approach to antimicrobial effectiveness [6] and One Health approaches to optimization of AMU [11] have been suggested as measures for prolonging the therapeutic life of available antimicrobial drugs.

To facilitate judicious AMU, a collective action towards promoting the prudent use of antimicrobials is being advocated on a global scale [12]. In the United States, the Food and Drug Administration (FDA) has taken steps to implement its policy on the judicious use of medically important antimicrobial drugs in animals through the Veterinary Feed Directive (VFD), which became effective on January 1, 2017 [13]. Researchers [14] have suggested that utilizing approaches appealing to farmers' internal motivators would increase the success of policy interventions, such as the VFD, that aim to improve AMU. Therefore, understanding current AMU practices of producers and factors that inform and influence those practices is critical for the success of interventions to improve AMU in beef production.

In Ontario, Canada, a 1999-2002 study found that oxytetracycline, penicillin, macrolides, florfenicol, and spectinomycin were the most commonly used antimicrobials by beef producers [15]. A previous study conducted in 60 cow-calf operations in Tennessee (TN) found that chlortetracycline was the most commonly used antimicrobial in the late 1980s for disease prevention [16]. Additionally, a previous 2007-2008 survey evaluating the producers' attitudes and practices related to AMU in TN cattle found that approximately 34% of the surveyed population reported using bacterial culture to determine the cause of disease, and 21.5% used culture and susceptibility test results to guide their choice of antimicrobials [17]. However, that 2007-2008 survey did not utilize focus group findings in the development of the questionnaire. Data on AMU in beef cattle in the United States is generally scarce. A 2014 systematic review [18] examined the relationship between AMU in food animals and the emergence and spread of foodborne AMR-*Campylobacter* and expressed the need for a robust data collection system in the United States that would help identify factors contributing to the persistence of AMR.

This present study is built on the preliminary findings of a previous qualitative study with the aim of exploring how much the results of the qualitative study holds true for the larger population of beef producers in the state. Therefore, our general aim was to assess the changes in AMU practices and drivers of AMU in TN beef cattle production. This present study, therefore, contributes to the wider knowledge of AMU by providing insights into the current practices, perceptions, and opinions of TN beef producers regarding AMU and AMR. Specifically, the objectives were to determine the following among Tennessee beef cattle producers: (1) the opinions on factors driving AMU among beef producers, (2) opinions on alternatives to antimicrobials, (3) the knowledge and perceptions regarding AMU and AMR, and (4) the preferred avenues for receiving information on prudent AMU.

Materials and Methods

Study design and administration of survey

A questionnaire consisting of a section for beef producers and a section for dairy producers was developed and evaluated by two professionals with expertise in AMU to ensure all critical issues were identified and covered (see appendix 3 for the survey questionnaire). Participants whose primary cattle production was beef, were required to complete the beef producer section of the questionnaire. The data obtained from five beef focus groups previously conducted by the authors was used to develop the questionnaire. The University of Tennessee Knoxville, Institutional Review Board for the Protection of Human Subjects in Research approved the study (Protocol number: UTK IRB-17- 03884-XP). The 56 survey questions targeted the producers' demographics and their AMU practices, factors driving producer's choice of antimicrobials, and perceptions, opinions, and concerns about AMU and AMR in cattle production.

The targeted producer demographic information included age, sex (male versus female), level of education, herd size, whether the producer raised on a livestock farm, and number of years in cattle farming. These demographic data were our explanatory variables of interest. Our main outcome of interest was the producers' degree of concern about antimicrobial resistant infections in cattle. Also, the association between levels of education and producers' perception of antimicrobial label instructions was of interest. Three-point scales and ordinal Likert scales were used to capture participant responses to questions related to AMU practices, factors driving choice of antimicrobials, and perceptions, opinions and concerns about AMU and AMR in beef cattle production.

With an assumed TN beef producer population size of 20,000 and a 50% response distribution, 377 participants were determined to be the appropriate sample size for this study at 95% confidence level and a margin of error of 5%. The survey questionnaire was made available to participants both in print and online. Producers who completed the print questionnaire were requested not to complete the online survey and vice versa in the informed consent statement. Qualtrics software (Provo, UT) housed the on-line version of the survey, which was adapted for computer, tablet, and cell phone responses. Participant responses were de-identified using the anonymize function in Qualtrics such that no personal information was collected. During the Tennessee Cattle Men's Association (TCA) annual meeting in January 2018, beef producers were notified about the online survey option to increase the response rate. Subsequently, all 2,712 producers on the TCA mailing list received an email invitation to take the survey.

Additionally, an anonymous survey link and QR code for the online survey were provided to the TCA vice president for distribution to producers willing to take the survey. To further increase the response rate, follow-up email reminders were sent to non-respondents of the on-line survey every two weeks.

The printed questionnaire was distributed to producers attending the TCA annual meeting and producer extension meetings across the state. Completed printed questionnaires were returned to the investigators or mailed to the last author. Both the printed and online survey remained open from January 26, 2018, through May 11, 2018. Participation in the survey was voluntary. All participants were invited to participate in a $10 gift card raffle taken at the end of the survey and the winners were randomly selected. Eligibility to participate in the raffle was not contingent upon survey completion.

Statistical analysis

A commercial statistical software (SAS, version 9.4, SAS Institute Inc, Cary, NC) was used to perform descriptive and inferential analyses. Descriptive statistics (frequencies and proportions) were used to summarize the data. Another commercial software (Tableau software, version 8.2, Seattle, WA) was used to create stacked bar charts for responses on the Likert scales. Missing data was treated as such.

Univariable and multivariable analyses were performed using ordinal logistic regression to test for associations between the captured demographic information and the producers' degree of concern about AMR. For the univariable analyses, herd size was reclassified into three categories 0 – 49, 50 – 99, and > 100 beef cattle, and age was reclassified into <30, 30-39, 40-49, 50-59, 60-69, and ≥70 using the quantile classification method. In assessing the producers' degree of concern about AMR, a multivariable ordinal logistic regression model was manually fitted using backwards elimination method and the probability of being less concerned was modeled. In the model building, the Score Test for the Proportional Odds Assumption was used to evaluate the proportional-odds assumption and the model fit was assessed using the standard Pearson Goodness-of-Fit Statistic. Briefly, potential predictors at a $P \leq 0.20$ from the univariable analyses were included in the multivariable model building. Possible effects of confounding were evaluated by comparing a change in parameter estimates with and without the suspected variables [19, 20]. A predictor variable that caused a ≥ 20% change in another parameter estimate upon removal from the model was considered a confounder and was retained in the final model regardless of its statistical significance [21]. In the final model, two-way interactions (type of cattle operation and age) were assessed based on plausibility and standard multiple pairwise comparisons were obtained.

Results

Participant characteristics and self-reported AMU practices

A total of 231 beef producers participated in the survey:103 completed the print survey while 128 completed the online version. Of the 231 participants, 200 provided their gender: 35 females and 163 males. Two of these respondents preferred not to report their gender. Complete responses were provided for most questions, with the exception of a few cases where the respondents left some questions unanswered. The demographic information of the respondents is presented in **Table 5.1**. More than 60% of the participants mentioned that they kept up-to-date written records on antimicrobial purchases and AMU, whereas 87% did not practice extra-label AMU (**Table 5.2**).

Table 5.1: Demographics of beef producers on survey to identify antimicrobial use practices, 2018

Variable	Number (%) of respondents
Gender	**n = 200**
Female	35 (17.5)
Male	163 (81.5)
Preferred not to report gender	2 (1.0)
Age group (years)	**N = 200**
< 30	12 (6.0)
30 – 39	29 (14.5)
40 – 49	41 (20.5)
50 – 59	44 (22.0)
60 – 69	46 (23.0)
>70	28 (14.0)
Education level	**N=202**
< College	47 (23.3)
≥ College	155 (76.7)
Years in cattle production	**N = 202**
< 5	23 (11.4)
6 – 10	19 (9.4)
11 – 15	17 (8.4)
16 – 20	24 (11.9)
21 – 25	24 (11.9)
26 – 30	21 (10.4)
>30	74 (36.6)
Beef cattle operation type	**N = 230**
Cow-calf production	171 (74.4)
Backgrounding-stocking	9 (3.9)
Seed-stock operation	6 (2.6)
Multiple operation type and others	44 (19.1)
Herd size	**n = 202**
1 – 49	84 (41.6)
50 - 99	54 (26.7)
100 – 149	28 (13.9)
150 - 199	12 (5.9)
200 - 299	13 (6.4)
300 - 399	5 (2.5)
400 - 499	1 (0.5)
500+	5 (2.5)
Raised on a cattle farm	**n = 202**
Yes	138 (68.3)
No	64 (31.7)

Table 5.2: Practices of Tennessee dairy producers related to antimicrobial use, 2018

Practice		Number of participants (frequency percentage)		
		Yes	**Not sure**	**No**
Farm kept up-to-date written records of antimicrobial drug purchases (n = 208)	Backgrounding-stocking (n = 9)	9 (4.3)	0 (0)	0 (0)
	Cow-calf production (n = 154)	90 (43.3)	17 (8.2)	47 (22.6)
	Multiple operation type, others (n = 39)	26 (12.5)	4 (1.9)	9 (4.3)
	Seed stock operation (n = 6)	6 (2.9)	0 (0)	0 (0)
Farm kept written records of medicated feeds purchased in the framework of VFD (n = 201)	Backgrounding-stocking (n = 9)	9 (4.5)	0 (0)	0 (0)
	Cow-calf production (n = 148)	69 (34.3)	21 (10.5)	58 (28.9)
	Multiple operation type, others (n = 38)	25 (12.4)	2 (1)	11 (5.5)
	Seed stock operation (n = 6)	6 (3.0)	0 (0)	0 (0)
Farm kept up-to-date written records of antimicrobial drugs used to treat animals (n = 209)	Backgrounding-stocking (n = 9)	9 (4.3)	0 (0)	0 (0)
	Cow-calf production (n = 155)	102 (48.8)	11 (5.3)	42 (20.1)
	Multiple operation type, others (n = 39)	28 (13.4)	3 (1.4)	8 (3.8)
	Seed stock operation (n = 6)	6 (2.9)	0 (0)	0 (0)
Cattle in the farm were sometimes treated with antimicrobials at dosages higher than the label provision (n = 204)	Backgrounding-stocking (n = 8)	0 (0)	0 (0)	8 (3.9)
	Cow-calf production (n = 151)	9 (4.4)	9 (4.4)	133 (65.2)
	Multiple operation type, others (n = 39)	6 (2.9)	1 (0.5)	32 (15.7)
	Seed stock operation	0 (0)	0 (0)	6 (2.9)
Farm practiced extra-label AMU (n = 201)	Backgrounding-stocking (n = 8)	0 (0)	0 (0)	8 (4.0)
	Cow-calf production (n = 149)	12 (6.0)	12 (6.0)	125 (62.2)
	Multiple operation type, others (n = 38)	7 (3.5)	1 (0.5)	30 (14.9)
	Seed stock operation (n = 6)	0 (0)	0 (0)	6 (3.0)
Farm had written protocols for treating sick animals with antimicrobials (n = 199)	Backgrounding-stocking (n = 8)	2 (1.0)	0 (0)	6 (3.0)
	Cow-calf production (n = 147)	22 (11.1)	6 (3.0)	119 (59.8)
	Multiple operation type, others (n = 38)	9 (4.5)	4 (2.0)	25 (12.6)
	Seed stock operation (n = 6)	3 (1.5)	0 (0)	3 (1.5)

Objective 1: Opinions on factors driving antimicrobial use

Profitability of the beef operation (economic gain) was a key factor influencing the decisions of many producers to use antimicrobials in their farms. Forty-six (22.6%) participants strongly agreed with the statement "profitability of your operation is an important factor influencing your decision to use antibiotics on your cattle." Ninety-five (46.6 %) agreed, 36 (17.6%) neither disagreed nor agreed with this statement, 20 (9.8%) disagreed, and seven producers (3.4%) strongly disagreed. Seventeen respondents (8.3%) strongly agreed with the statement "aggressive marketing of antibiotics by pharmaceutical companies greatly influences producers' use of antibiotics." Eight four (41%) respondents agreed, 71 (34.6%) neither disagreed nor agreed with this statement, 26 (12.7%) disagreed, and seven (3.4%) strongly disagreed with this statement.

The rating of the level of importance of factors influencing Tennessee dairy producers' choice of antimicrobials before (**Figure 5.1**) and after **(Figure 5.2)** the VFD final rule became effective on January 1, 2017, were not significantly different. Noticeably, antimicrobial efficacy was rated as an extremely important influencer of producers' choice of antimicrobials by 54% of the 213 respondents (before the VFD became effective), concerns for animal welfare were rated as extremely important by 48.8% of the 213 respondents, and concerns for food security were rated as extremely important by 47.4% of the 213 respondents, while culture and susceptibility (C/S) tests were rated as extremely important by 13.6% respondents **(Figure 5.1)**. Antimicrobial efficacy was rated as extremely important by 53.1% of the 207 respondents (after the VFD became effective), concerns for animal welfare were rated as extremely important by 47.8%, and concerns for food security were rated as extremely important by 51.7% of the 207 respondents **(Figure 5.2)**.

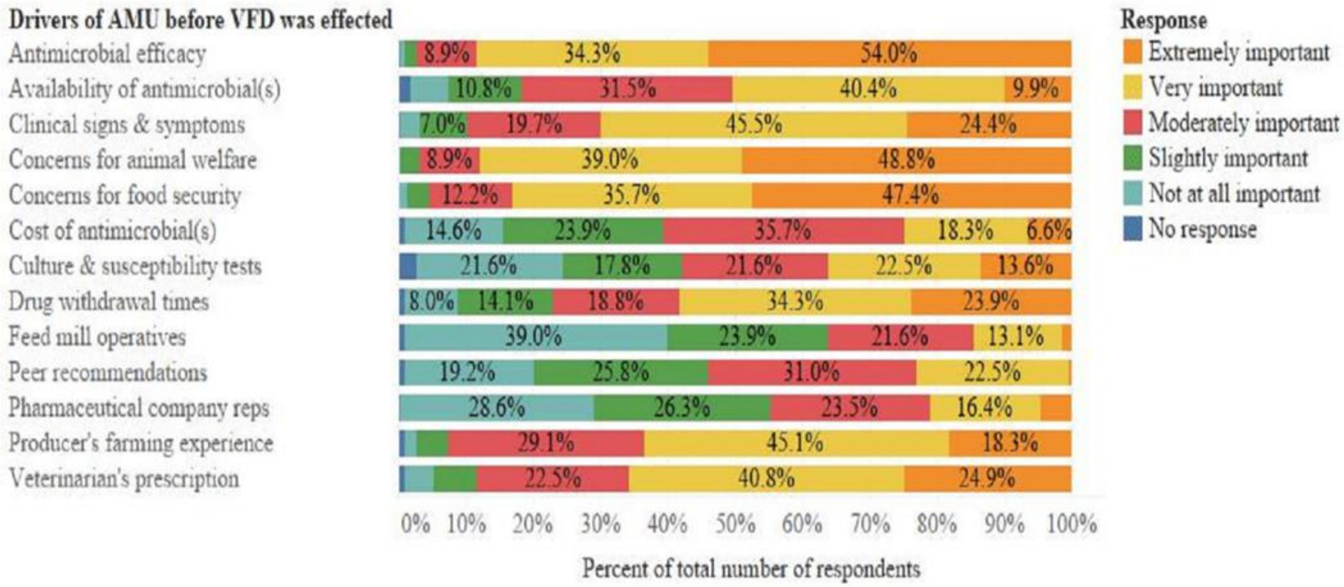

Figure 5.1: Level of importance of factors influencing Tennessee beef producers' (n = 213) choice of antimicrobials before the veterinary feed directive-final rule became effective on January 1, 2017.

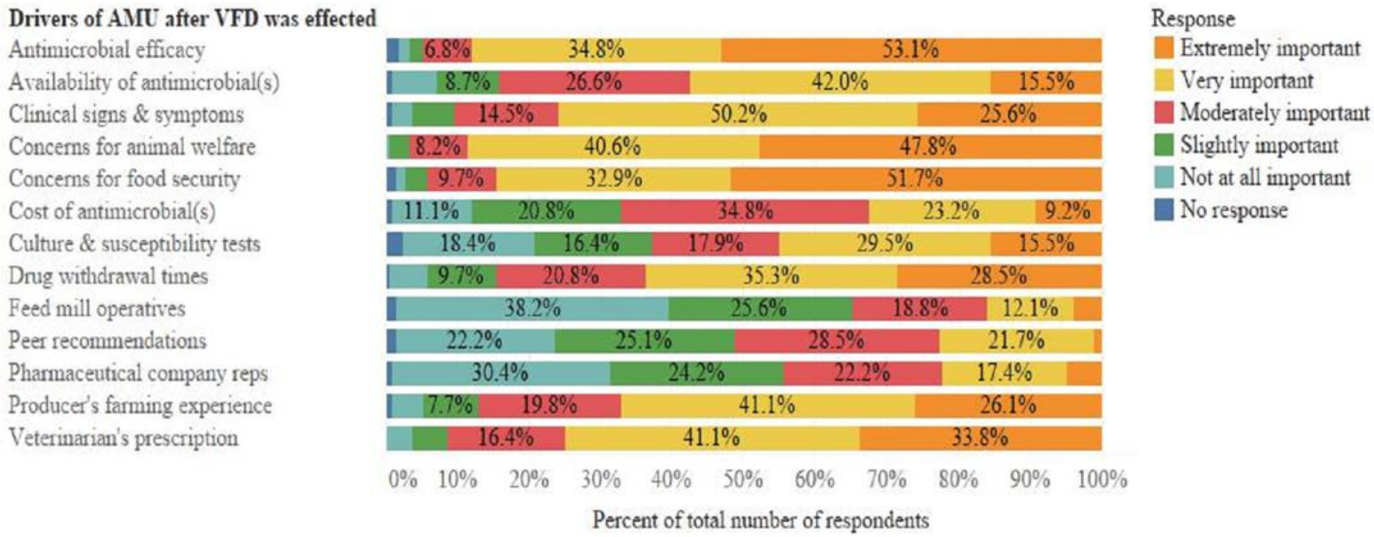

Figure 5.2: Level of importance of factors influencing Tennessee beef producers' (n = 207) choice of antimicrobials after the Veterinary Feed Directive-final rule became effective on January 1, 2017.

Clinical signs and symptoms of disease were rated as a very important influencer of producers' choice of antimicrobials by more than 40% of respondents and as an extremely important influencer by more than 20% before and after the VFD became effective (**Figures 5.1 & 5.2**). Respiratory infections/pneumonia (n = 19) and lameness/hoof problems (n = 16) were mentioned as the most common diseases/conditions for which antimicrobials were used. Other diseases/conditions mentioned included: enteric problems/scours (n = 2) and infectious bovine keratoconjunctivitis (n = 7). The most commonly used antimicrobial drugs for disease management by the participants belonged to tetracyclines (n = 81), penicillins (n = 9), cephalosporins (n = 4), amphenicols (n = 12), fluoroquinolones (n = 1), macrolides (n = 13), and sulfonamides (n =2) antimicrobial classes. Ceftiofur (n = 10), cephapirin (n = 3), long acting oxytetracycline preparations (n = 60), tulathromycin (n = 10), tylosin (n = 2), tildipirosin (n = 1) and florfenicol (n = 12) were the most commonly mentioned individual antimicrobials used. Producers mostly mentioned these individual antimicrobials using their proprietary names.

One hundred and twenty-eight (56.6%) participants reported they never used bacterial culture to determine disease cause on their farms; 75 (33.2%) participants reported they sometimes used bacterial culture to determine causes of disease on their farms. Seven (3.1%) respondents reportedly used bacterial culture for disease detection half the time, nine (4%) used bacterial culture for disease detection most of the time, and seven (3.1%) always used bacterial culture for disease detection. Regarding the use of bacterial C/S testing in selecting antimicrobials, 133 (59.4%) participants reported they never used C/S, 61 participants (27.2%) reported that they sometimes used C/S to select antimicrobials, seven (3.1%) about half the time, 13 (5.8%) most of the time, 10 (4.5%) always used C/S. Regarding who makes the laboratory requests for bacterial culture testing for the farm, 67 of the 91 producers (73.6%) mentioned the veterinarian, 20 (22%) mentioned the producer, and four (4.4%) mentioned the manager.

Objective 2: Opinions on alternatives to antimicrobials

Additional training of beef producers on infection prevention and control was supported by many survey respondents. Thirty-three participants (16%) strongly agreed that infection prevention and control measures (farm-level biosecurity and vaccination) would reduce AMU in beef operations. One hundred and nineteen (57.8%) respondents agreed, 38 (18.5%) neither disagreed nor agreed, 15 (7.3%) disagreed, and one (0.5%) strongly disagreed.

Objective 3: Knowledge of and perceptions regarding AMU & AMR

Of the 231 producers, 58 (25.1%) believed there was over-use of antimicrobials in beef production, 92 (39.8%) believed there was no over-use, and 81 (35.1%) were not sure. Regarding the beef production system(s) where antimicrobials were most used, 97 (42%) believed antimicrobials were most used in feedlot operations, 63 (27.3%) in back-grounding stocking, 17 (7.4%) in cow-calf production, five (2.2%) in backgrounding-stocking and feedlot operations, one (0.4%) in seed-stock operation, and 48 (20.8%) were not sure.

The extent to which survey participants were familiar with AMR varied among the 226 respondents. Twenty-five producers (11.1%) reported being extremely familiar with AMR, 59 (26.1%) were very familiar, 97 (42.9%) moderately familiar, 37 (16.4%) slightly familiar, eight (3.5%) not familiar at all. In rating their degree of concern about AMR, of the 228 producers who completed the question on degree of concern about AMR, 50 (21.9%) reported that they were very concerned about AMR, 133 (58.3%) moderately concerned, and 36 (15.8%) reported they were not concerned about AMR. Nine producers (4%) did not rate their degree of concern about AMR because they were not familiar with what antimicrobial resistance meant.

Twelve producers (5.8%) strongly agreed with the statement “some antibiotics you use on your cattle have become ineffective (there is resistance to antibiotics used in cattle).” Fifty-four (26.2%) respondents agreed, 84 (40.8%) neither disagreed nor agreed, 48 (23.3%) disagreed, and eight producers (3.9%) strongly disagreed with this statement. For the statement “antibiotic drugs work less effectively than in the past,” eight (3.9%) participants strongly agreed, 43 (21%) agreed, 105 (51.2%) neither disagreed nor agreed, 39 (19%) disagreed, and 10 (4.9%) strongly disagreed.

Additional training of beef producers on prudent AMU was supported by the majority of survey respondents. Twenty-two producers (10.7%) strongly agreed that producers required additional training on prudent AMU. One hundred and twenty-nine (62.9%) respondents agreed, 37 (18.1%) neither disagreed nor agreed, 15 (7.3%) disagreed, and two (1%) strongly disagreed.

Of the 200 participants who completed the question on antimicrobial drug labels, 149 respondents (74.5%) found antimicrobial drug label instructions easy to understand and interpret while 51 (25.50%) believed antimicrobial drug label instructions were difficult to understand and interpret. All of the 201 survey participants (100%) who responded to the question on the preferred language for antimicrobial label instructions preferred antimicrobial drug labels to be in English. Education level was not significantly associated with producers’ perceptions of difficulty to comprehend antimicrobial label instructions (College/professional vs high school/vocational OR = 1.19; 95% CI = 0.57, 2.5; P = 0.641).

Simple associations between demographic variables and producers' degree of concern about AMR

Producer's gender (male vs female; P = 0.856), being raised on a cattle farm (P = 0.472), herd size (P = 0.431), education level (P = 0.319), number of years in cattle farming (P = 0.273), and operation type (P = 0.19) were not significantly associated with producer's degree of concern about AMR (**Table 5.3**). Age was significantly associated with producer's degree of concern about AMR (P = 0.048).

Multivariable analyses

In the multivariable ordinal logistic regression model, producers' age was significantly associated (*P* = 0.022) with their degree of concern about AMR, after controlling for type of cattle operation (**Table 5.4**). For this model, the Score Test for the Proportional Odds Assumption ($\chi^2(8.03) = 8$; $P = 0.431$) indicated that the proportional-odds assumption was met, and the standard Pearson Goodness-of-Fit statistic (*P* = 0.109) showed that the model fit the data very well. Compared to producers in the 40 – 49, 50 – 59, 60 – 69 and > 70 age groups, those in the 30 – 39-year age group were significantly less concerned about AMR (**Table 5.4**). Similarly, compared to cow-calf producers and producers with multiple or other types of cattle operations, seed-stock operators were significantly less concerned about AMR.

Table 5.3: Univariable analyses for associations between various demographic predictors and Tennessee beef producers' degree of concern about antimicrobial resistant infections, 2018.

Variable	**Category**	**OR (95% CI)**	***P* Value**
Gender	Male vs Female	1.07 (0.51 – 2.23)	0.856
Raised on a cattle farm	Yes vs No	1.25 (0.69 – 2.26)	0.472
Herd size	†Overall	—	0.431
	50 – 99 vs 0 – 49	1.57 (0.79 – 3.12)	0.199
	50 – 99 vs ≥100	1.23 (0.6 – 2. 54)	0.571
	≥100 vs 0 – 49	1.27 (0.66 – 2.45)	0.47
Education level	High school/vocational vs college/professional	1.4 (0.72 – 2.72)	0.319
Age	†Overall	—	0.048
	30 – 39 vs 40 – 49	2.71 (1.03 – 7.11)	0.043
	30 – 39 vs 50 – 59	4.2 (1.63 – 10.83)	0.003
	30 – 39 vs 60 - 69	3.53 (1.38 – 9.03)	0.009
	30 – 39 vs > 70	4.1 (1.42 – 11.87)	0.009
	30 – 39 vs < 30	1.74 (0.44 – 6.88)	0.43
	40 – 49 vs 50 – 59	1.55 (0.66 – 3.67)	0.319
	40 – 49 vs 60 – 69	1.3 (0.55 – 3.07)	0.545
	40 – 49 vs > 70	1.5 (0.56 – 4.07)	0.411
	<30 vs 40 – 49	1.56 (0.41 – 5.92)	0.517
	60 – 69 vs 50 – 59	1.19 (0.52 – 2.3)	0.678
	> 70 vs 50 – 59	1.02 (0.4 – 2.66)	0.961
	<30 vs 50 – 59	2.41 (0.65 – 9.02)	0.191
	60 – 69 vs > 70	1.16 (0.45 – 3.01)	0.758
	< 30 vs 60 – 69	2.03 (0.55 – 7.55)	0.292
	<30 vs >70	2.36 (0.58 – 9.6)	0.232

Table 5.3: Continued

Variable	Category	OR (95% CI)	*P* Value
Number of years in cattle farming	†Overall	–	0.273
	6 – 10 vs <5	2.2 (0.63 – 7.67)	0.216
	6 – 10 vs 11 – 15	3.64 (0.98 – 13.53)	0.054
	6 – 10 vs 16 – 20	1.4 (0.41 – 4.74)	0.591
	6 – 10 vs 21 – 25	0.81 (0.24 – 2.75)	0.729
	6 – 10 vs 26 – 30	1.62 (0.46 – 5.62)	0.452
	6 – 10 vs >30	1.92 (0.69 – 5.35)	0.213
	11 – 15 vs <5	0.6 (0.17 – 2.11)	0.43
	11 – 15 vs 16 – 20	0.38 (0.11 – 1.32)	0.129
	11 – 15 vs 21 – 25	0.22 (0.06 – 0.78)	0.019
	11 – 15 vs 26 – 30	0.44 (0.13 – 1.56)	0.205
	11 – 15 vs >30	0.53 (0.19 – 1.48)	0.224
	16 – 20 vs <5	1.57 (0.49 – 5.08)	0.447
	16 – 20 vs 21 – 25	0.58 (0.18 – 1.83)	0.35
	16 – 20 vs 26 – 30	1.16 (0.36 – 3.73)	0.809
	16 – 20 vs >30	1.37 (0.54 – 3.48)	0.505
	21 – 25 vs <5	2.73 (0.83 – 8.95)	0.097
	21 – 25 vs 26 – 30	2.01 (0.61 – 6.55)	0.23
	21 – 25 vs >30	2.38 (0.92 – 6.16)	0.073
	26 – 30 vs <5	1.36 (0.41 – 4.5)	0.612
	26 – 30 vs >30	1.19 (0.54 – 3.11)	0.725
	>30 vs <5	1.15 (0.44 – 2.99)	0.779
Cattle operation type	†Overall	–	0.19
	Seed-stock vs Backgrounding-stocking	4.41 (0.55 – 35.56)	0.164
	Backgrounding-stocking vs Multiple operation and others	1.5 (0.33 – 6.74)	0.601
	Backgrounding-stocking vs Cow-calf	1.22 (0.3 – 4.97)	0.783
	Seed-stock vs Multiple operation and others	6.59 (1.19 – 36.38)	0.031
	Seed-stock vs Cow-calf	5.37 (1.07 – 27.02)	0.042
	Cow-calf vs Multiple operation and others	1.23 (0.6 – 2.49)	0.573

†Overall = overall effect of predictor on outcome variable

Table 5.4: Ordinal logistic regression model of multivariable analyses of factors associated with Tennessee beef producers' degree of concern about antimicrobial resistant infections, 2018.

Variable	Category	OR (95% CI)	*P* Value
Age	†Overall	—	0.022
	30 – 39 vs 40 – 49	3.18 (1.19 – 8.54)	0.022
	30 – 39 vs 50 – 59	4.54 (1.73 – 11.88)	0.002
	30 – 39 vs 60 - 69	3.72 (1.43 – 9.65)	0.007
	30 – 39 vs > 70	5.53 (1.85 – 16.52)	0.002
	30 – 39 vs < 30	1.76 (0.44 – 7.04)	0.427
	40 – 49 vs 50 – 59	1.43 (0.59 – 3.43)	0.429
	40 – 49 vs 60 – 69	1.17 (0.49 – 2.8)	0.728
	40 – 49 vs > 70	1.74 (0.64 – 4.71)	0.278
	<30 vs 40 – 49	1.81 (0.47 – 7.03)	0.389
	60 – 69 vs 50 – 59	1.22 (0.53 – 2.83)	0.644
	50 – 59 vs > 70	1.22 (0.46 – 3.23)	0.691
	<30 vs 50 – 59	2.59 (0.68 – 9.88)	0.165
	60 – 69 vs > 70	1.49 (0.56 – 3.93)	0.423
	< 30 vs 60 – 69	2.12 (0.56 – 8)	0.268
	<30 vs >70	3.15 (0.75 – 13.2)	0.117
Cattle operation type	†Overall	—	0.071
	Seed-stock vs Backgrounding-stocking	7.4 (0.85 – 64.59)	0.07
	Backgrounding-stocking vs Multiple operation and others	1.49 (0.32 – 6.89)	0.612
	Backgrounding-stocking vs Cow-calf	1.14 (0.27 – 4.72)	0.86
	Seed-stock vs Multiple operation and others	11.02 (1.85 – 65.51)	0.008
	Seed-stock vs Cow-calf operators	8.42 (1.56 – 45.37)	0.013
	Cow-calf vs Multiple operation and others	1.31 (0.63 – 2.72)	0.471
†Overall = overall effect of predictor on outcome variable			

Objective 4: Avenues for receiving information on prudent AMU

Regarding avenues for receiving information on prudent AMU, no single medium was most preferred by all producers. The most commonly mentioned avenues for receiving information on prudent AMU included brochures (n = 19), educational seminars (n = 71), and a producers' handbook on prudent AMU (n = 37). These formats for receiving information were chosen individually or in combination with others, such as videos on prudent AMU and laminated posters. Of the 202 participants who answered the question on the preferred language for receiving information on prudent AMU, 200 (99%) preferred to receive AMU information in English.

Discussion

The findings of the study provide insight into the AMU practices of TN beef producers and identify opportunities for improving AMU among these producers at a time when AMU in food animals is under public scrutiny. Results of this study suggests that extra-label AMU among TN beef producers could be very low. Written AMU protocols could reduce treatment errors since most of antimicrobial treatments in farms are often administered by non-technical farm personnel (the farmer or farm employees) [22, 23]. In the present study, a majority of the farms did not utilize written protocols for treating sick animals with antimicrobials, suggesting a need for veterinarians and TN beef extension agents to emphasize and encourage the development and use of written AMU protocols.

Although a large proportion of producers in the present study were either extremely familiar or moderately familiar with AMR, many were either slightly familiar or not familiar at all with AMR, suggesting a need for more education on AMR and AMU. Moreover, producers in the 30 – 39 age group were significantly less concerned about AMR when compared to those in the 40 – 49, 50 – 59, 60 – 69, and > 70 age groups. Also, seed-stock operators were significantly less concerned about AMR when compared to cow-calf producers and those with multiple or other types of cattle operations. Possibly this result may reflect a lack of awareness of the consequences of AMR among producers in the 30 – 39 year age group and among seed-stock operators. Perhaps, producers in the 30 - 39 years age-group rarely participate in educational programs related to AMR when compared to those in other age groups and, as such, could be less informed about AMR and its consequences. It is important to note that the number of seed-stock operators in the survey was small (n = 6). Therefore, this finding may not be generalized to all seed-stock operators in the state.

In the present study, 63% of the surveyed producers kept written records of antimicrobial drug purchases and 69.4% kept written records of antimicrobial drugs used to treat animals, whereas in the 2007/2008 survey of TN beef producers, 39.4% of the surveyed producers kept records of antimicrobial purchases and 32.2% kept records of AMU [17]. The findings of the present study suggest there was an increase in the number of TN beef producers keeping records on antimicrobial purchases and AMU over the last 10 years. This increase in record keeping could reflect an increased awareness of the importance of farm record keeping among beef producers. Similarly, compared to the 2007/2008 survey findings where 13.5% of producers treated their cattle with antimicrobials at dosages higher than the label instructed, the findings of this present study found that only 7.3% of the surveyed producers mentioned that they sometimes treated their cattle with antimicrobials at dosages higher than the label provision. This finding suggests that producers' practice of treating animals with antimicrobials at higher dosages contrary to the label indication may have dropped by half (50%) over the past 10 years.

This drop could be due to the producers' recognition of the importance of adhering to label instructions or due to the improvement in producers' knowledge of AMU.

In the present study, 56.6% of the participants reported they never used bacterial culture to determine disease cause on their farms and 59.4% of the participants mentioned they never used C/S in selecting antimicrobials. Many producers rated C/S as an either not at all important, slightly important, or moderately important factor influencing their choice of antimicrobials, before or after the VFD final rule became effective on January 1, 2017. These findings generally suggest that, although reportedly practiced in some beef farms, the use of bacterial culture to determine disease cause and the use of C/S tests for antimicrobial selection is currently not widely practiced on TN beef farms. A 2007-2008 survey [17] found that 34% of producers used bacterial culture to determine disease cause and 31.5% of the surveyed beef producers reported using C/S to choose antimicrobials. Compared to the 2007/2008 survey, the findings reported in the present study suggest that there has not been any significant change (increase) in the use of C/S test results among TN beef producers over the last 10 years. Possibly, many producers have not adopted the use of C/S due to cost implications or lack of awareness about the benefits of C/S. Again, veterinarians and TN beef extension agents should create more awareness regarding the benefits of C/S among TN beef producers.

A previous review [24] identified farmers' belief that AMU will improve profitability as a barrier to sustainable AMU because it hinders the reduction of AMU. In the present study, 69% of the producers agreed that profitability of the beef operation (economic gain) was a key factor influencing the decisions of many producers to use antimicrobials in their farms. This finding is not surprising given that the risk of disease transmission may exert significant economic pressure on producers to use antimicrobials for infectious disease management and prevention [2].

However, producers need to be informed that profitability can be realized with minimal or no AMU, if appropriate infection prevention and control measures are implemented on the farm.

It is a common practice in many countries for pharmaceutical company representatives to directly market antimicrobials to farmers. The marketing of antimicrobials directly to food animal producers is discouraged by the World Organization for Animal health [25]. Our findings show that many producers (41%) believed the aggressive marketing of antibiotics by pharmaceutical companies greatly influenced producers' AMU, although 16.1% did not believe pharmaceutical companies influenced AMU, and over 50% of the respondents rated pharmaceutical company representatives as either not at all important or slightly important both before and after the VFD was effected. Many producers (25.5%) in the present study believed that antimicrobial drug label instructions were difficult to understand and interpret. Although this finding may not be generalized to the entire United States beef producer population, it suggests that veterinary pharmaceutical companies should consider labeling antimicrobial drugs in non-technical, easy-to-understand language for increased comprehension among producers. A countrywide investigation of the perceptions among beef producers about current antimicrobial labels and information on the antimicrobial package inserts may prove useful.

In the present study, no single medium/avenue for receiving AMU information was most preferred by all producers. This finding confirms the findings of previous studies, where farmers differed in their preference for receiving information on management and infection/disease prevention and control [14]. Previous scholars have suggested that veterinarians should act as the main information source for farmers on AMU because they are perceived as trust worthy social referents for farmers [26]. In the present study, over 60% of producers rated a veterinarian's prescription as either very important or extremely important in their antimicrobial choice, suggesting that veterinarians could act as agents of change towards prudent AMU among beef producers. It could be beneficial for policy interventions towards prudent AMU to channel AMU-related behavioral change messages to beef producers through veterinarians, where possible. Furthermore, targeted behavioral change messages towards prudent AMU should be integrated into routine veterinary farm visits and beef extension training programs. Behavioral techniques, such as motivational interviewing informed by assessing producers' readiness for change, could be used [27]. Additionally, these behavioral change messages could be packaged for beef producers in the form of brochures, a producer's handbook on prudent AMU or prudent AMU videos. Educational seminars should be used to identify AMU training needs and raise more awareness about AMR and prudent AMU among beef producers. However, scholars in Europe suggested that providing a sense of ownership of the recommendations for judicious AMU can be useful in causing behavioral change among producers [26]. Exploring appropriate methods for quantifying on-farm AMU in the U.S., may be invaluable since such measures could cause behavioral change towards prudent AMU.

Although previous studies have shown that peers influence farmers decision making [14], our findings suggest that peer recommendations could be a less important factor influencing choice of antimicrobials for many TN beef producers. Additionally, personal experience with specific AMU practices have been found to influence farmers attitudes towards antimicrobial treatment [26]. In the present study, over 40% of respondents rated their farming experience as very important, both before and after the VFD became effective, and over 18% rated it extremely important in their antimicrobial choice. Personal experience was rated as a more important factor influencing choice of antimicrobials when compared to peer recommendations, suggesting that there could be limited sharing of experiences among beef producers in TN, perhaps due to limited social interactions among the beef producers. Use of peers as agents of change towards prudent AMU in TN beef production may be less valuable. A study investigating the possible reasons why peer recommendations could be less useful to TN beef producers would be beneficial.

The strength of the present study was that preliminary findings from our previous qualitative study were used in developing the survey questionnaire, and the survey was anonymous, voluntary, and self-administered. Nevertheless, it is possible that the results of this study could have been influenced by social desirability bias, which is a form of response bias in which respondents provide socially desirable answers to survey questions [28]. Socially desirability bias, if any, could be minimal. Additionally, selection bias could be minimal because the demographic characteristics of late respondents and their responses to survey questions were similar when compared with early respondents [29], suggesting the survey answers of the respondents could be similar to those of non-respondents.

Conclusions

The proportion of TN beef producers keeping farm records on antimicrobial purchases and AMU may have increased over the last 10 years. The proportion of beef producers treating cattle with antimicrobials at dosages higher than the label indication may have reduced by 50% over the last 10 years. Culture and sensitivity tests for antimicrobial selection are currently not widely used in TN beef farms, perhaps due to cost implications. Peer recommendations could be a less important factor influencing the choice of antimicrobials among TN beef producers. There is need to promote the use of written antimicrobial treatment protocols among TN beef producers. Continued training for beef producers on infection prevention and control, and prudent AMU is needed.

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CHAPTER 6

Perceptions of Tennessee cattle producers regarding the Veterinary Feed Directive

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This chapter is a manuscript that will be submitted for publication in an appropriate journal. My contributions to this paper included gathering and review of literature; design and execution of the study; data preparation and analysis; interpretation of results; formulation of discussion topics; drafting and editing of the manuscript.

Abstract

Background

To prevent potential public health consequences of AMR, many countries have instituted measures to reduce and minimize AMU in food animals. Since January 1, 2017, the United States Food and Drug Administration (FDA) has implemented the Veterinary Feed Directive (VFD) aimed at facilitating judicious use of medically important antimicrobials in food producing animals. The objective of this study was to identify the common perceptions of Tennessee cattle producers regarding the VFD.

Materials and Methods

We used a combination of focus groups and survey questionnaires to explore Tennessee (TN) cattle producers' perceptions regarding the VFD. Preliminary findings from 7 focus groups of 62 producers were used in the development of the survey questionnaire sent both online and in-print to rest of cattle producers in TN.

Results

The beef focus group participants perceived the VFD: to be a top-down policy; to have led to unregulated access to in-feed antimicrobials; a regulation that has limited the producers' ability to prevent disease and leading to economic losses; to negatively affect small producers; and to be affected by challenges related to prescription writing and disposal of un-used medicines. The dairy focus group participants perceived the VFD as unnecessary and burdensome, to have affected small producers, and introduced additional costs. Twenty-eight beef producers (12.3%) believed the VFD is a very useful policy, 97 (42.5%) believed the VFD is somewhat useful, 32 (14.0%) took a neutral stand (neither not useful nor beneficial), and 27 (11.8%) believed the VFD is not useful. Among the dairy producers, one (2.3%) mentioned the VFD is a very useful policy, 10 (22.7%) mentioned the VFD is somewhat useful, 16 (36.4%) took a neutral stand (neither not useful nor beneficial), nine (20.4%) mentioned that VFD is not useful. Thirty-five beef producers (15.4%) were not familiar at all with the VFD while 48 (21.1%) were slightly familiar. Among dairy producers, six (13.6%) were not familiar at all with the VFD, whereas 11 (25%) were slightly familiar.

Conclusions

Many cattle producers were either not familiar or were slightly familiar with the VFD and perceived it as not useful. Therefore, more awareness regarding the VFD and its benefits is needed among both beef and dairy producers in TN.

Key words

Mixed methods study, Qualitative, Quantitative, Focus group discussions, Antimicrobial use, Antimicrobial resistance, Veterinary Feed Directive, Tennessee-dairy cattle producers

Background

Antimicrobial resistance (AMR) is a major global public health problem [1, 2] that has triggered global concerns over non-judicious antimicrobial use (AMU) in food animals [3]. Non-judicious AMU and inadequate antimicrobial stewardship (AMS) are known modifiable factors driving the occurrence of AMR [4]. To prevent potential public health consequences of AMR, many countries have instituted measures to reduce and minimize AMU in food animals [4] and have restricted AMU for growth promotion and disease prevention [5]. In Europe, the primary goal of banning the use of antimicrobial growth promoters was to reduce AMR traits in the microbial flora of food-producing animals [6]. Restrictions on the use of medically important antimicrobials in food-producing animals is a major strategy for addressing AMR [7]. The World Health Organization (WHO) recommends complete restriction of AMU in food animals for growth promotion and for disease prevention, and also recommends reduction in the overall use of medically important antimicrobials in food animals [1].

Antimicrobial use restrictions generally aim at mitigating AMR in humans and animals, are often administered through national-level policy [8]. These restrictions are based on the precautionary principle of public health, because there is currently no robust evidence of the public health impacts of AMU in food animals on antimicrobial resistance (AMR) in human pathogens [4]. Evidence from recent systematic reviews showed that although a large proportion of primary studies did not provide evidence supporting AMR transmission from and between food animals and humans, some primary studies suggested evidence for such transmission [9-11]. Recent studies have shown that indiscriminate AMU for both therapeutic and non-therapeutic purposes in animals leads to propagation and shedding of substantial amounts of AMR microorganisms [4, 12].

Beginning January 1, 2017, the United States Food and Drug Administration (FDA) implemented the Veterinary Feed Directive (VFD). The VFD is aimed at ensuring judicious use of medically important antimicrobials in food-producing animals [13]. The VFD authorizes the use of medically important antimicrobials in feed and water for therapeutic purposes, under the supervision of a licensed veterinarian. A previous review that evaluated evidence on unintended consequences of AMU restrictions in food animals recommended that more research should be conducted to evaluate, document, and report the unintended consequences of interventions targeting AMR reduction [7]. Since implementation, and prior to this present study, U.S. cattle producers' experiences with the VFD, to the best of our knowledge, had not been studied. No previous study to our knowledge had comprehensively explored the perceptions of Tennessee (TN) cattle producers regarding the VFD. Specifically, the objective of the study was to identify the common perceptions of TN cattle producers regarding the VFD. The findings reported here could inform VFD awareness campaigns and could help in the improvement of the VFD and the development of VFD-related policies.

Materials and methods

Study design

A mixed methods design using a combination of focus groups and survey questionnaires was utilized. To develop a robust questionnaire that captured our objective, focus group discussions with cattle producers were first conducted to gather opinions about the VFD. Preliminary findings from the focus group discussions were used in the development of the survey questionnaire that was administered to the rest of the cattle producers in TN. The University of Tennessee Knoxville, Institutional Review Board for the Protection of Human Subjects in Research reviewed and approved both the qualitative (Protocol number: UTK IRB-17-03702-XP) and the quantitative (Protocol number: UTK IRB-17- 03884-XP) parts of this study. Informed consent was obtained from each producer before participation in the study.

Qualitative methodology

Focus group design, structure, and procedure

In total, seven focus group discussions with 62 cattle producers were conducted. Of the seven focus groups, five involved beef producers and two were dairy producer groups. The five-beef producer focus groups were conducted in East TN, Middle TN, and West TN in June 2017 and had a total of 39 participants. For recruitment of beef producers, the leadership of the Tennessee Cattlemen's Association (TCA) invited members (via e-mail) with experience in different cattle production systems and from different geographical areas to represent a range of beef producers in TN. Each beef focus group comprised of 5 - 9 producers and lasted approximately 90 minutes. The two dairy producer focus groups were conducted in Middle TN and East TN in July 2017 and March 2018 respectively. The middle TN dairy focus group (dairy focus group 1) was conducted with dairy producers attending an annual dairy producer meeting while participants in the east TN focus group (dairy focus group 2) were recruited from dairy producers attending a master dairy training meeting. Dairy focus group 1 was held in a local restaurant while the second one was conducted at a county extension center. Prior to the dairy producer meetings, the University of Tennessee Institute of Agriculture extension agents notified and requested eligible producers to participate in our focus group meetings. Each focus group meeting lasted approximately 60 minutes. The first dairy focus group comprised 12 producers (participants) while the second one had 11 participants. In both the beef and dairy focus groups, each participant was given an informed consent form with an overview of the study and a signed consent was obtained before participation at the focus group discussion. Participants could opt out of the focus groups at any time. All invited participants were provided with a meal irrespective of their active participation.

A semi-structured interview guide which was modified after the very first focus group was utilized (see appendix 2). The modified interview guide (appendix 2B) consisted of 11 open-ended questions. We assigned each participant an identity number for confidentiality and to maintain anonymity. These identity numbers were used throughout the discussion and participants announced these numbers before speaking. All the seven focus groups were moderated by one of the authors (EBS) and all the four authors attended each focus group. Three members of the research team (JE, MC and CO) took hand written notes of key points, provided clarifications to questions, and asked follow-up questions were necessary. Debriefing meetings were held at the end of each focus group meeting and before the next focus group discussion as previously described [14]. In the beef focus groups, data saturation was reached during the fifth focus group discussion. However, data saturation was not reached in the dairy focus groups. For thematic analysis, each focus group discussion was video-recorded and later transcribed verbatim by a professional transcription service provider.

Data analysis

The beef and dairy transcripts were analyzed separately using a software (NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 12, 2017). Thematic analysis was performed using a recursive six-phase approach (familiarization with the data, generation of initial codes, search for themes, review of themes, definition and naming of themes, and report production) as described previously [15]. For data familiarization, each member of the team (JEE, MC, ES and CCO) read all transcripts. The percent of word similarity between the focus groups was assessed using Jaccard's coefficient. Two separate master projects (beef and dairy) with the transcripts uploaded were developed by the primary author (JEE) and distributed to the other authors for individual coding. For the beef master project, the initial nodes were identified through consensus at the debriefing meetings held after each focus group and each author was at liberty to use either the already prescribed coding frame in the master project (theoretical/deductive approach) or to create new nodes independent of the prescribed coding frame (the inductive approach) during the thematic analysis. For the dairy master project, an inductive approach was used to develop a coding frame (each author created independent nodes). Upon completion of the individual coding, the primary author (JEE) imported the other team members' coded data into the master project and examined if the themes from the individual coding were related to the coded extracts and all the data transcripts. The degree of agreement in the data coding among the coders (JEE, MC, EBS and CCO) was determined in NVivo using percent agreement. Results harmonization meetings were held by the research team to define and name/re-name themes. The identified themes were refined to identify sub-themes and to ensure that each theme is meaningful, clear and distinct.

Quantitative methodology

Study design and administration of survey

This survey targeted both beef and dairy cattle producers and was part of the broader survey of drivers of AMU practices among cattle producers in TN. First, a questionnaire was developed and evaluated by two professionals with expertise in AMU to ensure all critical issues were identified and covered (see appendix 3 for the survey questionnaire). Preliminary results obtained from the five beef focus groups and dairy focus group one was used to develop the questionnaire. The questionnaire captured the producer's demographics and had five questions on producers' perceptions regarding the VFD. The captured producer demographic information included age, sex (male versus female), level of education, herd size, whether raised on a livestock farm or not, and number of years in cattle farming. A three and a four-point scale as well as ordinal Likert scales were used to capture participant responses to questions on perceptions regarding the VFD.

For beef participants, the sample size required for this survey was determined to be 377 participants at 95% confidence level, a margin of error of 5%, 50% response distribution, and an assumed TN beef producer population size of 20,000. The survey targeted all dairy producers in the state (the estimated number of dairy producers in TN as of 2017 was 300) [16]. The survey questionnaire was made available to participants both in print form and online. Producers who completed the print questionnaire were requested in the informed consent statement not to complete the online survey and vice versa. The on-line version of the survey was housed in a survey software (Qualtrics software, Provo, UT) and was adapted for computer, tablets, and cell phone responses. Participant responses were de-identified using the anonymize function in Qualtrics such that no personal information was collected. Beef producers were notified about the online survey option during the TCA annual meeting in January 2018. Subsequently, all 2,712 producers on the TCA mailing list received an email invitation to take the survey. Additionally, an anonymous survey link and QR code for the online survey were provided to the TCA vice president for distribution to producers willing to take the survey. Dairy producers were also notified about the online survey option during an annual dairy producer meeting in January 2018. Subsequently, an email invitation to take the survey was sent out to all the 87 dairy producers on the University of Tennessee Animal Science department email list. To further increase the response rate, follow-up email reminders were sent to both beef and dairy on-line survey non-respondents every two weeks.

The printed questionnaire was distributed to beef producers attending the TCA annual meeting, and producer extension meetings across the state and to dairy producers attending dairy extension meetings such as the master dairy training sessions. Completed printed questionnaires were returned to the investigators. The survey (both the printed and online) remained open from January 26, 2018, through May 11, 2018. Participation in the survey was voluntary. All participants were invited to participate in a $10 gift card raffle taken at the end of the survey. The winners were randomly selected and eligibility to participate in the raffle was not contingent upon survey completion.

Statistical analysis

A commercial statistical software (SAS, version 9.4, SAS Institute Inc, Cary, NC) was used to complete descriptive analyses. Descriptive statistics (frequencies and proportions) were used to summarize the data. Stacked bar charts created in another commercial software (Tableau software, version 8.2, Seattle, WA) were used to visualize responses captured on the Likert scale.

Results

Perceptions of beef producers regarding the VFD: Qualitative results

Focus group participant characteristics

Of the 39 beef producers who participated in the five focus group discussions, one was female and 38 were male. Participants' perceived ages ranged from late twenties to early seventies and the reported herd size per producer ranged from approximately 20 to 225 cattle (**Table 6.1**). Jaccard's similarity index showed there was diversity among participants in the different focus groups (Jaccard's similarity index ranged from 27% to 33%). Percent agreement (in coding) between each pair of coders was >75 %.

Table 6.1: Beef focus group participant characteristics (n = 39)

Focus group	Geographic region (location)	Number of participants (n)	Herd size range	Gender of participants
1	Johnson City, East Tennessee	9	40 - 80	All male
2	Dickson county, middle Tennessee	9	40 - 135	All male
3	McNairy county, west Tennessee	8	30 - 200	All male
4	Jefferson county, East Tennessee	8	20 - 200	All male
5	Athens, McMinn county, East Tennessee	5	30 - 225	4 males, 1 female

Perceptions regarding the VFD

Although a section of participants stated that they were unaffected by the VFD, the VFD was commonly perceived to have negatively impacted production **(Figure 6.1)**. Broadly, the producers described the VFD: to be a top-down policy; to have led to unregulated access to in-feed antimicrobials; a regulation that has limited the producers' ability to prevent disease and leading to economic losses; to negatively affect small producers; and to be affected by challenges related to prescription writing and disposal of un-used VFD feed. Below, we give a detailed description and excerpts of the participants' perceptions about the VFD.

Top-down policy

The participants described the VFD as government over-reach that has created additional costs to producers and introduced additional difficulties to producers. Others perceived the VFD as red tape, and a policy that is ineffective. The VFD was also perceived to be a waste of time and money, not only for the producer and the veterinarian, but also for the government.

> *…I'm idea on the Veterinary Feed Directive is it did come from the top-down. It was implemented before the education process really even started. And building the plane while you're flying it doesn't work. It normally results in a crash… [No. 3 focus group 4].*

> *…I'd think they (government) jumped the gun with this VFD deal … I think they're taking things way far more than what – it's run good for years and years…. [Unidentified participant, focus group 5].*

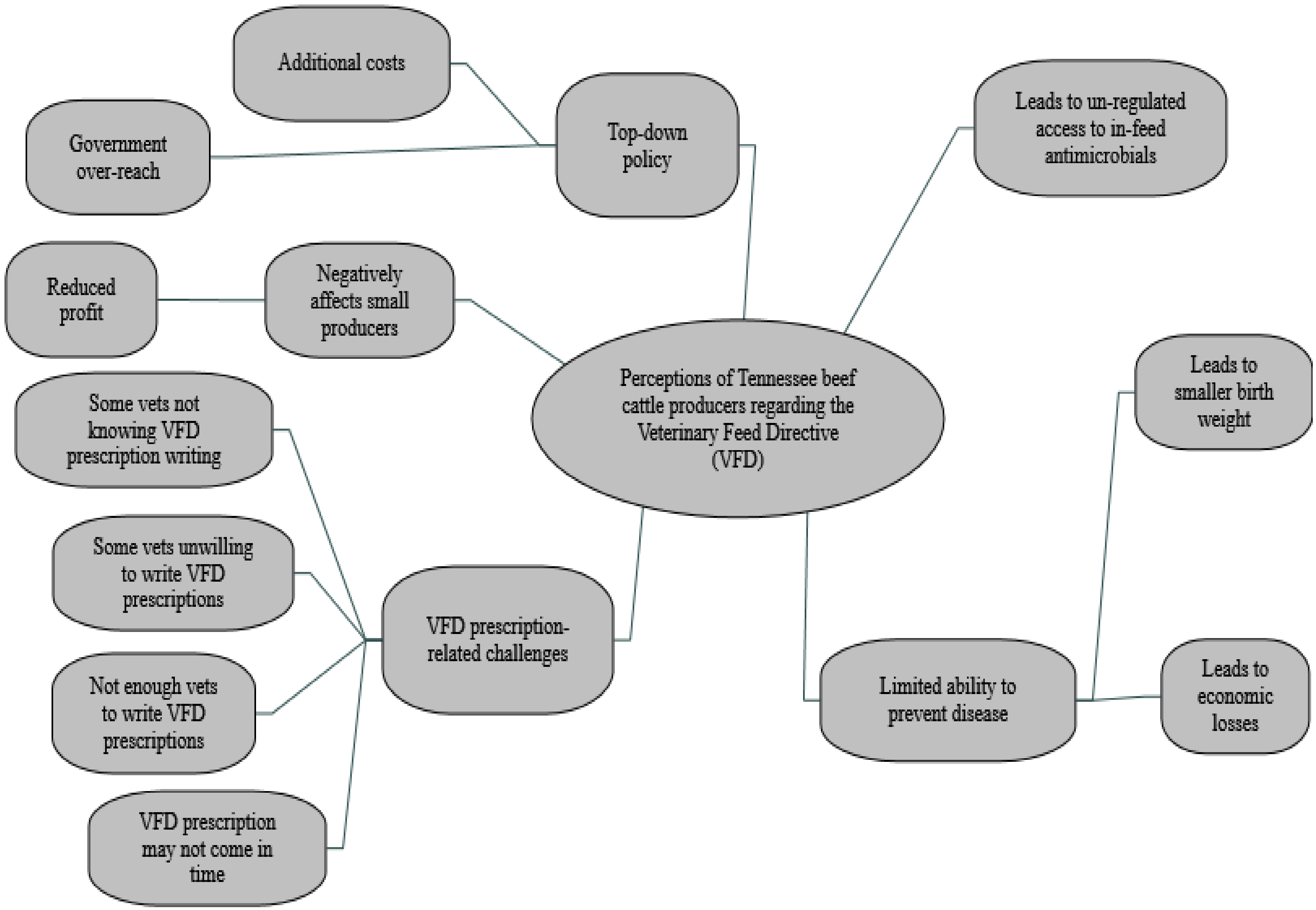

Figure 6.1: A thematic map showing relationship between major and minor themes for the perceptions of Tennessee beef cattle producers regarding the Veterinary Feed Directive (VFD)

The producers also frequently stated that the VFD adds to management by introducing additional labor associated with the work of getting the cattle up to give them an injectable, especially when the cattle may be a long distance away from the working/handling facilities. Additionally, the VFD was seen to have complicated farm record keeping.

… [VFD is] Additional hardship and burden on a business already……I think extra cost is all I can see, less profit…. [No. 5, focus group 4].

Unregulated access to in-feed antimicrobials

Un-regulated access to antimicrobials was mentioned as a likely un-intended consequence/outcome of the VFD. A section of participants in the west Tennessee focus group mentioned that the VFD would drive some producers to look for alternative sources of in-feed antimicrobials. These alternative sources would mostly be illegal and un-traceable.

…But you're gonna cause little things to go kind of illegal to get the job done… [No. 4, focus group 3]….There's gonna be people that are gonna do things to circumvent law that's not right… [No. 1, focus group 3]. …That's when the black market's gonna [supply in-feed antimicrobials] … [No. 2, focus group 3].

Limited producers' ability to prevent disease

The VFD limiting producers' ability to prevent disease was frequently expressed in all the focus groups. The producers expressed concern that the VFD has disabled disease prevention in their operations and is leading to economic loss and that the VFD is affecting the economic performance of the animals and setting up producers to financial losses. The VFD was commonly mentioned to have negatively affected calf health, led to reduced productivity and negatively affected animal welfare.

… the VFD has removed an ounce of prevention…They've set us up for financial loss… [No. 7, focus group 3].

…It's [VFD] a loss of money. When we have this in our feed system, our cow[s] were getting treated. …When we have these ingredients [antimicrobials] in our minerals and in our feed, most of the time it helps a lot to keep the pinkeye down, the sore foot down. If they've got a sore foot, they're not going to want to walk to the water trough and to the feed trough. They're not gaining weight. We're not making money… [No. 2, focus group 1].

The producers also mentioned that, because of the VFD, the lack of access to in-feed antimicrobials for prophylactic purposes would lead to smaller birth weight of calves, and lead to increased culling of calves due to disease.

…You'd think the public would want to see a healthy calf going to market or a sick calf going to market. That's what it's going to be. There're going to be more and more sick calves slaughtered… [No. 3, focus group 5].

VFD negatively affects small producers

There was a consensus among all the focus group participants that the VFD has negatively affected the small producers by introducing additional costs of involving a veterinarian and the costs of setting up facilities for handling cattle and therefore, affecting the profit margins of small producers. It was clear from the discussions that small scale beef producers rarely involved veterinarians in their operations.

… To get the Veterinary Feed Directive, it's going to require you to have that call. And that small producer – where's the profit margin at? If you spread that veterinarian client

relationship over 100-150 cows, you're alright. And you have that connection. But if you have nine, that one farm call may have cost you your profit… [No. 4, focus group 5].

…My impression and my opinion is the Feed Directive is particularly impacting negatively the small stocker operation, which is me… If I feed according to script – which we're probably not going to do anymore – I have to feed 11 pounds per head per day for five days, stop. These calves won't be eating 11 pounds a week for the first week. [No. 2, focus group 2].

…. A lot of these smaller producers don't have the facilities to get these animals up. And they might [have] five or ten head of cattle. And if they don't have that measure in the feed, they don't have a way of treating them at all. …And their production, if they've only got five head of animal[s] and they lose one, that's 25 percent of their whole herd or 20 percent. That affects their production greatly… [No. 5, focus group 5].

VFD prescription-related challenges

Some focus group participants commonly expressed concern that some veterinarians did not know how to write VFD prescriptions.

… And it's been a nightmare. We get prescriptions that aren't worth the paper they're written on. I mean, the vets don't understand how to write them. And lots of times I have to send an example. They'll say send me an example of how it should read. I mean, there's just not been a lot of education on the proper way to write them… [No. 6, focus group 1].

…Even the vets that we deal with didn't know how to write a VFD. It didn't have all the items on there that needed to be for us to legally sell the items. If the vets didn't know

> *how to do it, it's for sure that the everyday producer didn't know how it worked. People would come in with the VFD from their vet that wouldn't even tell what product to give them or what level or quantity to give them. It's a real struggle, and it still is. We still get those things after months of this that these people don't know… [No. 5, focus group 5].*

On the other hand, some producers mentioned that some veterinarians were unwilling to write VFD prescriptions. While others mentioned that in their areas, there are not enough veterinarians to write VFD prescriptions. That even when it is possible to get a VFD prescription, the prescription may be delayed thus limiting their ability to manage disease in their farms. One focus group participant in the McNairy county focus group (West-Tennessee) stated that disposal of un-used in-feed antimicrobials was a challenge because the garbage collectors considered un-used VFD medicines medical waste that is not supposed to be placed in garbage.

> *…Some vets won't write them. They're just not going to fool with it. It's just not worth their time …. [No. 6, focus group 1].*

> *…I mean, I called the vets. They weren't around for our program, not in Tennessee. No, sir. I got one, but I never used it. I sent $75.00 to another state and got. A vet in this area would not write one, period… [No. 2, focus group 1].*

Perceptions of beef producers regarding the VFD: Quantitative results

A total of 231 beef producers participated in the survey. Of the 231 participants, 103 completed the hard copy survey while 128 completed the online version. Of the 231 participants, 200 provided their gender: 35 females and 163 males. Two of these respondents preferred not to report their gender. Complete responses were provided for most questions with the exception of a few cases where the respondents left some questions unanswered. The demographic information of the respondents is presented in **Table 6.2**.

Table 6.2: Demographics of beef producers on survey of the perceptions of Tennessee beef producers regarding the veterinary feed directive, 2017

Variable	Number (%) of respondents
Gender	**n = 200**
Female	35 (17.5)
Male	163 (81.5)
Preferred not to report gender	2 (1.0)
Age group (years)	**N = 200**
< 30	12 (6.0)
30 – 39	29 (14.5)
40 – 49	41 (20.5)
50 – 59	44 (22.0)
60 – 69	46 (23.0)
>70	28 (14.0)
Education level	**N=202**
< College	47 (23.3)
≥ College	155 (76.7)
Years in cattle production	**N = 202**
< 5	23 (11.4)
6 – 10	19 (9.4)
11 – 15	17 (8.4)
16 – 20	24 (11.9)
21 – 25	24 (11.9)
26 – 30	21 (10.4)
>30	74 (36.6)
Beef cattle operation type	**N = 230**
Cow-calf production	171 (74.4)
Backgrounding-stocking	9 (3.9)
Seed-stock operation	6 (2.6)
Multiple operation type and others	44 (19.1)
Herd size	**n = 202**
1 – 49	84 (41.6)
50 - 99	54 (26.7)
100 – 149	28 (13.9)
150 - 199	12 (5.9)
200 - 299	13 (6.4)
300 - 399	5 (2.5)
400 - 499	1 (0.5)
500+	5 (2.5)
Raised on a cattle farm	**n = 202**
Yes	138 (68.3)
No	64 (31.7)

Perceptions regarding VFD

Regarding the beef producers' familiarity with the VFD, 35 (15.4%) were not familiar at all, 48 (21.1%) were slightly familiar with VFD, 75 (32.9%) were moderately familiar, 55 (24.1%) were very familiar, and 15 (6.6%) mentioned extremely familiar. A large proportion (36.4%) of respondents were either not at all familiar or slightly familiar with the VFD. Twenty-eight beef producers (12.3%) believed the VFD is a very useful policy, 97 (42.5%) believed the VFD is somewhat useful, 32 (14%) took a neutral stand (neither not useful nor beneficial), 27 (11.8%) believed the VFD is not useful. Forty-four producers (19.3%) did not give their opinion on the usefulness of VFD because they were not familiar with the VFD. Of the 227 producers who responded to the question on whether they were aware of the VFD before its implementation, 128 respondents (56.4%) mentioned that they were aware of the VFD before its implementation, eighty-six (37.9%) mentioned they were not aware of VFD before its implementation, while 13 (5.7%) were not sure.

The beef producer responses as to whether the VFD influenced producers to seek veterinary services varied. Forty-five participants (20.2%) mentioned that the VFD has caused them to seek veterinarian services more frequently, 137 (61.4%) reported VFD has not influenced them to seek veterinarian services, 10 (4.5%) reported VFD has reduced their use of veterinarian services, and 31 (13.9%) did not specify how the VFD influenced their use of veterinary services. More perceptions of survey participants regarding the VFD are provided in **Figure 6.2.**

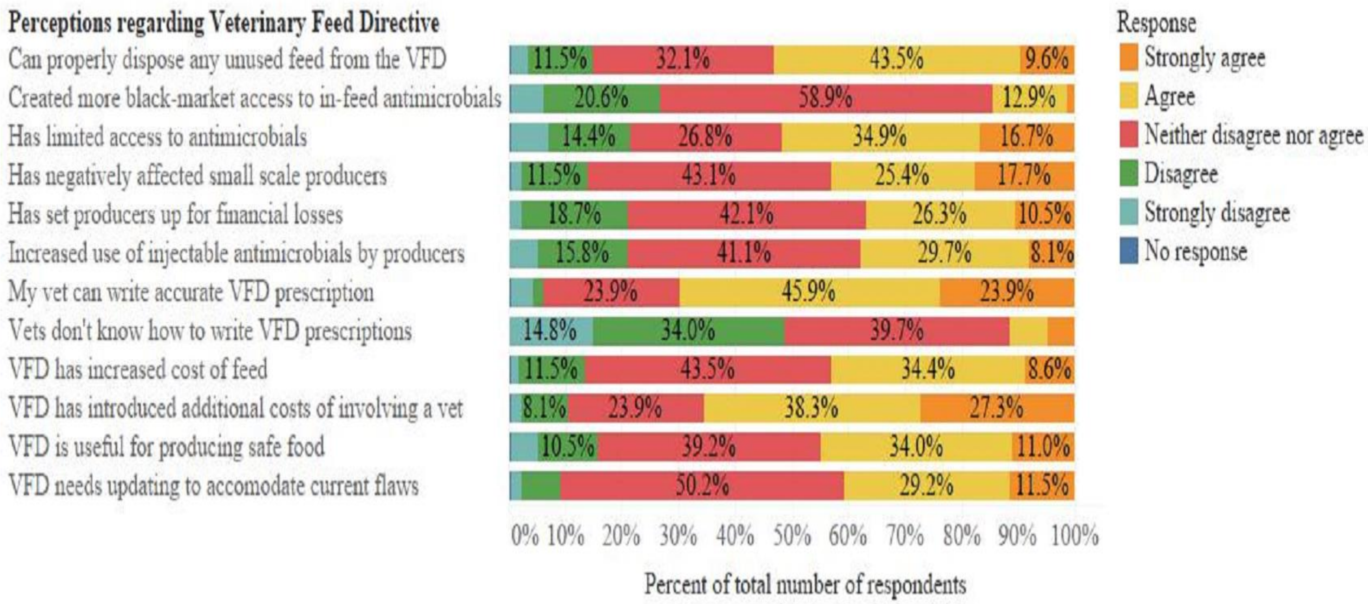

Figure 6.2: Tennessee beef producers' perceptions (n = 209) regarding the Veterinary Feed Directive, 2018

Perceptions of dairy producers regarding the VFD: Qualitative results

Focus group participant characteristics

A total of 23 dairy producers participated in the 2 focus groups. Dairy focus group 1 had one female, and 11 male participants while the second one had 2 females and 9 male participants. The reported milking herd size per producer ranged from approximately 40 to 1100 dairy cattle.

The responses from the 2 focus groups were 31.2% similar (Jaccard's similarity index = 0.312). This Jaccard's similarity index provided evidence that there was diversity among participants. Percent agreement (in coding) between each pair of coders was > 80 %.

The VFD perceptions

The general perceptions from the dairy producer focus groups were that the VFD is an unnecessary and burdensome policy that has affected small producers and introduced additional costs that cannot be passed along to consumers.

> *…It's just more cost. I think it's $25.00 for the veterinarian – I mean, that $25.00 aingt [is not] going to make or break nobody. But it's still $25.00. That's just something else you gotta deal with. And who gets that?... [No.6, dairy focus group 2].*

> *…There's no problem with it [VFD] in one sense if I could pass my additional cost along. …You made my cost of production go up. I can't do a thing about it. I cannot pass that along to the milk processor. I cannot do anything to recoup that cost. I've got to bear it all myself… [No.9, dairy focus group 2].*

That the VFD has limited producers' access to essential antimicrobial medicines necessary for preventive care and subsequently leading to increased disease occurrence especially among calves, increased animal deaths and reduced productivity, and increased use of injectable antimicrobials.

> *…Like on the foot bath for your dairy cows, it's hard to get the tetracycline now unless you do whatever. That's our biggest problem because if you don't keep those warts under control, then you've got sore feet. And you've got cold cow. That is our biggest problem… [No.8, dairy focus group 2].*

> *… we used to use aureomycin 700. And it was a preventative type thing and a useful thing that we can't use now. It's just too much hassle to get it. I couldn't say that it was that harmful. … [No.1, dairy focus group 1].*

> *…We had to do what we could to get the downtime to try to save our animals. We lost some, and we saved some… [No.7, dairy focus group 2]*

However, some producers mentioned that they did not have difficulty accessing these medicines because they have a good veterinarian-client-patient relationship with their veterinarians.

> *…Some heifer feeds and other feeds, we go through our vet to get – prescription or whatever you want to call it – even in the beef cattle – mainly Aureomycin that we use in some different feeds. If you have a working relationship with your vet and your vet knows what he's doing, you don't have any problems if you'll do what he says. If you go haphazardly, you're going to have problems… [No.9, dairy focus group 2].*

Perceptions of dairy producers regarding the VFD: Quantitative results

A total of 45 producers participated in the dairy section of the survey. Complete responses were provided in most questions except for a few cases where some respondents left some questions unanswered. Of the 45 dairy participants, 40 completed the hard copy survey while only five completed the online version. Thirty-nine (39) provided their gender: 31 males and seven females. One respondent preferred not to report his/her gender. The demographic information of the survey respondents is presented in **Table 6.3**.

Table 6.3: Demographics of dairy producers on survey to identify common perceptions of Tennessee dairy producers regarding the veterinary feed directive, 2018

Variable	**Number (%) of respondents**
Gender	**n = 39**
Female	7 (18.)
Male	31 (79.5)
Preferred not to report gender	1 (2.6)
Age group (years)	**n = 37**
20 – 29	2 (5.4)
30 – 39	6 (16.2)
40 – 49	8 (21.6)
50 – 59	13 (35.1)
60 – 69	8 (21.6)
Education level	**n = 37**
High school	16 (43.2)
Vocational	2 (5.4)
College	18 (48.7)
Professional	1 (2.7)
Years in dairy cattle production	**n = 38**
< 5	1 (2.6)
6 – 10	6 (15.8)
16 – 20	1 (2.6)
21 – 25	4 (10.5)
26 – 30	4 (10.5)
> 30	22 (57.9)
Herd size	**n = 37**
1 – 49	2 (5.4)
50 – 99	8 (21.6)
100 – 149	7 (18.9)
150 – 199	5 (13.5)
200 – 299	7 (18.9)
300 – 399	3 (8.1)
400 – 499	1 (2.7)
500+	4 (10.8)
Raised on a cattle farm	**n = 39**
Yes	2 (5.1)
No	37 (94.9)

Perceptions regarding VFD

Regarding the dairy producers' familiarity with the VFD, 6 (13.6%) were not familiar at all, 11 (25%) were slightly familiar with VFD, 18 (40.9%) were moderately familiar, and 9 (20.5%) were very familiar. A substantial proportion (38.6%) of respondents were either not at all familiar or slightly familiar with the VFD. One dairy producer (2.3%) believed the VFD is a very useful policy, 10 (22.7%) believed the VFD is somewhat useful, 16 (36.4%) took a neutral stand (neither not useful nor beneficial), nine (20.4%) mentioned that the VFD is not useful. Eight producers (18.2%) did not give their opinion on the usefulness of VFD because they were not familiar with it.

The dairy producer responses as to whether the VFD influenced producers to seek veterinary services varied. Thirteen participants (30.9%) reported that the VFD had caused them to seek veterinarian services more frequently, 23 (54.8%) reported VFD had not influenced them to seek veterinarian services, four (9.5%) reported VFD had reduced their use of veterinarian services, two (4.8%) stated that VFD had not influenced their use of veterinary services in any way. More perceptions of survey participants regarding the VFD are provided in **Figure 6.3.**

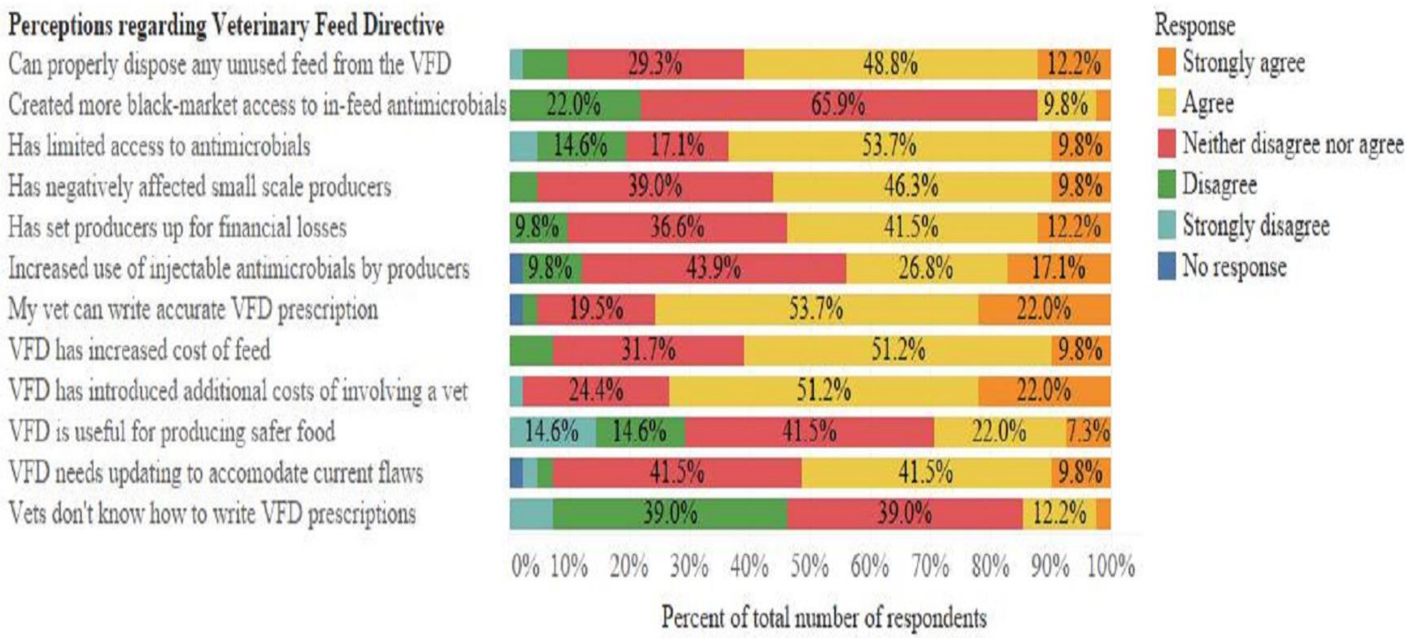

Figure 6.3: Tennessee dairy producers' perceptions (n = 41) regarding the Veterinary Feed Directive, 2018

Discussion

The present study identified the perceptions of TN cattle producers regarding the VFD and presents the first published perceptions among cattle producers in TN since the VFD final rule became effective on January 1, 2017. In the present study, the VFD was generally perceived by most producers to have negatively affected them. This finding is similar to the that of a 2015 survey of U.S. beef producers, that was conducted prior to the VFD becoming effective on January 1, 2017 where 70% of the surveyed population expressed a negative attitude towards the VFD [17]. Many participants in the present study were either not familiar or slightly familiar with the VFD suggesting a need for more producer awareness regarding the VFD. Producers' negative perceptions regarding the VFD may reflect the challenges and frustrations experienced by the producers since its implementation.

In the present study, the producers were concerned that the VFD had and would lead to increased occurrence of disease in herds and increased mortalities, has limited their ability to prevent disease, would lead to smaller birth weight of calves, and lead to increased culling of calves due to disease. A previous review study provided evidence from mostly Europe showing that the unintended consequences from national-level restrictions on AMU on food-producing animals is temporary and minor [8, 18]. Tennessee producers' concerns regarding the VFD may be justified and warrant more research on other states. A nationwide evaluation of these perceptions may be useful. Although the intended consequence of the VFD is to ensure judicious AMU and mitigate AMR, its negative effects on animal health, welfare, and production could definitely be unintended.

According to the FDA [19], disposal of VFD feed that is no longer needed/left over should be in a manner that is in accordance with state or local requirements for medicated feeds.

In the present study, a beef focus group participant mentioned that disposal of un-used in-feed antimicrobials had become a challenge because the garbage collectors considered un-used VFD medicines or medical waste that is not supposed to be placed in regular garbage. Similarly, although more than half of the survey questionnaire respondents (both beef and dairy) either agreed or strongly agreed that they were aware of how to properly dispose any un-used VFD feed, a considerably large number (14.5% beef and 9% dairy) either strongly disagreed or disagreed. These findings suggest that (1) for many TN cattle producers, disposal of un-used VFD feed is problematic, (2) there is a need for more awareness among producers of the FDA guidance on disposal of un-used/expired VFD feed. To ensure proper disposal, veterinarians and beef/dairy extension agents should conduct routine producer awareness regarding the Tennessee requirements (or local area requirements) for disposal of medicated feeds.

In the present study, the producers mentioned that the VFD's limiting of access to in-feed antimicrobials has affected the economic performance of their herds and would lead to smaller birth weight of calves. Although this concern warrants more research in the U.S. context, it has been suggested that growth response to in-feed antimicrobials is small in optimized production systems [20]. Additionally, changes in antimicrobial consumption following the implementation of policies to discontinue AMU for growth promotion in Denmark did not have a negative impact on swine productivity [21]. Researchers in Europe suggested that coercive instruments such as regulations and fines may result in unintended consequences such as illegal AMU practices among producers [22]. In the present study, some focus group participants mentioned that the VFD "would" lead to un-regulated access to in-feed antimicrobials through the black market. Also, more than 12% of beef participants and more than 9% of dairy producers either agreed or strongly agreed with the statement "the VFD has created more black-market access to in-feed antimicrobials by producers". Because black market access is possible if there is public demand [23], the farmers assertion that the VFD has created un-regulated access to in-feed antimicrobials through the black market needs to be studied further across the nation so that appropriate interventions to curtail un-regulated access are designed and instituted.

In the present study 37.8% of the beef producers and 43.9 % of dairy producers who completed the survey questionnaire either agreed or strongly agreed that the VFD would lead to increased use of injectable antimicrobials by producers. This perception suggests that there might be a compensatory increase in the use of injectable antimicrobials for therapeutic and prophylactic purposes from the time the VFD became effective. It would be beneficial to further investigate the perceived increase in injectable AMU. Improved veterinary oversight, linking antimicrobial surveillance to remedial action on excessive AMU, implementation of mandatory AMU reduction targets, and improvements in animal health are suggested as measures for containing compensatory increases in AMU following restricted use [7]. However, for Tennessee and the U.S. in general, increased campaigns for improved animal health may be the only feasible option for avoiding any compensatory increase in AMU due to the VFD. This is because in TN and the U.S. in general, there is currently: (1) shortage of food animal veterinarians in some areas, (2) lack of data on antimicrobial consumption in cattle farms (which data would be an indicator of the appropriateness of AMU), and (3) absence of mandatory AMU reduction targets.

The strengths for this present study were that: (1) there was diversity of opinions among participants as shown by Jaccard's similarity index and the survey participant demographics, (2) a mixed methods research design was utilized, (3) both focus group and survey respondents were assured that the data collected was anonymized and participation was voluntary, and (4) the survey questionnaire (both print and online) was self-administered. Additionally, the focus group discussions were moderated by one of the authors (EBS) with a background in the behavioral/social sciences and wide experience in moderating such meetings. Nevertheless, the focus group and survey participants could have given socially desirable responses, thus introducing bias to our findings. However, such bias, if any, could be very minimal. Participants are likely to have given their true perceptions regarding the VFD.

Conclusions

The findings of this study could inform future VFD policy review processes. Many cattle producers were either not familiar or slightly familiar with the VFD and perceived it as not useful. Disposal of VFD feed, as required of the VFD rule, could be problematic for many TN producers. More awareness regarding the VFD is needed among both beef and dairy producers in TN. For antimicrobial stewardship purposes, campaigns targeting improved animal health in cattle farms should be stepped up to contain the unintended compensatory increase in injectable AMU due to the VFD. A nationwide survey of the perceptions of cattle producers regarding the VFD should be conducted to inform future policy making and implementation.

Declarations

Consent for publication

The authors declare that the manuscript does not contain any personally identifiable information and all personal data were anonymized.

Availability of data and material

The open-ended focus group interview guide and the survey questionnaire are available in the appendices section of this dissertation. All data (focus group transcripts) pertaining to the manuscript can be obtained from the corresponding author of this manuscript upon reasonable request.

Competing interests

The investigators declare that they have no competing interests.

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Authors Contributions

The primary author (JEE) participated in designing and executing the study, performed both the qualitative and quantitative data analysis, and prepared the manuscript draft. MC, EBS and CCO participated in study design and execution, performed qualitative data analysis and edited the manuscript. All authors read and approved the final manuscript.

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CONCLUSIONS, RECOMMENDATIONS AND FUTURE RESEARCH DIRECTIONS

General conclusions

To my knowledge, this is the first study to comprehensively investigate the epidemiology of veterinary AMU among clinicians at UTVMC and among TN dairy and beef cattle producers. The findings of this research can help improve veterinary AMU among clinicians in UTVMC and among TN cattle producers. After controlling for UTVMC clinicians' primary patient load, clinicians' concern about AMR decreased among those who graduated after 1999 compared to those that have been in clinical practice for longer.

Tennessee cattle producers generally perceived their use of antimicrobials to be discreet. Compared to beef producers, the use of culture and sensitivity tests for on-farm pathogen surveillance and for selecting antimicrobials is a more common practice among TN dairy farmers. Blanket dry cow therapy is still commonly practiced by some dairy producers in TN. The proportion of TN beef producers keeping farm records on antimicrobial purchases and AMU may have increased over the last 10 years. Many TN cattle producers were either not familiar or were slightly familiar with the VFD and perceived it as not useful. Disposal of VFD feed could be problematic for many producers in the state. Due to similarities in cattle production systems, the findings from the studies with the TN cattle producers could hold true for most of the southeastern U.S. Similar studies need to be conducted in other parts of the U.S.

Recommendations

This dissertation recommends the following as key strategies for antimicrobial stewardship in the studied populations.

1. An AMS program should be developed and implemented at UTVMC hospital.
2. Awareness about judicious AMU practices as well as AMR among clinicians and clients at UTVMC, and among cattle producers, should be increased. Client education on prudent AMU and on AMR should be integrated into routine clinical practice at UTVMC. Cattle producer education on prudent AMU should be integrated in routine farm visits by the veterinarian.
3. Campaign efforts targeting behavioral change on AMU among producers should focus on encouraging producers to continue benchmarking AMU practices from peers.
4. Selective dry cow therapy should be promoted among TN dairy cattle producers and blanket dry cow therapy discouraged. A policy shift towards banning blanket dry cow therapy in TN and the entire US should be explored.
5. Use of written antimicrobial treatment protocols among TN cattle producers should be promoted.
6. More awareness regarding the VFD and its associated benefits should be conducted among cattle producers in TN.
7. For antimicrobial stewardship purposes, campaigns targeting improved animal health in cattle farms should be stepped up to contain the likely unintended compensatory increase in AMU due to the VFD.
8. Awareness among producers of the FDA guidance on disposal of un-used/left over VFD feed should be conducted. Veterinarians and beef/dairy extension agents should conduct

routine producer awareness regarding the TN requirements (or local area requirements) for disposal of medicated feeds.

Future research directions

Future studies investigating AMU in TN and perhaps other parts of the U.S. should consider evaluating the following:

1. Antimicrobial use practices of clinicians in primary care veterinary practices.
2. Judicious /non-judicious AMU in the teaching as well as first opinion (primary care) veterinary hospitals using actual prescription records.
3. The types of antimicrobial purchases and antimicrobial use records used by cattle producers in TN so that areas for improvement are identified for appropriate, and accurate data collection on AMU.
4. Objective, reproducible, and transparent methods for quantifying on-farm AMU in TN and the U.S.
5. The appropriateness of dosage rates indicated on drug labels for currently used veterinary antimicrobials in the U.S.
6. The actual impact of the VFD on the use of injectable antimicrobials among TN and U.S. cattle producers.
7. The actual impact of the VFD on un-regulated access to in-feed antimicrobials among TN and U.S. cattle producers in general.

APPENDICES

Appendix 1: Survey questionnaire for antimicrobial use practices at a U.S. veterinary teaching hospital

Thank you for participating in this study. Please read the informed consent statement before proceeding by clicking on this link. (Consent form will open in a new window or tab.)

Approved informed consent statement

I have read and understood the above informed consent statement and I have voluntarily chosen to participate in this study.

- ○ Yes
- ○ No

Skip To: End of Survey If Answer = No

Q1. Which of the following best describes your primary patient load?

○ Small animal

○ Equine

○ Food animal

○ Mixed animal

○ Exotic

○ Others ____

Q2. Which of the following best describes the nature of your clinical position?

○ Faculty member with clinical duty expectations

○ Resident

○ Intern

Q3. Which of the following best describes your areas of service? (Please check all that apply)

☐ Oncology and radiation oncology

☐ Ophthalmology

- [ ] Nutrition
- [ ] Radiology and veterinary imaging service
- [ ] Rehabilitation and physical therapy
- [ ] Soft tissue surgery
- [ ] Orthopedic surgery
- [ ] Avian, exotic and zoological medicine
- [ ] Neurology
- [ ] Internal medicine
- [ ] Emergency/critical care/ICU
- [ ] Dermatology
- [ ] Cardiology
- [ ] Anesthesia
- [ ] Behavioral medicine

☐ Dentistry

☐ Field services-equine

☐ Field services-food animal

☐ In - hospital equine

☐ In - hospital food animal

☐ Theriogenology

☐ Others ____

Q4. Which of the following describes the period of your graduation from veterinary school?

○ 1960s

○ 1970s

○ 1980s

○ 1990s

○ 2000s

○ 2010 and above

Q5. Which of the following best describes your total number of years in clinical practice from the time you graduated from veterinary school?

- ◯ < 1 year
- ◯ 1 - 5 years
- ◯ 6 – 10 years
- ◯ 11 - 15 years
- ◯ 16 - 20 years
- ◯ 21 - 25 years
- ◯ 26 - 30 years
- ◯ > 30 years

Q6. How many years have you been in clinical practice at UT Veterinary Medical center?

- ◯ < 1 year
- ◯ 1 - 5 years
- ◯ 6 – 10 years
- ◯ 11 - 15 years
- ◯ 16 - 20 years

○ 21 - 25 years

○ 26 - 30 years

○ > 30 years

Q7. From where did you obtain your veterinary degree?

○ U.S veterinary school

○ Non - U.S veterinary school

Q8. Do you have specialty board certification?

○ Yes

○ No

○ Approved for exam, but not yet certified

Q9. What proportion of your total professional activity is dedicated to clinical practice?

○ Less than 20%

○ 20-39%

○ 40-59%

○ 60-79%

○ 80-100%

Q10. How often do you prescribe antimicrobials for therapeutic treatment of infectious diseases in your clinical setting?

○ Never

○ Once a week

○ 2 times a week

○ 3 - 5 times a week

○ > 5 times a week

Q11. How often do you prescribe antimicrobials for **metaphylaxis**?

- ◯ Never
- ◯ Once a week
- ◯ 2 times a week
- ◯ 3 - 5 times a week
- ◯ > 5 times a week

Q12. How often do you prescribe antimicrobials for **prophylaxis** of infectious diseases?

- ◯ Never
- ◯ Once a week
- ◯ 2 times a week
- ◯ 3 - 5 times a week
- ◯ > 5 times a week

Skip To: Q16 If Q12 = Never

Q13. How often do you prescribe antimicrobials for **peri-operative** prophylaxis of infections?

○ Never

○ 1 - 2 cases out of every 10 surgical patients

○ 3 - 5 cases out of every 10 surgical patients

○ 6-8 cases out of every 10 surgical patients

○ > 8 cases out of every 10 surgical patients

Q14. How often do you prescribe antimicrobials for **pre-operative** prophylaxis of infections?

○ Never

○ 1 - 2 cases out of every 10 surgical patients

○ 3 - 5 cases out of every 10 surgical patients

○ 6 - 8 cases out of every 10 surgical patients

○ > 8 cases out of every 10 surgical patients

Q15. How often do you prescribe antimicrobials to prevent **post-operative** infections?

○ Never

○ 1 - 2 cases out of every 10 surgical patients

○ 3 - 5 cases out of every 10 surgical patients

○ 6 - 8 cases out of every 10 surgical patients

○ > 8 cases out of every 10 surgical patients

Q16. How familiar are you with "The Veterinarian-Client-Patient-Relationship"?

○ Not familiar at all

○ Slightly familiar

○ Moderately familiar

○ Very familiar

○ Extremely familiar

Q17. How often do you utilize "The Veterinarian-Client-Patient-Relationship" in your antimicrobial prescription practice?

○ Never

○ Rarely

○ Sometimes

○ Often

○ Always

Q18. Which one of the following best represents your opinion about antimicrobial use at UT Veterinary Medical Center?

- ◯ Antimicrobials are sometimes prescribed based on no documented evidence of infection.
- ◯ Antimicrobials are sometimes prescribed for suspected (but not confirmed) infections.
- ◯ Antimicrobials are prescribed based only on confirmed infection.
- ◯ Not sure

Q19. How important are the following factors in determining your choice of antimicrobial for clinical use?

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Clinical signs	◯	◯	◯	◯	◯
History of previous antimicrobial use on the animal	◯	◯	◯	◯	◯
Pressure from clients/producers	◯	◯	◯	◯	◯
Peer or colleague recommendations	◯	◯	◯	◯	◯
Cost implications	◯	◯	◯	◯	◯

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Results of cytological evaluation	○	○	○	○	○
Results of bacteriological culture and antimicrobial susceptibility testing	○	○	○	○	○
Route of administration	○	○	○	○	○
Frequency of administration	○	○	○	○	○
Medication size or volume	○	○	○	○	○
UT Veterinary Medical Center antimicrobial use policy/guidelines	○	○	○	○	○
Potential for adverse reactions	○	○	○	○	○

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Availability of antimicrobial agent(s)	○	○	○	○	○
Concerns about antimicrobial resistance issues in animals	○	○	○	○	○
Concerns about antimicrobial resistance issues in humans	○	○	○	○	○
Fear of litigation by the client/producer in the event of an undesirable clinical outcome	○	○	○	○	○
Concerns about animal welfare	○	○	○	○	○
Prudent use guidelines	○	○	○	○	○
Drug withdrawal periods	○	○	○	○	○
Compliance by the client/producer to the prescription	○	○	○	○	○

Q20. How important are the following sources of antimicrobial information in determining your choice of antimicrobial for clinical use?

	Not at all Important	Slightly important	Moderately important	Very important	Extremely important
Pharmaceutical company representative	○	○	○	○	○
Label or package insert	○	○	○	○	○
Peer-reviewed scientific literature	○	○	○	○	○
Peers within my service	○	○	○	○	○
Peers outside of service (clinician or pharmacist)	○	○	○	○	○
Veterinary Information Network (VIN)	○	○	○	○	○
UTCVM formulary	○	○	○	○	○
Online resource e. g. blog, media post, or web search	○	○	○	○	○
Textbook or drug handbook	○	○	○	○	○
Applications on a smart phone or tablet	○	○	○	○	○
Online formulary	○	○	○	○	○

Q21. How would you rank the following classes of antimicrobials based on your frequency of prescription?

	Never	Rarely	Sometimes	Very often	Always
Aminoglyosides	○	○	○	○	○
Cephalosporins	○	○	○	○	○
Fluoroquinolones	○	○	○	○	○
Lincosamides	○	○	○	○	○
Macrolides	○	○	○	○	○
Penicillins	○	○	○	○	○
Sulfas	○	○	○	○	○
Tetracyclines	○	○	○	○	○

Q22. To what extent did your DVM (veterinary medical) training alone, adequately equip you with knowledge on rational use of antimicrobials?

○ Not at all

○ A little

○ Somewhat

○ Quite a bit

○ Very much

Q23. Do present day veterinary medical students receive adequate training on rational use of antimicrobials?

○ Not at all

○ A little

○ Somewhat

○ Quite a bit

○ Very much

Q24. How frequently do you read FDA/AVMA guidelines for judicious use of antimicrobials? (Check only one.)

○ Never

○ Rarely

○ Sometimes

○ Very often

○ Always

Q25. Antimicrobial stewardship programs are coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of optimal antimicrobial regimen, dose, and duration of therapy and route of administration. Does the UT Veterinary Medical Center have an antimicrobial stewardship program?

- ◯ No
- ◯ Not sure
- ◯ Yes

Display This Question:
If Antimicrobial stewardship programs are coordinated interventions designed to improve and measure... = No

Q26. Do you think the UT Veterinary Medical Center should develop and implement an antimicrobial stewardship program?

○ Yes

○ No

○ Not sure

Q27. Which one of the following best represents your opinion about antimicrobial prescription at the UT Veterinary Medical Center?

○ Antimicrobials are under prescribed

○ Antimicrobials are optimally prescribed

○ Antimicrobials are over-prescribed

Q28. How do you rate your degree of concern about antimicrobial-resistant infections?

○ Not concerned

○ Slightly concerned

○ Moderately concerned

○ Quite concerned

○ Very concerned

Q29. How do you rate other veterinarians' concerns about antimicrobial resistance?

◯ Not concerned

◯ Slightly concerned

◯ Moderately concerned

◯ Quite concerned

◯ Very concerned

Q30. How do you rate the majority of your clients' concerns about antimicrobial resistance?

◯ Not concerned

◯ Slightly concerned

◯ Moderately concerned

◯ Quite concerned

◯ Very concerned

Q31. To what extent do you agree or disagree with the following statement? "Antimicrobial classes commonly used in human medicine should not be used in veterinary medicine because their use in veterinary medicine selects for antimicrobial resistance in microbes affecting humans."

- Strongly disagree
- Disagree
- Neither disagree nor agree
- Agree
- Strongly agree

Q32. To what extent do you agree or disagree with the following statement? "Antimicrobial drug use in veterinary practice may lead to antimicrobial resistance in pathogens affecting humans."

- Strongly disagree
- Disagree
- Neither disagree nor agree
- Agree
- Strongly agree

Q33. To what extent do you agree or disagree with the following statement? "Veterinarians who grew up on farms tend to prescribe antimicrobials more often than veterinarians who did not grow up in farms."

○ Strongly disagree

○ Disagree

○ Neither disagree nor agree

○ Agree

○ Strongly agree

Q34. What are the 5 antimicrobial drugs that you commonly prescribe? (Rank from the most to the least.)

○ 1. *Most used* ____

○ 2. ____

○ 3. ____

○ 4. ____

○ 5. *Least used* ____

Q35. What is your year of graduation from veterinary school?

____

Q36. Which of the following best describes your gender?

○ Male

○ Female

○ Prefer not to answer

Additional comments:

____

____

Appendix 2: Focus group interview guide

Appendix 2A: The first focus group interview guide

General questions

1. Is your current use of antimicrobial agents in feed additives or in treatment of ill animals and how does the Veterinary Feed Directive (VFD) improve or hinder effective your cattle production?
2. How far is your closest food animal veterinarian and does this proximity affect you in any way in light of the VFD regulations?
3. Who or what influences your decision to start (or continue/discontinue) the use of antimicrobials? Take a piece of paper and jot down the factors (things) that are important to you when deciding to use antimicrobial drugs.
4. There is a proposal by certain groups that antimicrobials that are essential for human use, should not be used in animals, even if they are useful to animals. Is restriction of

antimicrobial agents for treatment of ill animals in cattle production feasible in your production practice?

5. What can producers, veterinarians, consumers and regulatory authorities do, in order to make antimicrobial use in cattle better?
6. If you are called to give your advice to the secretary of Health and Human Services on antimicrobial resistance problems in food animals and in humans, what do you think are the contributors to the development of antimicrobial resistance problems in food animals and in humans and what advice would you give the secretary for prevention of this challenge?
7. Have you used or thought about using alternative agents that are not antimicrobial agents in your production and what are those?
8. In your opinion, what specific type of information would you as cattle producers need and like to be receiving about antimicrobial use? What is the best format for receiving this information?
9. In one word, describe the current VFD.
10. Of all the things we have talked about antimicrobial use, what is most important to you?

Appendix 2B: The modified focus group interview guide

1. What kind of operation do you run?
2. How do you use antibiotics?
3. How does the veterinary feed directive affect your cattle production?
4. How easy is it to access a food animal veterinarian in your area?
5. Who or what influences your decision to start or discontinue the use of antibiotics? Please share things that are important to you when deciding to use antibiotics.

6. What is your opinion about restricting antibiotics for human use only? How would this affect your production practice? What do you believe about antibiotic resistance?
7. What can producers, consumers, veterinarians, and regulatory authorities do in order to make antibiotic use in cattle better?
8. What would you advice the secretary of health and human services to do about the causes and solutions of human and animal antibiotic resistance?
9. Please share other management practices or products besides antibiotics that you use to prevent or treat disease.
10. In your opinion, what specific type of information would you as cattle producers need and like to be receiving about antibiotic use? What is the best format?
11. What is important to you about this topic?

Appendix 3: Survey questionnaire for antimicrobial use practices of cattle producers in Tennessee

Thank you for participating in this study. Please read the attached informed consent statement before proceeding.

I have read and understood the information in the above informed consent statement. Please choose the option below that best represents your consent.

- ○ I agree to participate in the survey and have the chance to win $10 Wal-Mart gift card (If checked, take the survey and then provide your information in the attached form for the raffle drawing).

- ○ I do not agree to participate in the survey, but I want to participate in the raffle for $10 Wal-Mart gift card (If checked, provide your information in the attached form for the raffle drawing).

- ○ I do not agree to participate in the survey and I do not want to participate in the raffle for $10 Wal-Mart gift card (If checked, you may exit the survey).

Q1. Which of the following best describes your primary cattle production?

◯ Beef production

◯ Dairy production

◯ Other (specify) ____

If your primary cattle production is dairy, please respond to questions 2 to 7. If beef production is selected, then skip to Q8.

Q2. How are antibiotic-treated cows distinguished from the rest of the milking herd at milking?

◯ Milked with a separate milking unit

◯ All cows are milked using the same milking unit

Q3. When are antibiotic-treated cows milked?

◯ Milked first

◯ Milked in-between

◯ Milked last

Q4. Are cows routinely screened after freshening for antibiotics with an antibiotic residue detection test?

- ○ No
- ○ Not sure
- ○ Yes

Q5. Were there any antibiotic residue violations in your milk in the past 6 months?

- ○ Yes
- ○ Not sure
- ○ No

Q6. To what extent do you agree or disagree with the following statement? “If all dairy producers in Tennessee followed best practices **in the use of antibiotics**, overall use of antibiotics in Tennessee dairy cattle would decrease".

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Neither agree nor disagree
- ◯ Agree
- ◯ Strongly agree

Q7. To what extent do you agree or disagree with the following statement? "If all dairy producers in Tennessee followed **best milk quality practices**, overall use of antibiotics in Tennessee dairy cattle would decrease".

- ◯ Strongly disagree
- ◯ Disagree
- ◯ Neither agree nor disagree
- ◯ Agree
- ◯ Strongly agree

If your primary cattle production is beef, please respond to Q8-Q13 below. If your primary cattle production is dairy, then skip to Q14.

Q8. Which of the following best describes your beef production system? (check all that apply).

- ☐ Cow-calf production
- ☐ Backgrounding-stocking
- ☐ Feedlot operations
- ☐ Seed stock
- ☐ Other (specify) ____

Q9. Do you think there is over-use of antibiotics in beef production?

- ○ Yes
- ○ Not sure
- ○ No

Q10. In which of the following beef production systems do you think, antibiotics are used most?

○ Cow-calf production

○ Backgrounding-stocking

○ Feedlot operations

○ Not sure

○ Other (specify) ____

Q11. Were there any antibiotic residue violations in beef (meat products) from cattle raised on your farm in the last year?

○ Yes

○ Not sure

○ No

Q12. To what extent do you agree or disagree with the following statement? “If all beef producers followed best practices **in the use of antibiotics**, overall use of antibiotics in Tennessee beef cattle would decrease".

- ○ Strongly disagree
- ○ Disagree
- ○ Neither agree nor disagree
- ○ Agree
- ○ Strongly agree

Q13. To what extent do you agree or disagree with the following statement? “If all beef producers followed best practices **in the management of their herds**, overall use of antibiotics in Tennessee beef cattle would decrease".

- ○ Strongly disagree
- ○ Disagree
- ○ Neither agree nor disagree
- ○ Agree
- ○ Strongly agree

Q14. How familiar are you with the Veterinary Feed Directive (VFD)?

○ Not familiar at all

○ Slightly familiar

○ Moderately familiar

○ Very familiar

○ Extremely familiar

Q15. What is your opinion about the Veterinary Feed Directive (VFD)?

○ I am not familiar with VFD

○ VFD is not useful

○ VFD is neither useful nor beneficial

○ VFD is somewhat useful

○ VFD is very useful

Q16. Were you aware of the Veterinary Feed Directive (VFD) before its implementation?

○ Yes

○ Not sure

○ No

Q17. How has the Veterinary Feed Directive (VFD), from the time it became effective, influenced your use of veterinary services?

○ VFD has reduced my use of veterinarian services

○ VFD has not influenced me to seek veterinarian services

○ VFD has caused me to seek veterinarian services more frequently

○ Other (specify) ____

Q18. Antibiotic resistance is the ability of bacteria (disease causing germs) to resist or be unaffected by the effects of medication. How familiar are you with the subject of antibiotic resistance?

○ Not familiar at all

○ Slightly familiar

○ Moderately familiar

○ Very familiar

○ Extremely familiar

Q19. How do you rate your degree of concern about antibiotic-resistant infections in cattle production?

○ I am not familiar about antibiotic-resistant infections in cattle production

○ Not concerned

○ Moderately concerned

○ Very concerned

Q20. How often do you observe antibiotic drug withdrawal times in your farm?

○ Never

○ Sometimes

○ About half the time

○ Most of the time

○ Always

Q21. How often do you use bacterial culture to determine the cause of disease on your farm?

- ◯ Never
- ◯ Sometimes
- ◯ About half the time
- ◯ Most of the time
- ◯ Always

Q22. How often do you use bacterial culture to select the most appropriate antibiotics to use on your farm?

- ◯ Never
- ◯ Sometimes
- ◯ About half the time
- ◯ Most of the time
- ◯ Always

If you answered never above, please skip to Q24.

Q23. Who makes the laboratory request for bacterial culture testing for your farm?

- ○ The producer
- ○ The manager
- ○ The veterinarian
- ○ Other (specify) ____

Q24. Thinking about your practices **BEFORE** the Veterinary Feed Directive-final rule became effective on January 1, 2017, how important were the following factors in determining the choice of antibiotics used in your farm?

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Recommendations from other producers	○	○	○	○	○
Clinical signs and symptoms	○	○	○	○	○
Cost of the antibiotic	○	○	○	○	○
Veterinarian's prescription	○	○	○	○	○
Positive culture and susceptibility tests	○	○	○	○	○

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Your farming experience	○	○	○	○	○
Drug withdrawal times	○	○	○	○	○
Recommendations from pharmaceutical company representatives	○	○	○	○	○
Recommendations from feed mill operatives	○	○	○	○	○

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Availability of antibiotic(s)	○	○	○	○	○
The ability of the drug to cure the infections	○	○	○	○	○
Concerns for animal welfare	○	○	○	○	○
Concerns for food security	○	○	○	○	○

Q25. Thinking about your practices **AFTER** the Veterinary Feed Directive-final rule became effective on January 1, 2017, how important are the following factors in determining the choice of antibiotics used in your farm?

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Recommendations from other producers	○	○	○	○	○
Clinical signs and symptoms	○	○	○	○	○
Cost of the antibiotic	○	○	○	○	○
Veterinarian's prescription	○	○	○	○	○
Positive culture and susceptibility tests	○	○	○	○	○

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Your farming experience	○	○	○	○	○
Drug withdrawal times	○	○	○	○	○
Recommendations from pharmaceutical company representatives	○	○	○	○	○
Recommendations from feed mill operatives	○	○	○	○	○

	Not at all important	Slightly important	Moderately important	Very important	Extremely important
Availability of antibiotic(s)	○	○	○	○	○
The ability of the drug to cure the infections	○	○	○	○	○
Concerns for animal welfare	○	○	○	○	○
Concerns for food security	○	○	○	○	○

Q26. To what extent do you agree or disagree with the following statements?

	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree
The Veterinary Feed Directive (VFD) has limited your access to antibiotics	○	○	○	○	○
Most veterinarians do not know how to write VFD prescriptions	○	○	○	○	○
VFD needs to be updated to accommodate current flaws in execution	○	○	○	○	○
My veterinarian can write an accurate VFD prescription	○	○	○	○	○

	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree
VFD has introduced additional costs of involving a veterinarian	○	○	○	○	○
You are aware of how to properly dispose any unused feed from the VFD	○	○	○	○	○
The VFD would lead to increased use of injectable antibiotics by producers	○	○	○	○	○
The VFD has created more black-market access to in feed antibiotics by producers	○	○	○	○	○

	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree
The VFD has increased the costs of feed	○	○	○	○	○
The VFD has negatively affected small scale producers	○	○	○	○	○
The VFD has set cattle producers up for financial loss because it has removed access to preventive in-feed medicines	○	○	○	○	○
The VFD is useful for producing safer food	○	○	○	○	○

Q27. To what extent do you agree or disagree with the following statements?

	Strongly disagree	Disagree	Neither disagree nor agree	Agree	Strongly agree
Producers require additional training on prudent use of antibiotics	○	○	○	○	○
Aggressive marketing of antibiotics by pharmaceutical companies greatly influences producers' use of antibiotics	○	○	○	○	○
Training producers on infection control (bio-security) and vaccination would reduce the use of antibiotics	○	○	○	○	○
Some antibiotics you use on your cattle have become ineffective (there is resistance to antibiotics used in cattle)	○	○	○	○	○
Profitability of your operation is an important factor influencing your decision to use antibiotics on your cattle	○	○	○	○	○
Antibiotic drugs work less effectively than in the past	○	○	○	○	○

Q28. Where do you buy antibiotics drugs for your farm?

- ○ From internet sites
- ○ Over-the- counter (local Cooperative/feed retailer)
- ○ From a veterinarian
- ○ Directly from a distributor (pharmaceutical Company Representative)
- ○ Directly from a drug company
- ○ Other (specify) ____

Q29. What criteria are used on the farm to determine the need for antibiotics treatment of sick animals?

- ☐ Clinical signs and symptoms
- ☐ Positive culture and sensitivity tests
- ☐ Other (specify) ____

Q30. Does your farm keep up-to-date written records of antibiotic drug purchases?

- ◯ No
- ◯ Not sure
- ◯ Yes

Q31. Does your farm keep written records on medicated feeds purchased in the frame work of the veterinary feed directive?

- ◯ No
- ◯ Not sure
- ◯ Yes

Q32. Does your farm keep up-to-date written records of antibiotic drugs used to treat animals?

- ◯ No
- ◯ Not sure
- ◯ Yes

Q33. How often does your veterinarian visit your farm?

- ◯ Never
- ◯ On routine calls
- ◯ As needed

Q34. In what format do you receive prescriptions (and other advice) from your veterinarian?

- ◯ Through Telephone conversation
- ◯ Through text messages
- ◯ Through e-mail
- ◯ Through face-to-face interactions during farm visits
- ◯ Social media
- ◯ Other (specify) ____

Q35. What are the 5 antibiotic drugs that you commonly use on your farm? (Rank from the most to the least)

◯ 1. Most used ____

◯ 2 ____

◯ 3 ____

◯ 4 ____

◯ 5. Least used ____

Q36. What are the 5 diseases/conditions that you commonly treat with antibiotics on your farm? (Rank from the most to the least)

◯ 1. Most treated ____

◯ 2 ____

◯ 3 ____

◯ 4 ____

◯ 5. Least treated ____

Q37. Prudent (responsible) use of antibiotics in farms involves decreasing unnecessary or inappropriate use of antibiotics. How often do you discuss about prudent antibiotic use with your veterinarian?

○ Never

○ Sometimes

○ About half the time the veterinarian visits

○ Most of the time

○ Always

Q38. Are the cattle in your farm sometimes treated with antibiotics at dosages higher than the label instructed?

○ No

○ Not sure

○ Yes

Q39. In your farm, who administers the antibiotic medications to the animals? (Check all that apply)

- ☐ Producer
- ☐ Herdsman
- ☐ Milk hand
- ☐ Veterinarian
- ☐ Manager
- ☐ Other (specify) ____

Q40. What are the appropriate methods for communicating information about prudent use of antibiotics to you? (Check all that apply)

- ◯ Producer's handbook on prudent use
- ◯ Laminated posters
- ◯ Videos
- ◯ Brochures
- ◯ Flow charts for the barn
- ◯ Educational seminars
- ◯ Other (specify) ____

Q41. In what language(s) would you like to be receiving information about prudent use of antibiotics?

- ○ English
- ○ English and Spanish
- ○ Spanish
- ○ Other (specify) ____

Q42. Do you use antibiotics for treatment of diseases other than those listed on the bottle/package insert that comes with the medicine)?

- ○ Yes
- ○ Not sure
- ○ No

If you answered yes above, please answer Q43. Otherwise, skip to Q44.

Q43. How is the use antibiotics for treatment of diseases other than those listed on the bottle/package insert done at your farm?

○ Based on past use on the farm for treatment of diseases other than those listed on the bottle/package insert

○ Based on recommendation of other farmers/producers

○ Based on the prescription (written guidelines) from a veterinarian

○ Based on my experience as a producer

○ Other (specify) ____

Q44. Do you strictly follow the prescribed course of treatment for each antibiotic medication?

○ Never

○ Sometimes

○ About half the time

○ Most of the time

○ Always

Q45. Does your farm have written protocols (plans) for treating sick animals with antibiotics?

- ◯ Yes
- ◯ Not sure
- ◯ No

Q46. Is a veterinarian's advice sought before administering antibiotics?

- ◯ Never
- ◯ Sometimes
- ◯ About half the time
- ◯ Most of the time
- ◯ Always

Q47. Which of one the following best describes your opinion about the label instructions for antibiotic medicines?

◯ Label instructions are difficult to understand and interpret

◯ Label instructions are easy to understand and interpret

Q48. In what language(s) would you prefer label instructions for antibiotic medicines to be written?

◯ English

◯ Spanish

◯ English and Spanish

◯ Other (specify) ____

Q49. To what extent does the consumer demand for antibiotic-free products influence your use of antibiotics?

- ○ Not at all
- ○ A little
- ○ To a moderate extent
- ○ Quite a bit
- ○ Very much

Q50. Which of the following best describes your number of years in cattle farming?

- ○ < 5 years
- ○ 6 - 10 years
- ○ 11 -15 years
- ○ 16 - 20 years
- ○ 21 - 25 years
- ○ 26 - 30 years
- ○ > 30 years

Q51. Were you raised on a livestock farm?

○ No

○ Yes

Q52. Which of the following best describes your gender?

○ Male

○ Female

○ prefer not to answer

Q53. Which of the following best describes your education level attained?

○ No school

○ Elementary

○ Junior high

○ High school

○ General Education Development (GED)

○ Vocational

○ College

○ Professional

○ Other (specify) ____

Q54. Which of the following best describes the number of cattle in your production unit?

○ 1 - 49

○ 50 - 99

○ 100 - 149

○ 150 - 199

○ 200 - 299

○ 300 - 399

○ 400 - 499

○ 500+

Q55. Which of the following best describes your age group?

○ 19 years and below

- 20 - 29 years
- 30 - 39 years
- 40 - 49 years
- 50 - 59 years
- 60 -69 years
- 70 -79 years
- 80+ years

Q56. Any additional comments/recommendations?

We thank you for taking our survey.

Appendix 4: Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

No	**Item**	**Guide questions/description**	
Domain 1: Research team and reflexivity			
Personal characteristics			
1	Interviewer/facilitator	Which author/s conducted the interview or focus group?	All the authors attended all the focus groups. The third author (EBS) moderated the focus group discussions.
2	Credentials	What were the researchers' credentials?	1st author (JEE): BVM, MVM, PgD, PhD Candidate 2nd author (MC): BS, DVM, PhD, DACVIM 3rd author (EBS): BA, MSSW, PhD 4th author (CCO): DVM, MS, PhD, DACVPM (Epi)
3	Occupation	What was their occupation at the time of study?	JEE: Graduate Research Assistant/PhD Candidate. MC: Assistant Professor, Large Animal Clinical Sciences. EBS: Director Veterinary Social work/ Clinical Associate Professor. CCO: Assistant Professor, Epidemiology and Food safety.
4	Gender	Was the researcher male or female	Male: JEE, MC, CCO Female: EBS
5	Experience and training	What experience did the researcher have?	JEE: Underwent qualitative research methods training while at graduate school and has experience in veterinary clinical practice, teaching senior veterinary students at a veterinary school. CM: Has extensive experience in food animal veterinary practice. EBS: Has wide experience in moderating group meetings. CCO: Has wide experience in epidemiology and food safety.

No	Item	Guide questions/description	
Relationship with participants			
6	Relationship established	Was a relationship established prior to study commencement	No relationship was established prior to study commencement.
7	Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Prior to the meetings, the participants knew nothing about the researchers. However, at the beginning of each focus group discussion, participants were informed about the purpose of the study as part of obtaining an informed consent prior to commencing with the discussions.
8	Interviewer characteristics	What characteristics were reported about the interviewer/facilitator? E.g. bias, assumptions, reasons and interests in the research topic.	Participants were informed that the moderator was a non-veterinarian with a background in the behavioral sciences (social work).
Domain 2: Study design			
Theoretical framework			
9	Methodological orientation and theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	Researchers were at liberty to use either inductive or the theoretical/deductive approach to thematic analysis.

No	Item	Guide questions/description	
Participant selection			
10	Sampling	How were participants selected? E.g. purposive, convenience, consecutive, snowball	Participants were purposively selected.
11	Method of approach	How were participants approached? E.g. face-to-face, telephone interview, mail, email	Participant recruitment e-mail was sent to the leadership of the Tennessee Cattlemen's Association (TCA) who then shared this email with TCA members and then purposively selected the volunteers for this study.
12	Sample size	How many participants were in the study?	39 beef producers and 23 dairy producers
13	Non-participation	How many people refused to participate or dropped out? Reasons?	No participant dropped out of the focus groups.
Setting			
14	Setting of data collection	Where was the data collected? Home, clinic, workplace?	Data was collected at county extension centers or at local restaurants were the focus groups were held.
15	Presence of non-participants	Was anyone else present besides the participants and researchers?	No
16	Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	Perceived age: ranged from late twenties to early seventies.

No	Item	Guide questions/description	
Data collection			
17	Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Yes, interview guide was provided. There was no specific separate pilot testing done. However, the interview guide was modified based on participant comments after the first focus group.
18	Repeat interviews	Were repeat interviews carried out? If yes, how many?	No repeat interviews were carried out.
19	Audio/video recording	Did the researchers use audio or visual recording to collect the data?	Data was video recorded.
20	Field notes	Were field notes made during and/or after the interview or focus group?	Yes
21	Duration	What was the duration of the interviews or focus groups?	The beef focus groups lasted approximately 90 minutes while the dairy focus groups lasted approximately 60 minutes.
22	Data saturation	Was data saturation discussed?	Data saturation was reached at the end of the 5th beef focus group. For dairy focus groups, saturation was not reached.
23	Transcripts returned	Were transcripts returned to participants for comment and/ or correction?	No. Participants could not be identified since data was de-identified at collection for protection of human subjects in research.

No	Item	Guide questions/description	
Domain 3: Analysis and findings			
Data analysis			
	Number of data coders	How many data coders coded the data	All the four authors coded the data
25	Description of the of the coding tree	Did authors provide a description of the coding tree?	The coding is described in the manuscript
26	Derivation of themes	Were themes identified in advance or derived from the data?	Themes were not identified in advance. Final themes presented in the manuscript were arrived at after two review & harmonization meetings to compare individual data coding.
27	Software	What software, if applicable, was used to manage the data?	NVivo qualitative data analysis Software; QSR International Pty Ltd. Version 11, 2017 was used.
28	Participant checking	Did participants provide feedback on the findings?	No. Participants were de-identified, hence could not be traced back.
Reporting			
29	Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified e.g. participant number	Yes, quotations were presented verbatim (in participants' own words) to illustrate the themes/findings. Each quotation was identified by participant number, except for a few un-identified participants.
30	Data and findings consistent	Was there consistency between the data presented and the findings?	Yes
31	Clarity of major themes	Were major themes clearly presented in the findings?	Yes
32	Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	Yes

VITA

John was born in Tororo district in eastern Uganda. He graduated with a Bachelor of Veterinary Medicine (BVM) degree in January 2009, at Makerere University, Uganda. From August 2010 to October 2013, he pursued a Master of Veterinary Medicine (Food Animal Health and Production) degree at Makerere University and graduated in January 2014. He further enrolled for a postgraduate Diploma in Public Policy and Governance, at the Uganda Management Institute (2013-2014) and graduated in May 2015. John has also undergone other management training programs in Uganda.

In August 2009, upon graduation with his BVM degree (DVM equivalent), John joined the College of Veterinary Medicine, Animal Resources and Biosecurity at Makerere University, as a Teaching Assistant, in the Department of Veterinary Pharmacy, Clinical and Comparative Medicine, and actively served up to December 2015. John has been active in the clinical training of veterinary students in Uganda. He has also been active in training of biomedical laboratory students in special clinical and diagnostic technologies at Makerere University. John is licensed to practice Veterinary Medicine in Uganda. Alongside, his teaching job, he practiced Veterinary Medicine in Uganda, from June 2008 to December 2015—60% large animal and 40% small Animal. In October 2008 and March 2009, John worked in Gulu/Amuru districts of northern Uganda as a volunteer veterinarian with the USAID/ U.S military project-VETCAP, contributing to the post-conflict reconstruction of northern Uganda.

In August/September 2012, John was a research scholar at Jilin Agricultural University, in Changchun, North East China-primarily studying the prevention and treatment of animal epidemics in China. He was sponsored by the Chinese Government. In September 2013, John was a research scholar at the Plum Island Animal Disease Center in New York, studying International Trans-Boundary Animal Diseases (sponsored by the USDA and CDC).

John is interested in furthering his career in the academia—teaching and research—in the field of epidemiology. His research and career interests are in: aspects of antimicrobial use, epidemiology and mechanisms of antimicrobial resistance, food safety epidemiology, zoonosis, epidemiology and ecology of infectious diseases, dynamics of disease transmission at the human-livestock-wildlife interface, neglected tropical diseases, and study designs in clinical trials.