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Antimicrobial Stewardship: A One Health approach with a focus on antimicrobial reduction in dairy cattle

by

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A THESIS
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ABSTRACT

Antimicrobial resistance (AMR) is considered one of the greatest threats facing humanity. Without intervention, AMR impacts are expected to be substantial, compromising human, animal, environmental health. The complex interplay of contributing factors highlights the need for a One Health approach in AMR mitigation. Improving antimicrobial stewardship (AMS) is an integral component of AMR mitigation success. Therefore, thesis objectives included: 1) describe the current state of AMR knowledge in Canada available in the literature, and identify the gaps in our understanding; 2) identify perspectives of AMS, including perceived drivers and barriers across the One Health spectrum of relevant Canadian professionals; 3) focus on the dairy industry as an example where AMS efforts are possible through selective dry cow therapy (SDCT); and 4) describe current SDCT uptake and related practices in the Canadian dairy industry.

Current limitations in the understanding of AMR in Canada are described through a comprehensive review focussed on: 1) treatment optimization; 2) surveillance of antimicrobial use (AMU) and AMR; and 3) prevention of transmission of AMR. Whereas identified barriers to AMS described by Canadian professionals included: 1) lack of various prescribing and AMU support mechanisms; 2) shift in prescriber attitudes to drive change; and 3) stronger economic considerations to support shifting prescribing practices.

Only treating cows who could benefit from antimicrobials at drying off (i.e., SDCT), represents an opportunity to reduce AMU in the dairy industry. A narrative review was conducted summarizing available literature regarding impacts of SDCT on udder health, milk production, economics, AMU motivations, and AMR.

An observational study was conducted utilizing 2 in-person questionnaires between July 2019 and September 2021 on 144 dairy farms in 5 Canadian provinces. Overall, 31% reported adopting SDCT, with approximately 50% less intramammary AMU at drying off compared to treating all cows. A slight majority of farms (56%) applied teat sealants (TS) to all cows at drying off, whereas 12% used TS selectively, and 32% did not use TS. Results highlighted the variability in antimicrobial and TS use protocols at drying off on Canadian dairy farms, and the potential for further AMU reduction with increased SDCT adoption.

PREFACE

This thesis consists of 4 manuscripts – 2 have been published, 1 is accepted for publication and 1 is to be submitted. The following manuscripts are included in this thesis:

Chapter 2

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Chapter 3

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Chapter 4

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W. Barkema. 2022. Invited review: Selective use of antimicrobials in dairy cattle at drying off. J Dairy Sci. 105:7161–7189. https://doi.org/10.3168/jds.2021-21455.

Chapter 5

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Statement of work done

Kayley McCubbin led the two scoping reviews (Chapter 2, 4). Kayley McCubbin led questionnaire development, data collection, and analysis, with analysis assistance from Ellen de Jong and Julia Bodaneze (Chapter 3). Kayley McCubbin and Ellen de Jong developed the 2 questionnaires and led data collection. Kayley McCubbin, Ellen de Jong, and Marit Biesheuvel contributed to the data analysis (Chapter 5). Kayley McCubbin wrote all manuscript drafts (Chapter 2, 3, 4, 5). Herman Barkema oversaw the design and execution of all chapters. All authors gave approval of the final versions to be published and agreed to be accountable for all aspects of manuscripts. Permission has been obtained from all co-authors and the publishing journals to reprint the manuscripts in this thesis.

The following manuscripts that I authored or co-authored while I was a PhD-student at the University of Calgary were not included in this thesis:

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Warder, L., L. C. Heider, D. Léger, D. Rizzo, J. McClure, E. De Jong, E., K. D. McCubbin, T. Uyama, M, Fonseca, A. S. Jaramillo, D. F. Kelton, D. Renaud, H. W. Barkema, S. Dufour, J-P. Roy, and J. Sanchez. 2023. Quantifying antimicrobial use on Canadian dairy farms using garbage can audits (Submitted, Front Vet Sci).

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Ida, J., W. Wilson, D. Nydam, C. Gerlach, J. P. Kastelic, E. Russell, K. D. McCubbin, C. Adams, and H. W. Barkema. 2022. Contextualized understandings of dairy farmers' perspectives on antimicrobial use and regulation in Alberta, Canada. J Dairy Sci. 106:547–564. https://doi.org/10.3168/jds.2021-21521.

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Uyama, T, D. F. Kelton, E. Morrison, E. de Jong, K. D. McCubbin, H. W. Barkema, S. Dufour, J. Sanchez, L. Heider, S. J. LeBlanc, C. B. Winder, J. McClure, and D. Renaud. 2021. Cross-sectional study of antimicrobial use and treatment decision for pre-weaned Canadian dairy calves. JDS Communications. 3:72–77. https://doi.org/10.3168/jdsc.2021-0161.

McCubbin, K. D., J. W. Ramatowski, E. Buregyeya, E. Hutchinson, H. Kaur, A. K. Mbonye, A. Mateus, and S. E. Clarke. 2021. Unsafe ‘crossover-use’ of chloramphenicol in Uganda: The Importance of a One Health Approach. J Antibiot. https://doi.org/10.1038/s41429-021-00416-3.

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LIST OF ABBREVIATIONS

AHS	Alberta Health Services
AMR	antimicrobial resistance
AMS	antimicrobial stewardship
AMU	antimicrobial use
BDCT	blanket dry cow therapy
BMSCC	bulk milk somatic cell count
CaDNetASR	Canadian Dairy Network for Antimicrobial Stewardship and Resistance
CARSS	Canadian Antimicrobial Resistance Surveillance System
CCA	Council of Canadian Academies
CE	continuing education
CI	confidence interval
CIHR	Canadian Institutes for Health Research
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CM	clinical mastitis
CMT	California mastitis test
CNISP	Canadian Nosocomial Infection Surveillance Program
CFU	colony forming unit
CVMA	Canadian Veterinary Medical Association
d	day
DCT	dry cow therapy
DHI	dairy herd improvement
DHIA	dairy herd improvement association
DIM	days in milk
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
eSTREP	National Laboratory Surveillance of Invasive Streptococcal Disease
EFSA	European Food Safety Agency
GASP-Canada	Gonococcal Antimicrobial Surveillance Program
IMI	intramammary infection
IMM	intramammary
kg	kilogram
LDH	lactate dehydrogenase
MIF	major innovation fund
mg	milligram
mL	milliliter
MDR	multidrug resistance
MLD	milk leukocyte differential

mo	month
MRSA	methicillin-resistant *Staphylococcus aureus*
MRSP	methicillin-resistant *Staphylococcus pseudintermedius*
NAS	non-*aureus* staphylococci
NMC	National Mastitis Council
NPV	negative predictive value
NSERC	Natural Sciences and Engineering Research Council of Canada
OHHLEP	One Health High-Level Expert Panel
OR	odds ratio
PCR	pathogen nucleic acid
PCU	population correction unit
PHAC	Public Health Agency of Canada
PPV	positive predictive value
SCC	somatic cell count
SCM	subclinical mastitis
SDCT	selective dry cow therapy
SDG	Sustainable Development Goals
TS	teat sealant
UNEP	United Nations Environment Programme
UK	United Kingdom
USD	United States dollar
USDA	United States Department of Agriculture
WHO	World Health Organization
wk	week
WOAH	World Organization for Animal Health

CHAPTER 1: General Introduction

1.1.1. One Health

The concept of One Health has been described by the tripartite (World Health Organization, World Organization for Animal Health, and the Food and Agriculture Organization) and the United Nations Environment Programme (UNEP) as "*an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and inter-dependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water energy and air, safe and nutritious, food, taking action on climate change, and contributing to sustainable development*" (One Health High-Level Expert Panel [OHHLEP] et al., 2022).

The goal of One Health is not only to acknowledge the interconnectedness of humans, animals, and the environment and their complexities, but to foster transdisciplinary understanding and develop practical solutions to complex problems outside traditional siloed approaches. One Health has only become pervasive in health discussions in recent years; however, it is a long-standing concept in Indigenous knowledge systems that encompasses a holistic view of health and an understanding that preservation of health for future generations hinges on protection of health of other species and the environment (Riley et al., 2021; Stephen, 2022).

Benefits of One Health can include increased efficiency in problem solving (Stephen, 2022). Without transdisciplinary collaboration, knowledge and technology from various disciplines and knowledge bases are used separately in pursuit of the same goal. Further, interventions could be developed that do not align with what is considered contextually appropriate, representing a barrier to implementation and long-term success. However, with social sciences inclusion and stakeholder consultation, different perspectives emerge that can improve the practicality and acceptance of proposed implementation activities.

Components of a One Health approach can vary depending on the issue. However, in general terms, the approach can include input from the natural sciences to address the issue from a scientific perspective, plus input from the social sciences contributing to an understanding of why and how the issue developed, how to drive behavior change, and identify current drivers and barriers that impede or block uptake of mitigation efforts. Additionally, contextual and community knowledge is also incredibly important to better understand perspectives of those impacted by the issue or proposed solutions, and if the solutions are practical and appropriate. Once mitigation efforts are developed, implementation can be aided by various policy and enforcement mechanisms appropriate for the context. Evaluation of solutions is another important component of a One Health approach to assess implementation success and long-term sustainability. Adaptation of the solution may be required as the context or situation changes over time.

The transdisciplinary nature of a One Health approach includes involvement of stakeholders and rightholders; they should be present for discussions as they may be impacted by the issue, their knowledge base may be needed to understand and develop realistic mitigation strategies and/or successfully enact them, or perhaps they will be key participants in a mitigation strategy. Their input is integral throughout all stages design and implementation. The specifics of who and what groups are involved will change depending on context and scope. Regardless, inclusion and collaboration among various professions, knowledge bases, stakeholders, and rightholders aims to promote success and promote health with shared goals.

Inclusion of social sciences is integral to the One Health approach to move past traditional scientifically driven infectious disease mitigation, towards a broader consideration of health (Zinsstag et al., 2015). An important example of social science inclusion is the understanding of health and the inequities that are the determinants of health; the latter are defined as “the broad range of personal, social, economic, and environmental factors that determine individual and population health” (Government of Canada, 2022). Further, social determinants of health are specific social and economic factors within determinants relating to a person’s place in society, and influenced by discrimination, racism, and historical trauma experienced by marginalized groups.

Health behaviours are also associated with a variety of health and well-being outcomes at both individual and population levels (Short and Mollborn, 2015). Inclusion of social sciences in One Health considerations and health issue mitigation recognizes complex interactions between behaviours and outcomes. Social, economic, and cultural norms impact both the willingness and ability of individuals to act, influence healthcare seeking behaviour, adherence to medical treatments, and capacity to use preventative measures to promote health (Short and Mollborn, 2015; Zinsstag et al., 2015); however, responses to external influences that constitute the social environment, and how they shape behaviours varies among individuals (Short and Mollborn, 2015).

Equity considerations must be included among human populations, as emphasized by the social determinants of health, but also in overall consideration of species and ecosystems equity in health (OHHLEP et al., 2022). Specifically, the “foolishness of human exceptionalism” (Haraway, 2008) is present by focusing on protection of human health to the detriment of animals and the environment. In addition to ethical considerations of maintaining the health of animals and environments impacted by human activity, human health cannot be maintained long-term without broader consideration of the health of other species and ecosystems. Therefore, a One Health approach aims to equally value health of humans, animals, the environment, and their vast connections.

1.1.2. Our Changing World

One Health has become an important focus of the quadripartite to address our changing world and the collaboration required to address emerging health concerns, respond to global health threats, and promote sustainable development (OHHLEP et al., 2022). Human actions and stressed ecosystems create opportunities for pathogens to emerge and spread within and between human and animal populations (World Health Organization [WHO], 2022). These stressors can include: increasing global human population and increased demands for animal protein; human and animal migration; widespread poverty; political and social instability; human conflicts; global travel and trade; agriculture; livestock farming; increased globalization and urbanization; climate change; natural resource degradation; deforestation; habitat fragmentation; environmental encroachment; etc. (Daszak et al., 2001; Zinsstag et al., 2015; Wall et al., 2016; Sabin et al., 2020; Stephen, 2022; WHO, 2022, UNEP, 2023).

Preventing dangerous pathogen emergence requires more than just veterinarians and physicians collaborating on zoonoses (Zinsstag et al., 2015). In response to emergence and detrimental impacts of the COVID-19 pandemic, G20 health ministers have committed to operationalizing One Health approaches at all levels (G20 Health Ministers, 2021).

Ecosystem changes influenced by climate represent another integral reason why a broader, One Health approach to infectious disease emergence is required. Changes in weather conditions and extreme weather events due to climate change continually disrupt the environment and therefore impact infectious disease dynamics (Sabin et al., 2020), increasing threat of deadly infections and impacting the ability to cope with infections (Burnham, 2021; Centers for Disease Control and Prevention, 2022; Prillaman, 2022; UNEP, 2023).

1.2.1. Antimicrobial Resistance and One Health

Human and animal health systems in addition to agricultural industries rely heavily on access to effective antimicrobials to treat and prevent bacterial infections (Council of Canadian Academies [CCA], 2019). However, antimicrobial resistance (AMR) is a slow-moving pandemic threatening socioeconomic prosperity and ability to effectively treat infections in humans and animals (Viens and Littman, 2015; CCA, 2019). As prevalence of AMR continues to increase worldwide, global health and socio-economic impacts of AMR are projected to be substantial (CCA, 2019). In Canada, from 2016 to 2020, AMR continued to increase for pathogens of concern (Public Health Agency of Canada [PHAC], 2022).

Canada must take coordinated action both domestically and globally to minimize detrimental impacts of increased resistance to antimicrobials and to preserve their effectiveness (PHAC, 2017). Given the interconnectedness of humans, animals, and their environments, it is increasingly paramount that strategies to address AMR use a One Health approach (McCubbin et al., 2021).

Development of AMR may occur from either an intrinsic genetic trait or acquisition of such a trait from extrinsic sources. Intrinsic resistance occurs naturally in a species, enabling it to resist chemical action due to inherent structural and functional characteristics (Reygaert, 2018). Extrinsic AMR can arise by genetic mutation, horizontal gene transfer, or other means of mobile genetic elements (e.g., integrons, transposons, or plasmids), acquisition from other microorganisms, or the environment (Wall et al. 2016; Leonard et al., 2017).

Development of AMR is a natural process but can be enhanced by antimicrobial use (AMU) or exposure to sub-therapeutic concentrations of antimicrobials that select for bacteria with genetic mutations or resistance determinants (Wall et al., 2016). Further, AMR development is complex and not fully understood; however, contributing factors include increased AMU, inappropriate AMU (e.g., use for viral infections), prescriptions taken incorrectly and/or with a lack of medical supervision, prophylactic or preventative AMU, inadequate biosecurity infrastructure/protocols, environmental contamination with antimicrobial residues, inadequate access to antimicrobials or diagnostics, among others (Laxminarayan et al., 2013; Holmes et al., 2016; Wall et al., 2016).

Bacteria can develop/acquire resistance to antimicrobials, heavy metals, biocides, and other xenobiotic compounds, and resistance to these various types of compounds can be related (Wales and Davies, 2015; Singer et al., 2016; Kurenbach et al., 2017; Maier et al., 2018; Dickinson et al., 2019; UNEP, 2023). Linkage of AMR genes between compounds of disparate classes means that heavy metal exposure, or use of non-antimicrobial chemicals or pharmaceuticals, may also select for AMR without actual AMU (Wales and Davies, 2015;

Kurenbach et al., 2017; Maier et al., 2018; Dickinson et al., 2019; UNEP, 2023). For example, zinc and copper are used extensively as nutritional supplements in animal feed and may select for improved environmental survival of AMR bacteria (Bearson et al., 2020; UNEP, 2023).

AMR-conferring mutations occur in structural or regulatory genes responsible for specific targets of antimicrobial action (Courvalin, 2008; Wall et al., 2016). Bacterial acquisition of multiple resistance mutations or mobile genetic elements with resistance to unrelated compounds, or mutations that can influence sensitivity to multiple compounds (i.e., efflux pumps) can lead to multidrug-resistant (MDR) bacteria that are increasingly difficult to treat (Nikaido, 2009; Wall et al., 2016).

There is rising awareness that the environment has a large role in maintaining the “resistome” of AMR genes and resistant organisms (McCubbin et al., 2021; Kim and Cha, 2021). Environmental importance in AMR is part of a larger issue of human influence on the world around us. The term “Anthropocene” has been applied to this geological era and describes measurable impacts of humans on the geology of our planet (British Geological Survey, 2017).

Environmental reservoirs of AMR pathogens and genes (i.e., those present in soil and water) represent a source of resistant genetic element acquisition for pathogens of potential concern to human and animal health. Air represents another potential AMR transmission pathway (Wall et al., 2016; UNEP, 2023).

Contributing factors to development and maintenance of these resistance reservoirs include AMU for crop management or antimicrobials released into aquatic environments through aquaculture, wastewater discharges, environmental contamination with antimicrobial residues or resistant organisms from application of sewage-derived biosolids, farm manure, or animal production facility runoff, and use of co-selecting agents for resistance (i.e., widespread use of biocides and disinfectants in water treatment) (Sarmah et al., 2006; Calero-Cáceres et al., 2014; Guo et al., 2015; Wales and Davies, 2015; Wall et al., 2016; Tang et al., 2017; Chen et al., 2018; Paulus et al., 2019; McCubbin et al., 2021; UNEP, 2023). Rivers, lakes, and oceans receive antimicrobials and AMR genetic pollution over time from the described variety of sources and can possess resistant genes or mobile genetic elements supporting AMR development and spread within the environment (Chen et al., 2019a, b; UNEP, 2023). Inland water sources are considered a critical vehicle of AMR transmission as they increase the proximity between bacteria from multiple sources (Fondi et al., 2016), potentially facilitating exchange of resistant genetic material (UNEP, 2023).

Other environmental changes such as intensification of agriculture, increasing human populations, can also impact AMR development by changing production system demands and subsequent AMU and infection dynamics (Wall et al., 2016; UNEP, 2023). Further, climate change impacts AMR development and maintenance (Burnham, 2021; UNEP, 2023). Development and propagation of AMR bacteria is exacerbated by higher temperatures, by increasing infection rates with these resistant pathogens, as well as increasing the frequency of resistant genetic material transfer (Burnham, 2021; UNEP, 2023).

There are many contributing to development of AMR. Further, pathogens and resistance genes of concern are not always limited to one sector or species, and antimicrobial ingredients are used across human and animal health sectors and released into the environment in numerous ways (Wall et al., 2016; McCubbin et al., 2021; Kim and Cha, 2021; UNEP, 2023). According to UNEP (2023), there are five key pollution sources impacting AMR development, transmission, and spread in the environment, including: 1) poor sanitation, sewage, and waste effluent; 2) pharmaceutical manufacturing waste and effluent; 3) healthcare facilities waste and effluent; 4) AMU, animal manure application, and irrigation for crop production; and 5) terrestrial and aquatic animal production waste and effluent. Consequently, antimicrobial and pathogen interactions are multifaceted and complex and require consideration across all sectors to limit pathogen exposure to antimicrobials.

Human behaviour represents another important consideration in continued AMR development. There are many factors influencing human and animal health, but more specifically antimicrobial prescribing and use, as well as the value placed on livestock and companion animals. Factors influencing human AMU are multifactorial and can depend on a variety of factors including healthcare access, prescriber preferences, prescriber and end-user knowledge and experiences, pressures, etc. (Schmiege et al., 2020). For example, there are documented differences regarding AMU and gender, with women more likely to be prescribed antimicrobials than men (Schröder et al., 2016; Smith et al., 2018). This remains true while accounting for potential differences in gender-based infection rates (i.e., urinary tract infections), with claims that reported differences can be largely explained by prescriber behaviour (Smith et al., 2018).

In the veterinary sector, regarding companion animal AMU, in addition to veterinarian prescribing preferences and factors, there are also pet-owner influences on antimicrobial prescription and consumption (Tompson et al., 2021). These factors include client willingness to pay for treatment or diagnostics, expectations associated with the clinic visit, pressure on the veterinarian to prescribe, among others (Tompson et al., 2021), as well as factors influencing administration of prescribed antimicrobials. Regarding livestock-associated AMU, veterinary antimicrobial prescribing and influence over AMU as well as producer AMU decision-making are also varied and complex and have an additional economic component related to the desire to maintain a viable business (Poizat et al., 2017; Speksnijder and Wagenaar, 2018).

The human behaviour component of AMR development highlights the importance of including social sciences in AMR research and mitigation efforts. Without consideration of behaviour or potential barriers, any mitigation effort may be at risk of failing, or lacking intended long-term success.

Despite the importance of AMR and profound impacts of continued development of resistance (CCA, 2019), there are still many unknowns. However, as AMU is identified as a major driver of AMR development and maintenance, an overarching goal of AMR mitigation and an important area of focus is antimicrobial stewardship.

1.3.1. Sustainable Development Goals

The Sustainable Development Goals (SDGs), adopted by all United Nations Members States in 2015, were established to promote prosperity while protecting the environment through identified areas for action (United Nations, 2023). The resulting 17 SDGs are described as representing "the world's best plan to build a better world for people and our planet by 2030" (WHO, 2020). Whereas the SDGs focus on a variety of important areas, such as gender equality, poverty, and climate change, AMR is intricately linked with several of these goals (WHO, 2020; UNEP, 2023).

Specifically, continued development of AMR impacts success of SDG 3, "Good health and well-being", as well as SDG 14 "Life Below Water", and 15, "Life on Land", as the One Health impacts of AMR on human and animal health have been described (Wall et al., 2016; McCubbin et al., 2021; UNEP, 2023). Success would be hindered for SDGs 6, "Clean Water and Sanitation", with increasing environmental pollution contributing to AMR development (UNEP, 2023), whereas success for SDG 13, "Climate Action" could limit described environmental pressure on AMR development (UNEP, 2023). Another SDG impacted by AMR is SDG 2, "Zero Hunger" as availability of effective antimicrobials, and the current reliance on widespread AMU in agriculture production systems represents a global health and food security issue as decreased antimicrobial effectiveness will negatively impact production systems. In addition to animal welfare concerns that emerge with limited access to effective antimicrobials, with an increasing global population, and increasing demand for animal protein, the ability to produce safe food is imperative for maintaining human health and well-being (UNEP, 2023).

Further, production industries contribute to overall country gross domestic product (GDP) and represent an important consideration in SDG 1 of "No Poverty" and SDG 8 "Decent Work and Economic Growth." It is reported that globally 24 million people will be pushed into extreme poverty due to AMR by 2050, due to the unequal impacts of AMR and substantial projected impacts on low-income countries (World Bank, 2017; UNEP, 2023). The complex relationship among gender, inequality, and poverty brings SDG 5 "Gender Equality" into the equation as well, whereas antimicrobial stewardship also concerns SDG 12 "Responsible Consumption and Production" through the responsible consumption of available antimicrobial products across all sectors. Therefore, AMR and how society uses antimicrobials must be addressed before substantial progress towards the SDGs can be made. However, the 2022 SDG progress report did not mention AMR but focused on detrimental impacts of the COVID-19 pandemic and concerns regarding limited progress towards to 2030 goals (United Nations, 2022).

1.4.1. Antimicrobial Stewardship

Antimicrobial stewardship (AMS) represents "multifaceted approaches required to sustain the efficacy of antimicrobials and minimize the emergence of AMR" (Weese et al., 2013). All antimicrobial prescribers and end-users must take responsibility for management of AMU to preserve effectiveness of these products across the human, animal, agriculture, and environmental sectors. Any AMS program or intervention must consider all of these important and interconnected sectors as part of their design, as AMR cannot be managed in isolation. As resistance to first-line antimicrobials is projected to increase from 26 to 40% by 2050 (CCA, 2019), we must consider how to best use available products in all sectors. The CCA (2019) reported that AMS requires a One Health approach in a coordinated effort.

Reducing indiscriminate and unnecessary AMU and improving AMS efforts must be done with careful consideration to maintain human and animal health and welfare. An important consideration in AMS efforts is infection prevention, thereby minimizing or eliminating the need for antimicrobials (PHAC, 2015). In livestock industries, the ability to medically alter infection rates through AMU, has created current standards for farm layout, stocking densities, and animal production potential (Heikinheimo et al., 2017). To reduce AMU, substantial changes must occur to production animal system and other agricultural sectors that may decrease production capacity in many countries (Heikinheimo et al., 2017). Therefore, the global health security issue of AMR could contribute to a larger global food security issue if the livestock sector is mismanaged. This supports the urgency of AMR as a global health issue, and how AMU in animals and future control policies are incredibly important in current AMR mitigation discussions.

A coordinated and collaborative approach is required in AMS initiatives to align actions among various government levels, livestock commodity groups, human and animal health associations and regulatory bodies, patients, health professionals, regulatory colleges, veterinarians, researchers, and the public to achieve meaningful progress (PHAC, 2017). All stakeholders must understand the importance of their role to encourage AMS and be supported by resources and transdisciplinary expertise to increase effectiveness of implemented AMS efforts (PHAC, 2017).

Activities supporting AMS include: 1) infection prevention and control (in livestock often referred to as biosecurity) to support overall health and limit infections that require treatment; 2) research to support new AMU protocols and identify areas for safe AMU reduction across various sectors and industries; 3) innovation and commercialization in non-antimicrobial alternatives; 4) improvement of and access to diagnostics and required antimicrobials to optimize treatment decisions; 5) surveillance to identify trends in resistant pathogens; 6) knowledge translation and dissemination to all relevant stakeholders to increase support and uptake of AMS programs; 7) inclusion of qualitative methods to elucidate overarching themes and sector-specific AMS drivers and barriers; and 8) acknowledgement of inherent structural limitations of current health and agricultural systems and the will to address them (HealthCareCAN, 2016; Wall et al., 2016; PHAC, 2017; McCubbin et al., 2021).

Sector- and species-specific stewardship guidelines are required, but their broader context must be considered to achieve AMR mitigation. The transdisciplinary nature of One Health requires consideration of AMU across sectors plus wider implications of AMS and AMR nationally, but also globally for substantial progress to be made in mitigation efforts as well as towards the SDGs.

1.4.2. Antimicrobial Stewardship in Canada

According to the most recent Canadian Antimicrobial Resistance Surveillance System Report (2022), nearly 1/4 of prescriptions in Canadian healthcare facilities between 2018 and 2019 were deemed inappropriate or suboptimal, whereas the quantity of medically important antimicrobials dispensed for use in animals slightly increased from 2019 to 2020, highlighting the need for increased AMS efforts in Canada.

The federal role in Canadian AMS is primarily limited to regulation of drug importation, approval, and sale (PHAC, 2017). In the agriculture and veterinary sectors, regulatory roles and responsibilities for antimicrobials are shared among federal, provincial, and territorial governments, whereas the actual use, distribution, and dispensing of antimicrobials are managed at provincial and territorial levels (PHAC, 2017).

Due to Federal Government oversight, starting in 2018, all ‘medically important antimicrobials’ (Government of Canada, 2009) for veterinary use are limited to prescription-only access in Canada (PHAC, 2021). The Québec government further restricted preventative use of ‘Category I’ antimicrobials (high importance in human clinical disease (Government of Canada, 2009)) in food animals, with clinical use only permitted where culture and sensitivity results indicate that a lower antimicrobial class of importance to human medicine will not be effective (Roy et al., 2020).

There are AMS initiatives that support both uptake and progress in Canada. The most recent Pan-Canadian AMR Framework (PHAC, 2017) and Pan-Canadian Action Plan (PHAC, 2015) used a One Health approach to highlight integrated strategies to tackle AMR across various sectors. The Pan-Canadian AMR Framework was developed in collaboration with federal, provincial, and territorial governments, academics, non-governmental organizations, industry, and content experts representing human health, animal health, and agriculture and has a dedicated AMS section (PHAC, 2017). AMS initiatives are most effective when supported by surveillance, research, and evaluation including audit and feedback mechanisms (PHAC, 2017).

There are also voluntary examples of AMS activities for Canadian livestock. Chicken Farmers of Canada introduced a voluntary stewardship initiative aimed at further reduction of antimicrobials deemed of high importance to human medicine for use in poultry (Chicken Farmers of Canada, 2021).

Research supports ongoing AMS efforts and overall AMU reduction. For example, research is required to develop best management practices to identify areas of safe AMU reduction, antimicrobial alternatives, and biosecurity practices that can reduce AMU. There is ongoing AMR and AMS-related research across Canada. For example, the pan-Alberta AMR – One Health Consortium represents a collaborative research and innovation platform, operating and overseeing many projects across an array of AMR disciplines (AMR – One Health Consortium, 2023).

Increasing knowledge and understanding regarding AMR and AMU among health professionals, livestock producers, and the public are integral to support effective AMS (PHAC, 2017). There is integrated surveillance regarding AMR pathogens in Canada for all sectors to a varying degree and including a variety of bacterial species and livestock commodities (PHAC, 2022; Otto et al., 2020). However, there is a general lack of comprehensive AMU data encompassing the full scope of AMU across sectors (Otto et al., 2020).

On the human side, there are AMU data gaps and surveillance mostly focuses on larger care centers, whereas on the agricultural side, AMU data are primarily regional/national distribution volumes (Otto et al., 2020). Therefore, at the community level, there are no consistent or comprehensive processes to assess national antimicrobial prescribing patterns (HealthCareCAN, 2016).

Despite the lack of available prescribing audit and feedback mechanisms, there are prescribing guidelines and AMS recommendations supported by licensing bodies. The veterinary sector provides AMS support through development of guidelines, including the Canadian Veterinary Medical Association (2017, 2023) and the National Farmed Animal Health and Welfare Council (2016). In the human health sector, there are no national guidelines for antimicrobial prescribing (HealthCareCAN, 2016).

Some resources to support antimicrobial prescribing decisions do exist, including websites (Alberta Health Services and British Columbia Centre for Disease Control, 2014; Choosing Wisely Canada, 202l; Alberta Health Services, 2021), as well as stewardship ‘apps’ in human and veterinary sectors (University of Calgary, 2016; Stewardship of Antimicrobial by Veterinarians Initiative, 2023).

Training and continuing education opportunities for human and veterinary health professionals are essential to ensure antimicrobials are prescribed appropriately, and to effectively communicate with patients and clients regarding AMU risks and benefits, further contributing to public understanding (PHAC, 2017). Other educational opportunities for antimicrobial prescribers and users include conferences. For example, the Alberta Veterinary Medical Association (ABVMA), with support from Alberta Agriculture and Forestry, the AMR – One Health Consortium, and the National Collaborating Centre for Infectious Diseases, hosted a virtual One Health AMS Conference in March 2021 (Babujee et al., 2021). The virtual environment enabled a diverse complement of speakers across the human-animal-environment AMR/AMU/AMS space. Presenters covered a variety of topics encompassing human and animal health, and they emphasized the importance of environmental reservoirs for AMR bacteria and genes and implications for future AMR considerations.

Despite support for AMS in Canada plus ongoing initiatives and opportunities, there are still many unknowns and substantial progress is required across all sectors. There is also a general lack of environmental considerations in AMS discussions. Although the environmental component differs from the prescribing guidelines perspective in human and animal medicine, it remains important in broader AMR discussions as the importance of environmental AMR reservoirs, and environmental pollution with antimicrobials and residues has been described (Huijbers et al., 2015; Kim and Cha, 2021; McCubbin et al., 2021; UNEP, 2023).

The AMS goal for 2020 outlined in the National Action Plan for Antimicrobial Stewardship by HealthCareCan (2016) states that we will "*have optimized the use of antimicrobials in Canada through a unified approach that connects human, animal, and environmental health, improves health outcomes, contributes to reducing antimicrobial resistance, and re-establishes Canada as a global leader in antimicrobial stewardship.*" This is an admirable goal, but it has yet to come to fruition; substantial progress must be made before this future can be realized.

1.5.1. Moving Forward

Despite many unknowns in the AMR landscape, AMS represents an important area of focus in overall AMR mitigation. Further, a One Health approach is required to guide AMS efforts that encompass commonalities and recognize potentially competing priorities of human, animal, and environmental sector goals to preserve antimicrobial effectiveness. Additionally, social sciences have an important role in the One Health approach to AMS research, including understanding drivers and barriers of proposed AMR mitigation efforts.

1.6.1. Thesis Rationale

The threat posed by AMR is widely acknowledged, yet substantial global health and economic impacts are still felt. Identification of exiting context-specific gaps in the understanding of AMR could serve as a roadmap for future action. Gap identification coupled with improved understanding of the drivers and barriers of AMS experienced by Canadians, could further elucidate how to improve AMS in a practical and sustainable manner.

Furthermore, AMU reduction in livestock is an important area of focus in AMR mitigation, especially preventative AMU. However, there is currently a lack of research regarding selective practices in the Canadian dairy industry. The newly initiated Canadian Dairy Network for Antimicrobial Stewardship and Resistance now allows for ongoing national implementation of AMU and AMR research in the Canadian dairy industry.

By focusing on actionable areas of AMU reduction and improved AMS practices in the Canadian dairy industry, there is an opportunity for substantial progress. Overall, this thesis will highlight important Canadian AMR and AMS considerations and discuss an actionable example of AMS from the Canadian dairy industry.

1.6.2. Research Objectives

The research described in this thesis had the following aims:

1) describe the current state of AMR knowledge in Canada available in the literature, and identify the gaps in our understanding (Chapter 2);

2) identify perspectives of AMS, including perceived drivers and barriers across the One Health spectrum of relevant Canadian professionals (Chapter 3);

3) focus on the dairy industry as an example where AMS efforts are possible through selective dry cow therapy (Chapter 4); and

4) describe current selective dry cow therapy uptake and related practices in the Canadian dairy industry (Chapter 5).

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CHAPTER 2: Knowledge gaps in the understanding of antimicrobial resistance in Canada

2.1. ABSTRACT

Current limitations in the understanding and control of antimicrobial resistance (AMR) in Canada are described through a comprehensive review focusing on: 1) treatment optimization; 2) surveillance of antimicrobial use and AMR; and 3) prevention of transmission of AMR. Without addressing gaps in identified areas, sustained progress in AMR mitigation is unlikely. Expert opinions and perspectives contributed to prioritizing identified gaps. Using Canada as an example, this review emphasizes the importance and necessity of a One Health approach for understanding and mitigating AMR. Specifically, antimicrobial use in human, animal, crop, and environmental sectors cannot be regarded as independent; therefore, a One Health approach is needed in AMR research and understanding, current surveillance efforts, and policy. Discussions regarding addressing described knowledge gaps are separated into four categories: 1) further research; 2) increased capacity/resources; 3) increased prescriber/end-user knowledge; and 4) policy development/enforcement. This review highlights the research and increased capacity and resources to generate new knowledge and implement recommendations needed to address all identified gaps, including economics, social, and environmental considerations. More prescriber/end-user knowledge and policy development/enforcement are needed, but must be informed by realistic recommendations, with input from all relevant stakeholders. For most knowledge gaps, important next steps are uncertain. In conclusion, identified knowledge gaps emphasised the need for AMR policy decisions to be considered in a One Health framework, while highlighting critical needs to achieve realistic and meaningful progress.

2.2. INTRODUCTION

Since antimicrobial use (AMU) became widespread in healthcare, antimicrobial resistance (AMR) is increasing worldwide (Roca et al., 2015; World Health Organization [WHO], 2015, World Bank, 2017; Browne et al., 2021). Antimicrobials have saved hundreds of millions of human and animal lives and their discovery is a critical medical advance (Davies et al., 2010; World Bank, 2017). However, increasing AMR may vastly reduce future antimicrobial efficacy. The WHO, the Food and Agriculture Organization of the United Nations (FAO), and the World Organization for Animal Health (WOAH) agree that AMR is a serious threat to human and animal health and negatively impacts the environment (WHO FAO WOAH, 2016). While the World Bank describes bacterial susceptibility to antimicrobials as a ‘public good’ that needs global protection (World Bank, 2017).

Due to a limited variety of efficacious antimicrobials, the same products or those within the same class are used in humans, animals (Tang et al., 2017), agricultural crops, and aquaculture (Sarmah et al., 2006; Centers for Disease Control and Prevention, 2019a; Fisheries and Oceans Canada, 2021). This promotes bacterial resistance by increasing exposure of microbes to the same or similar antimicrobials (Tang et al., 2017), complicating AMR containment. Few drugs belonging to new antimicrobial classes have recently been released (Deoghare, 2013; WHO, 2015; Malani, 2019; United States of America Food and Drug Administration, 2019) and efforts to reduce AMU and limit use of new antimicrobials reduce economic incentives for product development.

The extent of selection of resistant bacteria often reflects the degree of AMU, the type of antimicrobials used, and the effectiveness of infection prevention and control (Gelband et al., 2013). The COVID-19 pandemic exacerbated the problem, as antimicrobial stewardship (AMS) efforts were often disregarded, with substantial AMU in COVID-19 patients for bacterial infections or prophylaxis (Strathdee et al., 2020; Charani et al., 2021; Pelfrene et al., 2021). Furthermore, disinfectant use has dramatically increased, affecting the microbiome and potentially exacerbating AMR development (Wales and Davies, 2015; Wall et al., 2016). Consequently, full impacts of the COVID-19 pandemic on development of AMR are unknown but may be substantial.

Current and projected AMR impacts require immediate and sustained action across human, animal, and environmental sectors using a true One Health approach, with multiple sectors communicating and collaborating to improve health outcomes while designing and implementing research, initiatives, policies, and legislation (Robinson et al., 2016; WHO, 2017). Livestock production is expected to be impacted, with a projected global decline of 2.6 to 7.5% annually (World Bank, 2017). In addition to effects on animal health and welfare, consumer costs, food availability, and production system sustainability will be affected (Council of Canadian Academies [CCA], 2019). It was estimated that by 2050, without interventions, every year there will be 10 million human deaths globally due to AMR infections (O'Neill, 2016). The incremental annual global healthcare costs due to AMR are expected to be ~US$0.33 to 1.2 trillion (World Bank, 2017). In Canada, AMR cost our national healthcare system an estimated $1.4 billion in 2018, with projected healthcare system costs reaching $120 billion by 2050 without interventions to slow predicted increases of bacterial resistance to first-line antimicrobials from 26 to 40% (CCA, 2019). In addition to healthcare, the CCA (2019) describes potential broader social impacts of AMR that include:

- decreases in social trust, social capital, quality of life, and equality among socio-demographic groups;
- weakened social connectivity;
- discrimination against those deemed at risk for or with AMR infections;
- unequal impacts of AMR, with higher risk for marginalized groups who experience poverty, homelessness, substance use disorder, overcrowding/poor housing/poor sanitation, and First Nations/Inuit/Metis populations; and
- a Canadian society that may become less open and trusting (i.e., less travel and increased support to close Canada's borders to immigrants and tourists).

There is substantial support regarding intricate connectivity of AMR in human, animal, and environmental sectors (Woolhouse and Ward, 2013; Leonard et al., 2017; Murphy et al., 2017; Tang et al., 2017) with spillover of AMR between microbial populations in livestock and humans (Wall et al., 2016). Furthermore, environmental bacteria are potential reservoirs for resistance genes acquired through exposure to antimicrobial residues from human, animal, and agricultural sources (Forsberg et al., 2012; Laxminarayan et al., 2014; Hatsosy et al., 2015; James and Wong, 2015; Leonard et al., 2017; United Nations Environment Programme [UNEP], 2023). These environmental bacteria could transfer AMR traits to commensal and pathogenic bacteria. Transmission of AMR bacteria is influenced by trade, travel, and human and animal migration (WHO, 2015) making AMR a global issue that is not contained by political borders.

A One Health framework was used to identify three review areas to describe current knowledge gaps in Canada that need to be addressed before realistic, practice-oriented AMR mitigation strategies can be developed and implemented. These areas include: 1) treatment optimization; 2) surveillance of AMU and AMR; and 3) prevention of transmission of AMR. Herein, we have conducted a scoping review focused on the Canadian context to identify the most pressing gaps in knowledge that currently hamper Canadian AMR prevention and control (summarized in Table 2.1). Where supporting data are lacking, expert opinion from of the AMR – One Health Consortium members was used to ensure the most up-to-date information was included and identify any additional gaps. Furthermore, requirements to address knowledge gaps are discussed with the intention to direct expert panels in identifying concrete next steps and are presented visually with their identified requirements in Figure 2.2.

2.3. TREATMENT OPTIMIZATION

AMU is considered one of the most important factors in development and spread of AMR, with misuse and overuse of particular concern (WHO, 2015; Wall et al., 2016; Public Health Agency of Canada [PHAC], 2017). Examples of the latter by prescribers, patients or antimicrobial administrators (i.e., farmers) include: excessive use for disease prevention or treatment in lieu of good hygiene, inappropriate off-label use, treatment of non-bacterial illnesses, growth promotion in livestock, improper dosing (quantity, interval, or duration), patient/administrator non-compliance, fraudulent formulation and incorrect antimicrobial selection (Ad-Hoc Committee for Antimicrobial Stewardship in Canadian Agriculture and Veterinary Medicine, 2014; Om et al., 2016; Wall et al., 2016; PHAC, 2017, 2021a). To maintain the efficacy of available antimicrobial treatments, treatment optimization is crucial and includes, as a minimum (British Society for Antimicrobial Chemotherapy, 2018; Guardabassi et al., 2018; Centers for Disease Control and Prevention, 2019b):

- use of the least broad-spectrum antimicrobial for the infection;
- avoiding unnecessary prophylactic and broad-spectrum AMU;
- avoiding antimicrobial prescribing before bacterial culture and sensitivity;
- optimal dosing (i.e., quantity, interval, duration); and
- patient compliance.

Development of AMS best practices does not ensure their uptake by various stakeholders, for societal, cultural (Lu et al., 2020) and economic factors. For example, there is frequently prophylactic or empirical AMU in lieu of more costly solutions (i.e., diagnostics and/or focused treatment). Understanding AMU economics is vital to promote support of AMS and AMU reduction efforts, at policy, prescriber, and patient-levels, but currently lacking (Table 2.1). Specific societal and cultural factors in human medicine include-short term benefits, including positive clinical outcomes and avoidance of clinical risks, maintaining prescriber-patient relationships, societal pressures and prescriber expectation outweighing long-term AMR community risks, and thus hampering judicious AMU (Lu et al., 2020). Antimicrobial prescribing can also be influenced by social hierarchies in the both the human (Charani et al., 2021) and veterinary medical settings (Higgins et al., 2017). Even when AMS strategies in human hospitals were developed, they often did not include who should act and failed to account for multi-professional care teams and details on when to start/stop antimicrobials (Duncan et al., 2020). Livestock-focused research suggests when AMR mitigation research is interdisciplinary, behavioural feasibility is also considered by identifying all actors in livestock AMU and power relationships (Baudoin et al., 2021).

To increase social science inclusion in AMR research and policy, focus groups with physicians, veterinarians, agricultural crop managers, livestock producers, and other relevant stakeholders should be utilized to identify factors hampering behavioural change and then to develop AMS interventions that ensure uptake. Integration with social science domains could identify considerations essential to each sector for support of AMU reduction strategies, in addition to described economic considerations. Close collaboration with social scientists is needed to successfully implement AMS programs.

Stewardship efforts can be supported by further development and availability of rapid diagnostic technology, to decrease empirical prescribing and increase appropriate antimicrobial treatment response times (Charani et al., 2021). An impediment to optimal dosing is the knowledge gap regarding quantitative relationships between AMU and AMR development, and interactions of resistant bacteria at the human, animal, and environmental interface (Table 2.1). Further research regarding a dose-response relationship of AMU and subsequent AMR development, including impacts and relative importance of number of antimicrobial doses, or duration of AMU in various contexts, is required to inform model development to understand impacts of AMU and mitigation efforts.

A key factor in reducing AMU is reducing disease prevalence/burden. Non-antimicrobial alternatives for infection prevention, e.g., vaccines and alternative therapies (i.e., phages, lysins, antimicrobial adjuvants, probiotics, and microbiome alterations) are being explored to prevent or treat infections (CCA, 2019). These alternatives should be considered crucial for treatment optimization, to reduce AMU; however, their short and long-term efficacy is not described in the literature and currently unknown (Table 2.1), and they have yet to dramatically reduce AMU.

2.3.1. AMU in Humans

2.3.1.1. *Current knowledge*

AMU for human health increased worldwide between 2000 and 2018, particularly in low- and middle-income countries (Browne et al., 2021). In Canada, as reported in the 2022 CARSS update (Canadian Antimicrobial Resistance Surveillance System) there was a decrease of 26.9% in annual antimicrobial consumption, between 2017 and 2021 (PHAC, 2022). Regardless, from 2016 to 2020, the overall incidence of blood stream infections with methicillin-resistant *Staphylococcus aureus* infections increased by 33.3% (PHAC, 2022).

Between 2017 to 2021, at least 90% of antimicrobials for human use in Canada were prescribed in community health care settings (e.g., by family physicians, dentists, pharmacists, nurse practitioners, etc.) (PHAC, 2022). In Canadian healthcare facilities from 2018 to 2019, approximately 1/4 of prescriptions were identified as either suboptimal or inappropriate (PHAC, 2022). Furthermore, 30% of antimicrobial prescriptions dispensed through Canadian pharmacies (National Collaborating Centre for Infectious Diseases, 2016) and 57% in long-term care facilities were unnecessary (Penney et al., 2018), highlighting opportunities to improve prescribing practices and patient expectations.

2.3.1.2. *What is missing?*

Most unnecessary AMU in humans is not related to gaps in prescriber knowledge, but instead to other factors at the provider and/or patient-level, interplaying with various contextual factors (McKay et al., 2016). Further understanding of these contextual prescribing factors represents a major knowledge gap that must be addressed for practical AMS recommendations to be developed and upheld (Table 2.1). For example, there is a perception of antimicrobials as 'magic bullets' or a harmless 'cure-all' (Grandmann, 2011). These perceptions must be altered to generate effective change in prescribing practices in all sectors and to prevent the addition of antimicrobials to medical regimes 'just in case.'

There is limited public knowledge regarding the harms of inappropriate AMU and AMR implications (Gualano et al., 2015). Receiving an antimicrobial prescription is part of the social contract of a medical appointment in human and veterinary medicine. Before substantial progress can be made, this gap in public knowledge regarding when AMU is appropriate must be addressed and prescribing guidelines improved to shift the dialogue and alter patient expectations. For example, "Using Antibiotics Wisely" is a national campaign developed by Choosing Wisely Canada to facilitate patient-physician conversations regarding unnecessary AMU in Canada (Choosing Wisely Canada, 2021). "Bugs and Drugs" is another resource developed by Alberta Health Services (AHS), and "Do Bugs Need Drugs" was developed by AHS and the British Columbia Centre for Disease Control (AHS, 2021; AHS and British Columbia Centre for Disease Control, 2014). Furthermore, an innovative AMS "app" has been modelled by many sites globally (University of Calgary, 2016). These initiatives represent advances in treatment optimization and information availability. However, there is opportunity for substantial progress regarding uptake of prescribing recommendations, including sustained behaviour change, increasing public knowledge and expectations, as well as altering the social environment, culture and value systems surrounding AMU.

2.3.2. AMU in Animals

2.3.2.1. *Current Knowledge*

Extensive AMU for treatment and prevention of infectious diseases in livestock has supported development of current animal production systems (Kirchhelle, 2018). In 2020, the total volume of antimicrobials (excluding ionophores and chemical coccidiostats) to treat Canadian livestock was almost five times the amount used in humans, with almost all used in production animals (PHAC, 2022). However, the context of AMU must be considered, including the population correction unit (PCU) that enables standardization of antimicrobial product weight (mg) per unit of animal or human biomass (kg) (PHAC, 2016). When the Canadian-specific animal PCU is considered, animal-intended antimicrobial distribution was only 1.8 times that prescribed for humans (PHAC, 2022). The quantity of animal-intended antimicrobials dispensed in 2020 in Canada increased by 6.5% compared to 2019; however, 2019 sales were slightly less than those in 2018 (PHAC, 2022). Overall, quantities of animal-intended antimicrobials dispensed have fluctuated over the recent decade, with no clear downward trend (PHAC, 2018, 2020, 2022). In 2020, the animal sector represented 82% of antimicrobials sold, the human sector was responsible for 17%, and crop AMU represented <1% (PHAC, 2022). Although the quantity of antimicrobials dispensed is not perfectly correlated to use, it provides a proxy to assess trends. Furthermore, antimicrobials intended for growth promotion (i.e., treatment/prevention of subclinical disease to improve health and increase production (Butaye et al., 2003)) in broiler and turkey flocks decreased to zero between 2014 and 2018 (PHAC, 2020).

As of December 1, 2018, all ‘medically important antimicrobials’ (Government of Canada, 2009) for veterinary use became limited to prescription-only access in Canada (PHAC, 2021b), which will improve assessment of AMU in Canada and reduce inappropriate use. Many antimicrobials deemed as ‘last resort’ to treat infections in people are already restricted from use in livestock, or limited to prescription-only access, and livestock industries are adopting voluntary policies to avoid these compounds for disease prophylaxis, as exemplified by the Chicken Farmers of Canada AMU reduction strategy (Chicken Farmers of Canada, 2021). Additionally, the Québec government restricted Category I AMU in food animals starting February 25th, 2019 (Category 1 antimicrobials are of high importance in human clinical disease) (Roy et al., 2020). Specifically, preventative use of Category I antimicrobials is banned, and clinical use is only permitted in livestock for cases where antimicrobials of a lower class of importance to human medicine will not be effective (e.g., based on culture and sensitivity) (Roy et al., 2020). Long-term impacts of this provincial stewardship program are unknown.

There are opportunities for further AMU reduction in Canadian livestock. For example, the majority of AMU on Canadian dairy farms is for mastitis treatment and prevention (Saini et al., 2012; Ruegg, 2017). Blanket dry cow therapy practices are most common; at the end of lactation (start of the dry period), dairy cows are prophylactically treated with intramammary antibiotics to cure current bacterial infections and prevent new ones (Lhermie et al., 2018). Alternatively, selective dry cow therapy targets cattle expected to benefit from antibiotics (Lhermie et al., 2018), with no effect on animal production and udder health if cattle are selected appropriately (Kabera et al., 2020; Rowe et al., 2020; Santman-Berends, et al., 2021; McCubbin et al., 2022). Therefore, this can reduce livestock-associated AMU in Canada.

This example highlights the importance of context when evaluating AMS initiatives. Research is required to develop best management practices to reduce livestock-associated AMU but maintain animal health and production (Table 2.1). In addition, research is underway on various approaches to reduce AMU in livestock, including vaccinations, pre- and probiotics, selection of animals less susceptible to disease (Ismail et al., 2017; Markowiak and Slizewska, 2018; Islam et al., 2020), etc. However, their development and uptake has yet to dramatically reduce on farm AMU, with further work required.

Antimicrobials for companion animals accounted for less than 1% of total antimicrobial sales in 2020 (PHAC, 2022). However, companion animals are more likely to receive Category I and II antimicrobials (PHAC, 2020) closely related to human medications. This, and the close proximity of humans and their pets creates potential for transmission of organisms resistant to highly important antimicrobials. AMR bacteria have been reported in companion animals. For example, methicillin-resistant *Staphylococcus pseudintermedius* (MRSP), causes common and sometimes untreatable skin and surgical site infections in dogs (Bryan et al., 2012). Furthermore, humans with methicillin-resistant *Staphylococcus aureus* (MRSA), a bacteria of public health concern, can infect companion animals, which are a source of infection or reinfection (Ferreira et al., 2011).

2.3.2.2. *What is missing?*

Similar to human medicine, prescribing guidelines on appropriate companion animal and livestock AMU require improvement. However, to improve uptake of AMS recommendations, veterinarian-public expectations must also be altered to shift prescribing expectations and limit social pressure on prescribers. The Canadian Veterinary Medical Association (CVMA) provides AMU guidelines to improve veterinary prescribing decisions (CVMA, 2021). Furthermore, relationships between companion animal AMR development or acquisition and impact on other species (including humans) or the environment are currently unknown (Table 2.1).

Current AMR impacts on wildlife and their contributions to dissemination of resistant bacteria or genes are unknown (Wall et al., 2016). However, wildlife has been reported as an important factor in the transfer of AMR bacteria and resistance traits to species usually not exposed to AMU and selection pressure (Cristóbal-Azkarate et al., 2014; Wall et al., 2016). Whereas AMR is reportedly higher in farmed animals versus wildlife (Skarzyńska et al., 2020), AMR bacteria were reported in remote wildlife (Rwego et al., 2008; Rabbia et al., 2016; Vittecoq et al., 2016), questioning impacts of human activities on wildlife populations. Overall, the intricacies of microbial population interactions among various animal species and their relationship to human and environmental AMR and use are unknown.

2.3.3. AMU in the Environment

2.3.3.1. *Current knowledge*

Antimicrobials are used in agriculture for crop management and released into marine environments through aquaculture via feed or water (Sarmah et al., 2006; Tang et al., 2017; Centers for Disease Control and Prevention, 2019a; PHAC, 2020; Fisheries and Oceans Canada, 2021). Less than 1% of Canadian antimicrobials sold are attributed to crop management (PHAC, 2022), including streptomycin for treatment of fire blight (Haynes et al., 2020). However, due to wastewater discharges (Brown et al., 2019; Khan et al., 2019; Paulus et al., 2019), application of sewage-derived biosolids (Calero-Cáceres et al., 2014), and farm manure and animal production facility runoff (Chen et al., 2018), the environment is where human and animal AMU intersect, in addition to specific AMU for agricultural purposes (Wall et al., 2016). The environment is also a primary source of resistance genes (Crtryn, 2013) and a site for persistence and amplification (i.e., horizontal gene transfer) to pathogens of potential concern (Aubertheau et al., 2017). Therefore, reducing human and animal AMU will not eliminate AMR (Manaia et al., 2016).

Environmental reservoirs may facilitate maintenance of high concentrations of AMR bacteria due to on-going use of co-selecting agents, e.g., widespread use of biocides (Wall et al., 2016; Living with Resistance project, 2018) and disinfectants in municipal water and wastewater treatment (Guo et al., 2015; Liu et al., 2018). *In vitro* studies demonstrated that using common herbicides on crops can modulate AMR to common antimicrobials in indicator bacteria (*Escherichia coli*) and foodborne pathogens (*Salmonella* spp.) (Kurenbach et al., 2017). Additionally, in paleontological studies of soil cores, heavy metal pollution in historical industrial areas may have co-selected for AMR genes to antimicrobials of importance to human medicine before the advent of penicillin (Maier et al., 2018). There is evidence for global dissemination of *E. coli* that is highly resistant to wastewater treatment and has resistance genes to antimicrobials important to human medicine, with genetic similarity to virulence genes of urinary pathogenic *E. coli*, raising questions about this exposure pathway for humans (Zhi et al., 2019; Zhi et al., 2020). The spread of resistant strains and resistance genes may be a dominant contributor to AMR maintenance, with sanitation and water treatment having a large role in reducing AMR transmission (Collignon et al., 2015, 2018; UNEP, 2023).

2.3.3.2. *What is missing?*

Direct impacts of human or animal AMU or antimicrobial residues in the environment and impact of AMR in the environment and subsequent impacts on humans and animals are not well characterized (Table 2.1). It is difficult to quantify impacts of human and animal AMU and AMR on the environment, but there is a strong correlation between socio-economic, health and environmental factors and AMR gene abundance in untreated human sewage (Hendriksen et al., 2019).

AMU is a major risk factor for development of AMR bacteria and their environmental presence. Although broad exposure may occur via pathways such as drinking water, there are limited data to quantify direct human health effects from environmental AMR, another major knowledge gap (Table 2.1) (Huijbers et al., 2015; Wall et al., 2016). Regardless, substantial reduction of antimicrobial misuse through treatment optimization/AMS programs can lessen selection pressure on microbial communities (Wall et al., 2016; World Bank, 2017). AMS programs should also include reductions in direct application of manures/biosolids to land (Graham et al., 2016). Although the environment may have a quantitatively minor role compared to human-to-human and animal/food-to-human pathways, it may still be critical in overall AMR impact reduction (Zhu et al., 2019), as demonstrated in developing areas (Collignon et al., 2018). Therefore, environmental reservoirs should be integral to development of strategic AMR mitigation. There must be research to quantify AMR presence in the environment, impact of AMU in humans and animals, and other factors promoting AMR development and maintenance in the environment.

2.4. SURVEILLANCE

2.4.1. Current knowledge

Surveillance is essential to demonstrate trends and monitor emerging and re-emerging AMR pathogens and AMU across all health sectors and provide data to support stewardship to address AMR (PHAC, 2017). Surveillance data provide crucial information to identify areas for strategic interventions, increase understanding of the magnitude of AMR impacts and provide context to assess impacts of AMS interventions. Without sustained surveillance regarding AMR/AMU across the One Health continuum, public health authorities and policymakers in government and industry will lack information to craft and evaluate appropriate policy responses (PHAC, 2017).

Surveillance for AMU/AMR in Canada has increased, but not all sectors or species affected by AMR are in a holistic system, which remains a compilation of multiple programs (Otto et al., 2020). There are currently surveillance systems at various levels of government aimed at data collection on AMR and AMU in Canadian settings such as hospitals, communities, and farms (PHAC, 2017; Otto et al., 2020). Ongoing National Canadian surveillance programs include (Stephen et al., 2007; Health Canada, 2009; PHAC, 2014, 2016, 2019, 2020; Otto et al., 2020; Fisheries and Oceans Canada, 2021):

- **Canadian Antimicrobial Resistance Surveillance System** (CARSS) - Incorporates epidemiological and laboratory AMR/AMU data from the Public Health Agency of Canada's surveillance systems (listed below), from human, production animal, and food sources.
- **Canadian Integrated Program for Antimicrobial Resistance Surveillance** (CIPARS) - Monitors trends in AMR/AMU for select bacteria mainly from humans, animals, and the food supply chain.
- **Canadian Nosocomial Infection Surveillance Program** (CNISP) - Collects information on AMR/AMU for nosocomial infections in hospitalized human patients.
- **Canadian Tuberculosis Laboratory Surveillance System -** All tuberculosis cases diagnosed in Canada are reported (with/without treatment started) for: citizens,

permanent residents, refugees, refugee claimants, and protected people. For temporary residents, only cases where treatment was started in Canada are reported.

- **The Gonococcal Antimicrobial Surveillance Program** (GASP-Canada) - Laboratory surveillance data for *Neisseria gonorrhoeae* isolated by provincial microbiology laboratories to the National Microbiology Laboratory (NML).
- **Pest Management Regulatory Agency (of Health Canada)** - Provides AMU data for crop production to CIPARS.
- **The National Laboratory Surveillance of Invasive Streptococcal Disease** (eSTREP) - passive and voluntary collaboration with provincial public health laboratories for *Streptococcus pneumoniae* and *Streptococcus pyogenes* surveillance, with some provinces only submitting a subset of isolates.

2.4.2. What is missing?

Regrettably, these systems do not encompass the full scope of Canadian AMR and AMU. Data on environmental AMR are typically outside their mandates and therefore missing, and information is frequently not linked across systems (Otto et al., 2020). CIPARS is the only program purposefully designed to be an integrated AMR/AMU surveillance program, whereas all others use various infectious disease platforms to collect AMR/AMU data (Otto et al., 2020). There are important gaps for a truly comprehensive, integrated, One Health AMR/AMU surveillance system in Canada (Table 2.1). Several of these gaps are identified in the ‘Federal action plan on antimicrobial resistance and use in Canada’ (PHAC, 2015) and the ‘Pan-Canadian framework for action’ (PHAC, 2017) but they still exist.

Without full integration and comparability of collected data, understanding is limited regarding local drivers of AMR and ensuing impacts. For example, CIPARS represents a national surveillance system with a One Health approach but consists only of active AMR surveillance for select bacteria in chickens, turkeys, pigs, dairy, and recently, feedlot cattle, and passive reporting in humans and other animal species (Figure 2.1) (PHAC, 2020). Further, on-farm components of CIPARS rely on a limited number of sentinel farms within their chicken, turkey, pig, and feedlot programs, and some (e.g., pigs) are limited to final production phases. There is also a lack of information on AMR prevalence in companion animals and risks due to close proximity to humans.

Up-to-date AMR prevalence estimates for other species/sectors, e.g., prevalence in the general human population, on-farm data for multiple livestock species, and wildlife are lacking. This represents an urgent knowledge gap (Table 2.1); without current AMR prevalence estimates across all relevant sectors in Canada, there are no benchmarks to evaluate established mitigation strategies or identify important areas for policy development. Furthermore, comprehensive surveillance of AMR prevalence could inform patient treatments (WHO, 2015).

According to the CCA (2019), weaknesses in current Canadian AMR/AMU surveillance include limited data on: 1) infections of priority pathogens in community settings (i.e., non-hospitalized patients); 2) AMU in many regions of Canada; 3) AMR in pathogens of domestic animals and wildlife; 4) lack of an established federal/provincial/territorial surveillance system; and 5) lack of access to collected data. Furthermore, sustained surveillance of AMR development, persistence and transmission through the environment is not established. There are very limited data on resistance determinants in the environment. CIPARS does track AMU in some agricultural components (PHAC, 2020), but there is no clear understanding of environmental AMR in Canada. CIPARS represents a substantial contribution to the surveillance and understanding of AMR in Canada and provides a world-recognized framework for integrated surveillance. It highlights the importance of continued AMR mitigation efforts (PHAC, 2020), yet also identifies important surveillance gaps needing more coordination and resources.

To fully utilize and integrate data generated by CIPARS and other agencies globally, international standards for AMR and AMU data collection and reporting among human health, veterinary, and agricultural sectors are required, but absent (WHO, 2015; Otto et al., 2020). Without comparable data among species, sectors, and regions, global understanding of AMU/AMR is impossible. In addition to implementation of reporting standards, data must be of good quality, and accessible to researchers and policymakers. There is also a need for measurable goals and evaluation criteria when considering surveillance data (Aenishaenslin et al., 2021). Without practical and actionable goals that meet provincial and national needs, progress to control development of AMR cannot be measured or made (WHO, 2015).

Human health care is primarily provincially funded and regulated in Canada, whereas veterinary and environmental sectors have substantial federal and provincial/territorial components, requiring cooperation/collaboration among governments and engagement of all sectors and relevant stakeholders. In summary, due to the interconnectedness of AMR development, Canada could benefit from integration and standardization of human, animal, and environmental AMU/AMR data collection. This requires coordination of existing surveillance systems and addition of broader environmental considerations to capture local drivers of AMR.

2.5. PREVENTION OF TRANSMISSION OF AMR

2.5.1. Current knowledge

Treatment optimization and AMS are important in preventing AMR transmission, as they reduce the overall burden of resistance on the microbiome, limiting risk of transmission. AMS efforts in human hospitals have improved AMU quality (Schuts et al., 2016), and there are associations between reductions in livestock AMU production system AMR prevalence (Tang et al., 2017; Nóbrega et al., 2021). Additionally, there were decreases in human occupation-associated AMR infections in affected production systems (Tang et al., 2017). Therefore, it is very important to promoting reductions in unnecessary AMU across sectors.

Antimicrobials are important to treat, prevent, and control infectious diseases and maintain animal health and welfare in intensive livestock production (Wall et al., 2016; Kirchhelle, 2018). By decreasing the reliance on AMU in intensive farming systems, emphasis on other forms of biosecurity must be increased, as well as farm infrastructure, management and breeding practices designed to improve animal health and resilience to reduce disease transmission risk, with increasing costs for producers and consumers.

Additionally, infection prevention and control procedures are invaluable to prevent transmission of AMR bacteria. Improved adjacent infection control efforts could further limit AMU. While this refers to sterility and hygienic practices for humans and animals (PHAC, 2017), it also refers to maintaining healthy microbial populations that resist recolonization and opportunistic infections with resistant bacteria. Maintaining healthy microbial populations is critical for immunocompromised individuals, livestock, and crop production systems.

"Every infection prevented is one that needs no treatment."

WHO, 2015

2.5.2. What is missing?

Despite new knowledge regarding the role of the environment in preventing AMR, much remains unknown; however, the environment is likely an important reservoir of resistance genes (Forsberg et al., 2012; Hatsosy and Martiny, 2015; James and Wong, 2015; Roca et al., 2015; Leonard et al., 2017; Maier at al., 2018). AMR development in the environment is attributed to AMU, plus other pharmaceutical agents and heavy metals (Ashbolt et al., 2013; Wales and Davies, 2015; Kurenbach et al., 2017; Maier at al., 2018; Dickinson et al., 2019; UNEP, 2023). Data and knowledge required to undertake a human health risk assessment for environmental development and transfer and AMR include: 1) surveillance of clinical and environmental AMU, AMR, and their determinants; 2) epidemiological investigations of AMR outbreaks and sporadic cases; 3) identification of selection pressures in various environments and transmission to human-relevant bacteria; 4) links between AMU and resistance (human, laboratory, and/or field animal/crop); 5) AMR characteristics and their determinants; 6) links among AMR, virulence, and ecological fitness; 7) environmental fate of antimicrobial residues in water and soil, and their bioavailability associated with AMR selection; and 8) risk assessments of AMR and related pathogens (Ashbolt et al., 2013). These data are lacking. Limitations for acquiring these data includes some soil bacteria are difficult to culture and acquiring accurate data from flowing water is difficult as it is inherently dynamic and diluting (Wall et al., 2016).

As much of the world’s population, including Canadians (Coleman et al., 2013), obtain drinking water from excreta-impacted waters that likely contain AMR bacteria, there is an urgent need to better understand what concentration limits should be considered to better manage potential mass-inoculation of people with resistance genes (Sanganyado and Gwenzi, 2019).

However, the only antimicrobial concentration limits under consideration relate to wastewaters (AMR Industry Alliance, 2018). Not surprisingly, there are AMR genes in Canadian urban sewage (Freeman et al., 2018; Hendriksen et al., 2019). Furthermore, the prevalence of AMR genes in treated effluent leaving water treatment facilities in the Canadian prairies provides evidence for human influence on local environmental reservoirs of resistance (Freeman et al., 2018).

Without considering all drivers and pathways of AMR introduction into the environment, any strategy to reduce resistance across all sectors risks failure (Wall et al., 2016). To mitigate development and transmission of AMR bacteria, the environment must be considered an important reservoir and policy changes must encompass agricultural and environmental best practices along with those in human and veterinary medicine. Currently, a key knowledge gap in AMR transmission prevention is limited understanding of quantitative risks to identify the relative importance of various AMR development and transmission incursion pathways (Table 2.1).

2.6. DISCUSSION

There are numerous knowledge gaps in understanding AMR in Canada. AMR is complex, with many contributing factors, numerous antimicrobial end users, countless microbial interactions, and varying policies and regulatory capacities around the world. Substantial progress will require much investment in AMR research, surveillance, and capacity building, coupled with effective policies at national, provincial/territorial, and local levels.

Various knowledge gap assessments (Bulteel et al., 2020; Charani et al., 2021) and action plans have been developed regarding AMR, including the WHO Global Action Plan (WHO, 2015) and the Federal action plan on antimicrobial resistance and use in Canada (PHAC, 2015). Most requirements detailed in this review (Figure 2.2), developed for the three key areas (treatment optimization, surveillance, and transmission), are logical continuations of described action plans with focus on the Canadian context. Moreover, the One Health approach used in this review identified additional novel gaps for Canada. Prioritization of required investments and activities must be considered with further cooperation and coordination among existing initiatives. Required efforts to address described knowledge gaps are described in Figure 2.2 and separated into categories: 1) further research, 2) increased capacity/resources, 3) increased prescriber/end-user knowledge, and 4) policy development/enforcement. Each knowledge gap has been assigned one or more categories as required changes for the gap to be addressed.

Research and increased capacity/resources are required to fully address all knowledge gaps. Required research is similar across the human, animal, and environmental sectors (Freeman et al., 2018) and will enable development of specific recommendations, to ensure they are effective and practical. Otherwise, general uptake and AMR mitigation may be limited.

Furthermore, understanding of environmental components is severely lacking, and requires immediate research and capacity building to ensure AMR mitigation efforts are effective. There are still many unknown regarding environmental AMR; however, immediate action can still be taken to minimize environmental pollution with antimicrobials and resistance pathogens by focusing on main identified sources of pollution, including waste and effluent and from pharmaceutical manufacturing plants, livestock and other agricultural industries, and healthcare facilities (UNEP, 2023).

In contrast, addressing the gap to increase end-user knowledge regrading appropriate AMU and challenging clinical visit expectations in both human and animal medicine is a shift in focus from research to increasing end-user knowledge. However, this must include further understanding of drivers and barriers of AMS to increase recommendation uptake to facilitate sustained behaviour change. Research surrounding this will focus on bridging the gap between knowledge and practice.

Increased capacity/resources should accompany further research, as increased funding, research activity design/development, laboratory capacity, data analysis and publishing/knowledge transfer are required for research to be effective and to inform decisions in policy and influence end-user decision-making. However, capacity and financial support for required research may be inadequate. For example, Canada's research and development support for new antimicrobials is severely lacking (Hollis, 2021). Therefore, without an incentivised market for new antimicrobial development, progress fostering required research is unlikely.

An emphasis on 'further research' and 'increased capacity/resources' does not imply that other requirements are less important. Rather, it highlights a lack of required knowledge and understanding to develop effective policy/recommendations. The lack of best management practices for AMU and AMS programs, serve as an example.

Reductions in prophylactic AMU were not considered possible but became feasible with better farm management and biosecurity. However, not all food animal industries are equally ready to implement management practices that reduce AMU. Research into best management practices is required for sustained AMU reduction that does not negatively impact animal health and welfare. However, this will require substantial investment in long-term research to establish a causal link between AMU reductions and AMR implications which progresses into practical policy development and enforcement. The Canadian poultry industry had some success with a voluntary AMS program (PHAC, 2020; Chicken Farmers of Canada, 2021). After banning 3rd generation cephalosporins in 2014, *Salmonella* isolates from sick people, and *Salmonella* and *E. coli* isolates from chickens at slaughter and retail meat had lower 3rd generation cephalosporin resistance (PHAC, 2020).

Additionally, further collaborative surveillance programs are required to assess the degree of human impact on various ecosystems and determine best relative mitigation efforts. Despite being previously identified as an important gap (PHAC, 2017), substantial progress has not occurred. This should also include research regarding impacts of co-selection of AMR by common cleaning agents in animal production facilities and human hospitals (Wall et al., 2016). This should be coupled with research into transmission of AMR bacteria between species, AMR contamination pathways of groundwater, including discharge of antimicrobial residues in sewage and disposal of antimicrobial waste (i.e., unused or expired drugs, packaging with residual drug).

Although surveillance is essential to understanding AMR and AMU trends, generalization of their results across bacteria or antimicrobials can falsely inform mitigation efforts. A substantial aid in development of AMS best practices and prioritization efforts will be quantitative risk-based assessments of AMR development and the relationship among human, animal, and environmental sectors. With risk-based models, policymakers can be better informed to use available resources to target areas of high importance. Coupled with the social and behavioural research components, this could promote improvements on a national level.

Prioritization of required activities is needed to focus efforts and available resources; however, without answers to some of these knowledge gaps, it is difficult to identify the most pressing areas to act (i.e., restrict AMU, prescribing best practices, environmental containment, etc.). Although, in general, AMR understanding and mitigation attempts should follow the following roadmap: 1) detailed understanding of missing data required to inform realistic policies and best management practices; 2) implementation and ongoing evaluation of policies and recommendations at the community, provincial/territorial, and national levels; and 3) sustainable implementation with ongoing evaluation to account for new innovations and AMU/AMR surveillance findings (Charani et al., 2021). Additionally, to lay the groundwork for changes in antimicrobial prescribing and use, mitigation efforts must be accompanied by public educational campaigns to improve general understanding of the risks associated with AMR and unnecessary AMU, but also to increase social responsibility. In summary, AMS cannot be considered as separate actions in human, animal, and environmental sectors. Bacteria that develop resistance in one sector have potential to extend to other sectors; therefore, immediate, and concerted action across all sectors is necessary. This can be done by taking a One Health approach that includes the perspectives of all sectors to optimize global health and wellbeing.

Prudent AMU can still allow development of AMR; however, rigorous management can limit the risks (World Bank, 2017). The victory over AMR is never final; rather there is an ongoing battle that requires constant surveillance and AMS practice. With continued surveillance and research into the described knowledge gaps, a more thorough understanding of the complex relationships between microbial communities can be obtained. Additionally, behaviours of antimicrobial prescribers, consumers, and distributors require further investigation, as they are key to appropriate AMS measures. If this is combined with collaborative and sustained mitigation efforts across all sectors, we can preserve effective treatment options for bacterial infections throughout the One Health continuum in the future.

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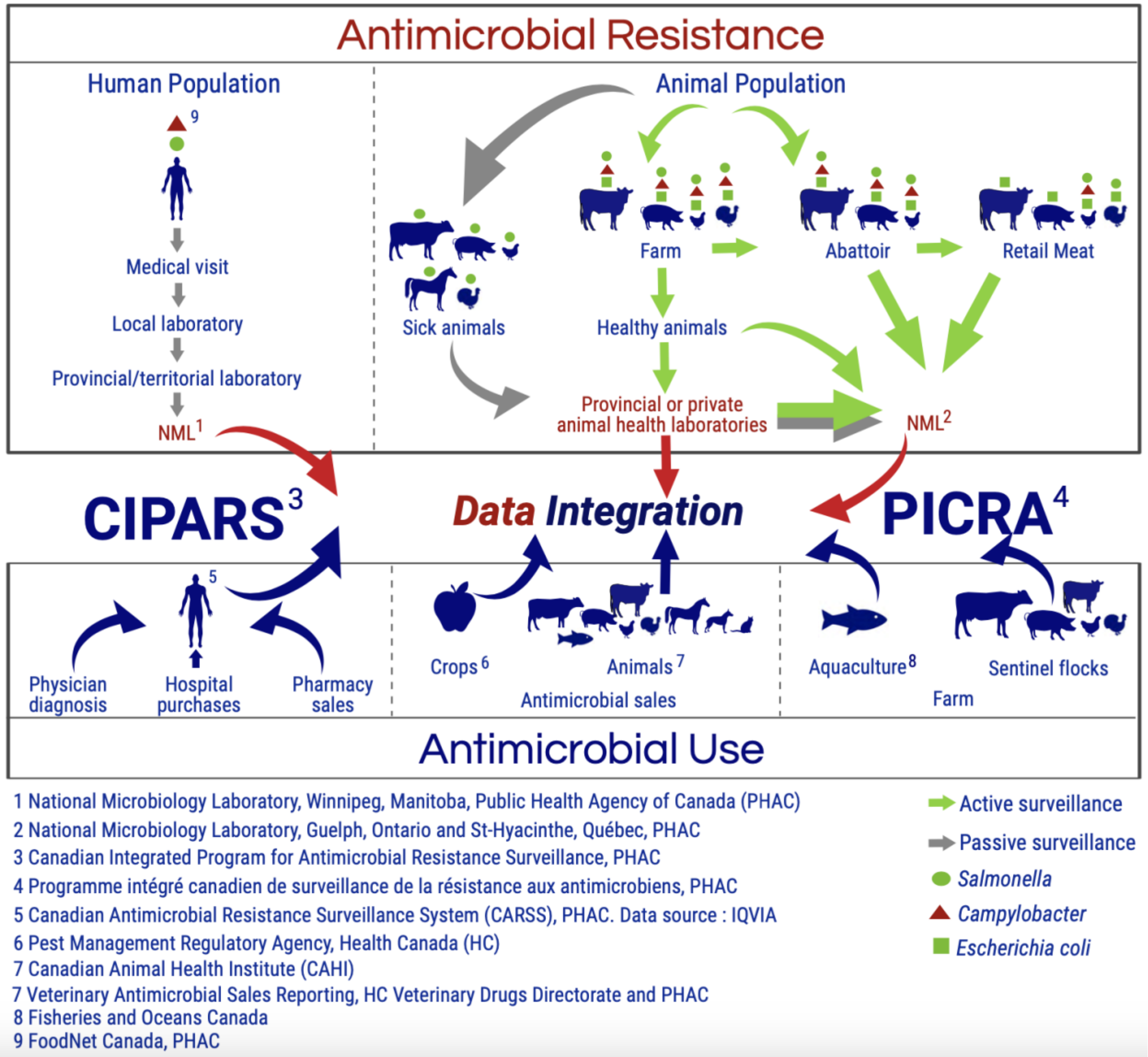
Table 2.1 Knowledge gaps that hamper prevention and control of antimicrobial resistance in Canada.

Area	Knowledge gap
Treatment Optimization	- Extent of antimicrobial misuse in Canada - BMPs[a] regarding antimicrobial prescribing in human/animal medicine - Economics of various efforts in lieu of AMU[b] - Socio-economic/behavioural drivers of AMU (prescriber and patient perspectives) - Efficacy of widespread adoption of alternative therapies to AMU - Understand and shift perspectives that identify AMU is a harmless 'cure all' - Identifying barriers and enablers of optimal human/animal AMU - BMPs to reduce livestock-associated prophylactic AMU - Rapid diagnostic testing to assist AMU decision-making
Surveillance	- Up-to-date prevalence estimates of AMR[c] in the community, domestic animals, wildlife, production animals not included in the current CIPARS[d] framework, and the environment - Overall trends of AMR bacteria and their emergence in Canada - BMPs for integration of AMU/AMR data collection and reporting
Prevention of Transmission of AMR	- Long-term efficacy of AMR mitigation efforts - BMPs for prevention of hospital-acquired AMR infectons - BMPs for reducing AMR in wastewater and subsequent impacts on human/animal health - How to reduce AMR prevalence in various resistance reservoirs - How to limit the risk of AMR in food systems - How to prevent cross-species AMR transmission - Quantitative risks associated with various incursion pathiways of AMR transmission *Development of AMR* - The direct relationship between AMU and AMR development - Role of the microbiome - Impact of heavy metals, cleaning agents and biocides and other xenobiotic compounds on AMR development - How AMU in one health sector directly impacts AMR development in another sector (i.e., human AMU and animal AMR, and the reverse) - Relative importance of various routes of antimicrobial administration in AMR development - How to employ policy to effective limit AMR development *Role of the Environment* - Impacts of human AMU/AMR on the environment - Impacts of AMU/AMR in livestock industries on the environment - Relative importance of various environmental transmission routes (including transmission through ground water and livestock derived manure spreading, etc.)

	- Impacts of antimicrobial residues in soil, water and pastures - Economic impacts of reducing environmental AMR reservoirs and antimicrobial residues *Role of Wildlife* - Impacts of AMR on wildlife health - Role of wildlife in transmission of AMR - Economic benefits of reducing AMR transmission from wildlife to livestock or humans

[a] BMPs = Best management practices
[b] AMU = Antimicrobial use
[c] AMR = Antimicrobial resistance
[d] CIPARS = Canadian Integrated Program for Antimicrobial Resistance Surveillance

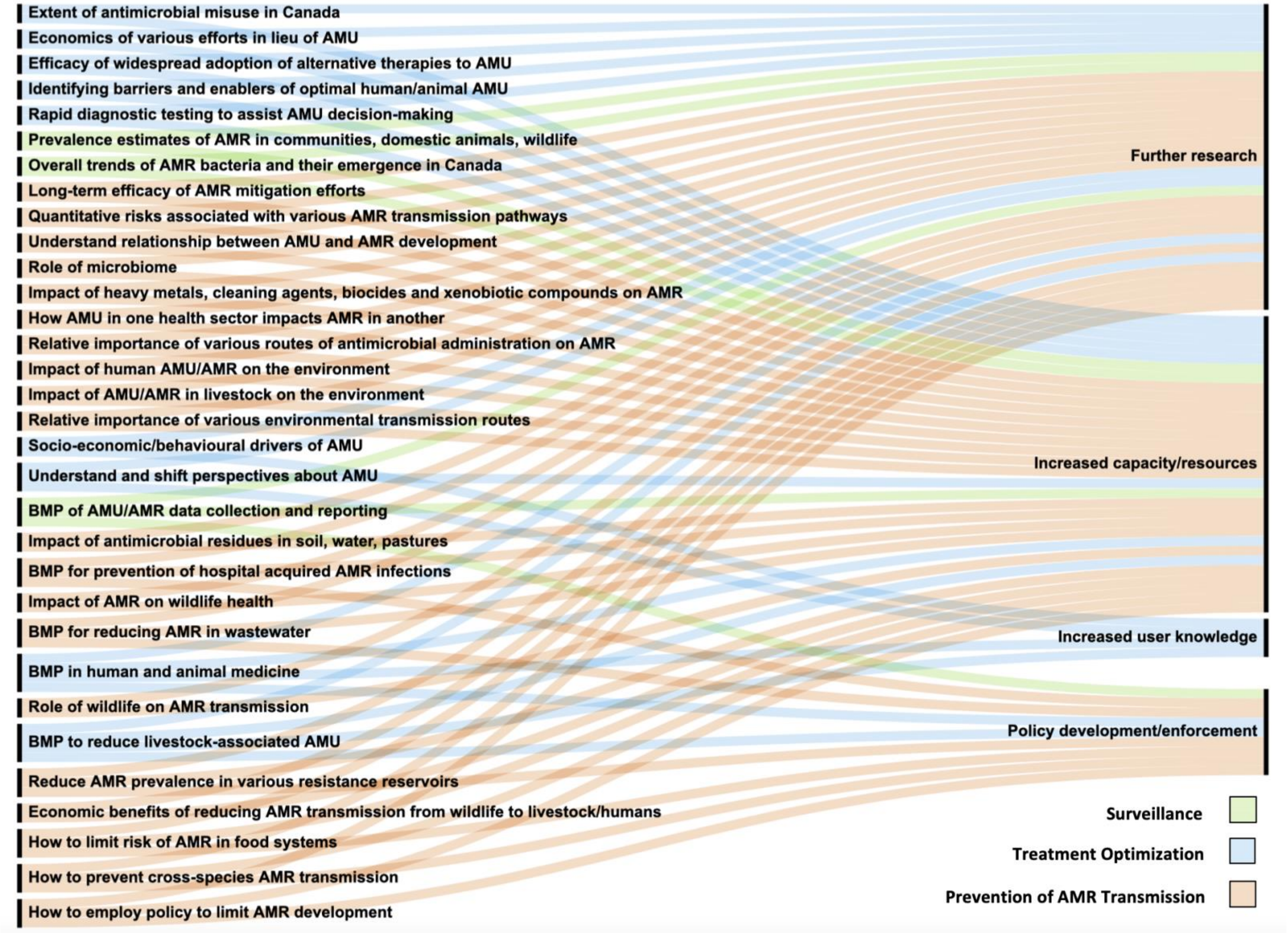
Figure 2.1. Canadian Integrated Program for Antimicrobial Resistance Surveillance program methods regarding AMR and AMU surveillance, from the Public Health Agency of Canada (PHAC, 2021a).



1 National Microbiology Laboratory, Winnipeg, Manitoba, Public Health Agency of Canada (PHAC)
2 National Microbiology Laboratory, Guelph, Ontario and St-Hyacinthe, Québec, PHAC
3 Canadian Integrated Program for Antimicrobial Resistance Surveillance, PHAC
4 Programme intégré canadien de surveillance de la résistance aux antimicrobiens, PHAC
5 Canadian Antimicrobial Resistance Surveillance System (CARSS), PHAC. Data source : IQVIA
6 Pest Management Regulatory Agency, Health Canada (HC)
7 Canadian Animal Health Institute (CAHI)
7 Veterinary Antimicrobial Sales Reporting, HC Veterinary Drugs Directorate and PHAC
8 Fisheries and Oceans Canada
9 FoodNet Canada, PHAC

Figure 2.2. Knowledge gaps and their requirements to be addressed as organized into four categories.

(BMPs = Best management practices, AMU = Antimicrobial use, AMR = Antimicrobial resistance)



CHAPTER 3: Perceptions of antimicrobial stewardship: Identifying drivers and barriers across various professions in Canada utilizing a One Health approach

3.1. ABSTRACT

As antimicrobial resistance (AMR) represents a substantial threat to the efficacy of available antimicrobial options, it is important to understand how to implement effective and practical mitigation efforts, including antimicrobial stewardship (AMS), across human, animal, and environmental sectors. A mixed-methods questionnaire was distributed virtually to attendees of the virtual One Health Antimicrobial Stewardship Conference (March 10-12, 2021) and their professional networks. Respondents (n = 81) were largely from the veterinary (75%) or human (19%) health sectors. Qualitative data were analyzed in NVivo using template analysis whereas quantitative data were analyzed in STATA using Kruskall-Wallis tests.

The questionnaire asked respondents about their perceptions of AMS, as well as the perceived barriers and drivers of AMS efforts. Perceptions of what AMS meant to the respondents personally and their profession as a whole were grouped into 3 main themes: 1) AMS strategies or considerations in antimicrobial prescribing and use; 2) responsibility to maintain health and preserve antimicrobial effectiveness; and 3) reducing antimicrobial use (AMU) as a goal of AMS efforts. Identified AMS barriers had 3 main themes: 1) lack of various prescribing and AMU support mechanisms; 2) shift in prescriber attitudes to drive change; and 3) stronger economic considerations to support shifting prescribing practices. Drivers of AMS had the following themes: 1) leadership to guide change; 2) education to support optimizing AMU; and 3) research to identify best practices and opportunities for action. Across all questions, 2

cross-cutting themes emerged: 1) a One Health understanding of AMS; and 2) blame placed on others for a lack of AMS success. Overall, sector-specific, but particularly cross-sectoral AMS drivers and barriers were identified, highlighting the importance of a One Health approach in AMR research and mitigation.

3.2. INTRODUCTION

Human, animal, and agricultural crop health rely heavily on effective antimicrobials to treat and prevent microbial infections (Canadian Council of Academies [CCA], 2019). Antimicrobial use (AMU) is the most important driver of the global increase of antimicrobial resistant (AMR) infections (World Health Organization [WHO], 2015; Wall et al., 2016). As the same active antimicrobial ingredients are used in products destined for use in humans, animals, and the environment, antimicrobial-bacterial interactions impacting AMR development are complex and multifaceted (Tang et al., 2017; McCubbin et al., 2021).

The natural environment has a large role in maintaining AMR genes and organisms (McCubbin et al., 2021; Kim and Cha, 2021). Environmental reservoirs of AMR pathogens and genes (i.e., in soil and water) represent a source of resistant genetic elements for pathogens of potential concern (United Nations Environment Programme [UNEP], 2023). Therefore, a One Health approach, involving key stakeholders in human, animal, and environmental sectors is required to coordinate efforts towards AMR mitigation (CCA, 2019).

To mitigate AMR, responsible use of antimicrobials is essential. Antimicrobial stewardship (AMS), defined as “multifaceted approaches required to sustain the efficacy of antimicrobials and minimize the emergence of AMR” (Weese et al., 2013), is an important priority in overall AMR mitigation efforts (Public Health Agency of Canada [PHAC], 2017; McCubbin et al., 2021). Successful AMS requires coordinated actions to preserve antimicrobial effectiveness in Canada and beyond and is an important focus of the AMR Pan-Canadian Framework for Action (PHAC, 2017).

Some AMS programs have been initiated in Canada, including voluntary AMU reduction initiatives, integrated AMU and AMR surveillance programs, prescribing guidelines, resources to support prescribing in a variety of health contexts, and ongoing research to support best practices, antimicrobial alternatives, and diagnostics (HealthCareCAN, 2016; Roy et al., 2020; Choosing Wisely Canada, 202l; PHAC, 2017, 2021, 2022). However, according to the most recent Canadian Antimicrobial Resistance Surveillance System Report (2022), human infections with AMR pathogens of concern have increased from 2016 to 2020, including infections with methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, the quantity (measured by weight) of medically important antimicrobials sold for use in all animals in Canada increased by 6.5% from 2019 to 2020 (PHAC, 2022). Although reductions of AMU in some production animal industries have been described, when considering treatments based on animal weight (population corrected unit or PCU), the mg/PCU fluctuated over the last decade (PHAC, 2018, 2022). Considering the One Health implications of AMU and AMR, improving AMS in Canada in all sectors is of utmost importance.

To safeguard antimicrobial efficacy, it is crucial to improve our understanding of how to optimize using available antimicrobials in all sectors (McCubbin et al., 2021). Antimicrobial prescribing and use in the human and veterinary sectors are influenced by a multitude of factors including knowledge, previous experiences, and patient/client expectations, as well as broader context and norms of AMU (Poizat et al., 2017; Smith et al., 2018; Speksnijder and Wagenaar, 2018; Schmiege et al., 2020; Tompson et al., 2021). Broader influences include, but are not limited to, access to healthcare services, geographical area, socio-economic factors, and time constraints (Schmiege et al., 2020; Tompson et al., 2021). By better understanding various stakeholder perspectives of AMS in general and of ongoing AMS efforts, current initiatives could be adapted, or new initiatives developed that meet identified practical needs and improve uptake and/or impacts.

Specifically, to improve AMS efforts, it is crucial to better understand what drivers and barriers of AMS practices exist across various stakeholders to identify areas for improvement, and to guide AMS conversations and future research questions. There may also be opportunities to harmonize ongoing efforts across sectors and identify current support for a shared goal.

In March 2021, the Alberta Veterinary Medical Association, with support from Alberta Agriculture and Forestry, the AMR – One Health Consortium, and the National Collaborating Centre for Infectious Diseases, hosted a virtual One Health AMS Conference. The virtual environment facilitated a diverse complement of Canadian participants working in the human-animal-environment AMR/AMU/AMS space. To benefit from the wide variety of stakeholders groups and professions included in this event, a mixed-methods questionnaire was developed to identify: 1) perceptions of AMS from a variety of professions in Canada, and 2) drivers and barriers Canadian participants experience in their professions regarding AMS practices.

3.3. MATERIALS AND METHODS

The University of Calgary Conjoint Faculties Research Ethics Board approved this study (REB21-0209).

3.3.1. Participant recruitment

This study was conducted with participants of the virtual One Health Antimicrobial Stewardship Conference (March 10-12, 2021) and their professional networks. The conference included >400 attendees from 6 continents, including 26 countries, and spanned the human, animal, and environmental health sectors.

The questionnaire was advertised throughout the conference via email, URL, and a QR code available through the virtual conference portal. After the conference, a reminder email was sent to conference participants and to selected professional networks (Alberta Veterinary Medical Association and the College of Physicians and Surgeons of Alberta). The questionnaire remained open until May 15, 2021.

Only responses from Canadian participants (93%; 81/87) were included in the analyses to understand the Canadian context. Questionnaire participants were categorized into sectors (veterinary, n = 61; human, n = 15; agricultural, n = 2; both veterinary and human, n = 2, undefined = 1) based on reported profession and/or area of focus.

3.3.2. Questionnaire

A questionnaire was developed using an online survey platform (Qualtrics, Provo, UT) to capture perceptions of AMS, as well as perceived drivers and barriers of AMS, as they related to the respondents' profession. The questionnaire contained 8 Likert scale questions where participants were asked to indicate their level of agreement regarding statements about their personal opinions of AMS, and the perceived opinion within their profession, on a 5-point scale (strongly disagree, disagree, neutral, agree, strongly agree), as well as 2 yes/no questions regarding the perceived existence of AMS drivers and barriers within their profession (see Appendix I). Not all questions were required to be completed for participants to submit their results.

To elucidate perceptions of AMS, participants were also asked the following open-ended questions: “What does antimicrobial stewardship mean to you in your profession?” and “What does antimicrobial stewardship mean to your profession as a whole?” Regarding existing barriers to AMS, participants were asked, “Do you believe there are barriers in antimicrobial stewardship in your profession?” Participants who responded ‘yes’ were asked the following: “What is preventing antimicrobial stewardship in your profession?”

To understand existing AMS drivers, participants who responded, ‘yes’ to “Do you believe there is support in place to promote/encourage antimicrobial stewardship in your profession?” were then asked, “What is currently in place that helps promote antimicrobial stewardship in your profession?”

3.3.3. Data analyses

Quantitative analyses were conducted in STATA (Version 15.1, StataCorp LLC, College Station, TX). A non-parametric test (Kruskal-Wallis) was used to explore if years of experience or professional sector influenced responses to the Likert scale and to yes/no questions. Years of experience was divided into 2 categories (≤17 and >17 years, based on the mean reported years of experience). Statistical significance was accepted when $P \leq 0.05$.

Qualitative data were analyzed using template analysis and a matrix analysis to elucidate differences in AMS perceptions, and AMS drivers and barriers between the sectors. Template analysis provides structure through hierarchical coding, in which sub-themes are classified under main themes (Brooks et al., 2015). This approach was chosen to identify potential cross-sectoral themes and allow for sector-specific components to be coded in the hierarchical framework. Given that using a One Health approach to further understand AMS drivers and barriers in Canada is a novel approach, themes were identified through inductive coding, to enable themes to emerge organically, allowing for flexibility in coding.

In qualitative analysis, quantity of responses under each theme does not necessarily reflect their importance. Rather, the themes that emerge, regardless of how many times they emerge, is of most importance (Kiger and Varpio, 2020). Therefore, commonly mentioned AMS drivers and barriers are important, but so are those mentioned less frequently as they still impact overall AMS success.

Two researchers (KDM and JB) with NVivo (QSR International, Pty Ltd., Version 12) training conducted data coding. Preliminary inductive theme identification was done by independent reviews of qualitative responses and compared, followed by discussions regarding emerging themes until agreement was reached. Then, main themes and sub-themes were finalized before the first round of coding was conducted independently using NVivo by creating nodes. The second round of coding was conducted by comparing independent coding results and nodes were adapted as required. Any differences among results were discussed to ensure agreement in coding.

A matrix analysis was conducted in Microsoft Excel to organize responses to open-ended questions by sectors to evaluate potential differences in themes between sectors (Averill, 2002). Based on non-emergence of new themes (i.e., inductive thematic saturation), the research team concluded that data saturation was reached at data analysis completion (Saunders et al., 2018).

3.4. RESULTS

3.4.1. Participants

A total of 81 Canadians encompassing a variety of professions across the One Health spectrum participated in this study. Participants worked in the following professions/areas: veterinary clinician (n = 36), academia (n = 31), government (n = 12), industry (n = 12), human or veterinary medical association (n = 8), producer (n = 6), producer association (n = 5), veterinary technician (n = 3), pharmacist (n = 3), physician (n = 1), and laboratory technician (n = 1) (participants could indicate >1 profession category). Participants had a median of 15 years of experience in their profession (range: 1 – 45 years; mean = 17 years). A total of 74 questionnaire participants attended the virtual One Health Antimicrobial Stewardship Conference, whereas 7 did not attend.

3.4.2. Quantitative data

Participants agreed that AMS was important in AMR mitigation (99%; 79/80 agreed or strongly agreed), whereas there was less agreement regarding whether their profession promotes AMS (80%; 63/79 agreed or strongly agreed), and whether it is viewed as important by their colleagues (76%; 61/80 agreed or strongly agreed) (Table 3.1).

There was agreement regarding the importance of AMS in livestock and companion animal health for maintaining human health (93%; 74/80 agreed or strongly agreed and 92%; 73/79 agreed or strongly agreed, respectively). However, agreement regarding the importance of human AMS for maintaining livestock health was slightly less (83%; 66/80 agreed or strongly agreed). Approximately half (51%; 41/80) of participants felt they had adequate support/resources to ensure AMS in their profession, and 65% (52/80) agreed there was more they could personally do to improve AMS in their profession.

Neither sector nor years of experience influenced participant responses to the majority of Likert scale statements. However, human sector participants tended to be more likely to ‘strongly agree’ whereas those in the veterinary sector were more likely to ‘agree’ (P = 0.06) regarding the statement that their colleagues viewed AMS as important. Veterinarians and veterinary technicians were slightly less positive (68%; 26/38 agreed or strongly agreed) compared to other professions (82%; 35/42 agreed or strongly agreed) regarding their colleagues’ views on AMS (P = 0.02). Further, veterinarians and veterinary technicians had a higher tendency to agree that AMS in livestock is important for human health (97%; 37/38 agreed or strongly agreed) compared to other professions (88%; 37/42 agreed or strongly agreed) (P = 0.052).

A total of 80% (63/79) of participants believed there were AMS barriers in their profession and 72% (56/78) believed there was AMS support in their profession. Responses by sector are in Table 3.2. No human sector participant responded ‘No’ regarding existence of AMS barriers and drivers. However, human sector participants with less experience (≤ 17 years) were more likely to respond “I don’t know” regarding existence of AMS barriers compared to their colleagues with more experience (> 17 years) who were confident that AMS barriers existed (P = 0.02). There were no significant differences between sector responses to yes/no questions.

3.4.3. Qualitative data

3.4.3.1. Perceptions of AMS

Participants provided various considerations in AMS strategies and prescribing decision-making, and they shared the overarching goal of AMS as limiting AMU when possible. The following main themes emerged: 1) AMS strategies or considerations in antimicrobial prescribing and use, 2) responsibility to maintain health and preserve antimicrobial effectiveness, and 3) reducing AMU as a goal of AMS efforts. Hierarchy of themes summarizing participant responses that emerged through the inductive coding process are provided in Figure 3.1.

3.4.3.2. *AMS Strategies*

The AMS strategies or considerations in antimicrobial prescribing and use theme represents thought processes or considerations reported as part of participant's antimicrobial prescribing or use, or as 1 participant described: "*Striking a balance between required use and perceived need*" (Veterinary clinician).

In their responses, participants provided broad descriptions of AMS with either concise or vague language to summarize concepts or various AMS strategies, rather than practical, actionable components (i.e., reducing inappropriate use versus increasing vaccine uptake to reduce need for AMU). Some participants included both conceptual and actionable components in their perceptions of AMS, highlighting evidence-based antimicrobial prescribing.

> *"[Stewardship] Means a dynamic process of refining strategies to preserve the access to effective antimicrobials to maintain animal health and welfare. The main components of stewardship are 1) Strategies to ensure proper use of antimicrobials when indicated. This is what we consider veterinary oversight (right drug, dose, duration, frequency route); and 2) The strategies that can be implemented to avoid the use of antimicrobials when possible, such as*

> *facilities design, vaccination strategies, genetic selection, handling systems, etc. Stewardship initiatives also involve a large component of education and knowledge translation."*
>
> – Veterinary clinician/Medical Association participant

Participants identified guiding factors influencing their AMS strategies, referring to regulations and policies aimed to reduce or control AMU, prescribing guidelines, using antimicrobials according to label instructions, and the importance of a valid patient-prescriber relationship.

Veterinary sector participants mentioned economic considerations influencing AMS strategies as they placed importance in ensuring both profitability for the producer and food affordability for the consumer.

> *"Responsible and judicious use of antimicrobial products (anti-parasitic products also included) to preserve human, animal and environmental health and welfare, while ensuring the production of safe and affordable food products for human consumption."*
>
> – Veterinary clinician

Diagnostics were also mentioned in both the human and veterinary sectors, primarily as the basis for antimicrobial prescribing decision-making. Specifically, bacterial culture and sensitivity testing were described as key components of AMS efforts, supporting evidence-based prescribing. Diagnostics were also mentioned regarding time limitations (i.e., the ability, or lack thereof, to provide a rapid diagnosis to guide antimicrobial choice and limited broad-spectrum AMU), and integral to ongoing AMR surveillance efforts.

3.4.3.3. *Responsibility*

It was evident in participant responses that AMS was synonymous with responsibility. This theme represented the context of AMU decisions (i.e., responsible AMU), with regards to personal or moral responsibilities participants placed on themselves regarding individual, day-to-day decisions, plus larger professional and societal duties to optimize AMU.

> *"Responsible use is something the profession is focused on. Realizing we will have to use them but need to put some thought into how we are using them."*
>
> – Industry/Human sector participant

The theme of risk avoidance emerged as the prescriber responsibility to maintain health of their patients via antimicrobial prescribing strategies. Food safety and animal welfare were mentioned solely by veterinary and producer participants as important considerations regarding AMU and AMS. Animal welfare was described as a moral responsibility to maintain animal health and welfare in addition to maintaining food system safety and productivity. Veterinarians and producers cited their obligations to the animals under their care, but also to humanity.

> *"Protection of the public. Safeguarding and assuring availability of antimicrobials for future treatment of humans and animals."*
>
> – Medical Association/Veterinary sector participant

In the human health sector, risk avoidance was also described as the prescriber's responsibility to maintain health and increase treatment success through AMU. However, risk avoidance also referred to minimizing AMR development by encouraging or facilitating AMU.

"In Family Medicine it means using the right antibiotic for the right patients, at the right dose for the right duration, and checking to ensure there are no harmful effects."
– Physician/Academic/Medical Association participant

Education and awareness of AMS and AMR were mentioned as important personal and professional responsibilities. Specifically, antimicrobial prescribers and end-users were considered to have the responsibility to be aware of their actions and potential contributions to AMR. Further, prescribers referred specifically to continuing education (CE) being their responsibility to continually improve prescribing practices, but also that their role was to educate patients/clients and facilitate public awareness and AMS support.

"I have a responsibility to follow guidelines regarding appropriate antimicrobial use and educate the public regarding the importance of minimizing drivers of AMR."
– Veterinary clinician/Medical Association participant

"To be [a] steward and effectively translate knowledge for public health professionals on AMR."
– Academic/Human sector participant

Participants referred to AMS practices as sustainable use of antimicrobials and overall responsibility to safeguard effective treatment options for future generations. Preservation of antimicrobial efficacy was considered an integral component of AMU sustainability, as well as sustaining human and animal health in general by ensuring future access to antimicrobials.

> *"The responsibility to use antimicrobials in a prudent and sustainable manner in order to preserve the use for the future and reduce current and future harm."*
>
> – Veterinary clinician/Academic/Producer/Medical Association participant

Finally, the veterinary sector described their responsibility to maintain positive perceptions of agriculture, as consumer safety and animal welfare contribute to maintain a social license to use antimicrobials in animal production and to production system sustainability.

3.4.3.4. *Reducing AMU*

The goal of reducing AMU was described as both reducing antimicrobial overuse and the need for AMU. Reducing the need for antimicrobials encompassed both prevention (i.e., limiting the need for AMU through various infection prevention and health improvement initiatives) and alternative treatment options to antimicrobials.

> *"Reduction of inappropriate exposure of antibiotics to help maintain antibiotic effectiveness for infection treatment."*
>
> – Government/Human sector participant

> *"We are looking for alternative ways to improve animal health without the use of antimicrobials."*
>
> – Academic/Veterinary sector participant

Many participants viewed their role in AMS not just as 'appropriate prescribing,' but also as educators and facilitators promoting stewardship and preventing unnecessary AMU.

> "*To me, antimicrobial stewardship means reducing inappropriate use of antimicrobials. It means educating those who prescribe and use antimicrobials. It means questioning prescriptions when there is insufficient evidence to determine appropriateness."*
>
> – Pharmacist/Human sector participant

3.4.4. Barriers to AMS

Participants described a vast array of existing AMS barriers that are both sector and profession-specific but were also experienced across sectors. Regarding AMS barriers, there was emergence of 3 main themes: 1) lack of prescribing and AMU support mechanisms, 2) a required shift in prescriber attitudes to drive change, and 3) a need for stronger economic considerations to support shifting prescribing practices (Figure 3.2).

3.4.4.1. *AMU support mechanisms*

The AMS barrier regarding the described lack of support to optimize antimicrobial prescribing and AMU practices had various sub-themes, including the lack of access to certain antimicrobials, potentially limiting appropriate antimicrobial selection. Juxtaposition of the desire to reduce AMU coupled with required antimicrobial access for treatment was present, as well as the need for diagnostics to inform prescribing decisions. Participants expressed that widespread availability of effective antimicrobial alternatives is currently lacking.

Participants indicated they did not have access to enough educational opportunities and identified limited research/knowledge in certain areas (i.e., to support development and implementation of best practices to optimize AMU and limit the need for AMU) to support required AMS education and resources.

The general lack of consequences if prescribers failed to meet AMS guidelines was identified as a barrier, or according to 1 participant, the "*intangible consequences of antimicrobial misuse*" (Pharmacist/Human sector participant). Participants described a general lack of antimicrobial prescribing oversight, and a lack of agreement regarding AMS in general, including clearly defined best practices. Participants stated if decisions were made regarding best practices, they were not communicated to enable everyone to clearly understand what is required.

> *"Family practice training programs do not have strong enough emphasis and monitoring of what we do."*
>
> – Physician/Academic/Medical Association participant

> *"There are no simple steps or actions producers or farmers can start implementing tomorrow or this evening. As a vet tech and producer, I know I should change my farming practices, but even I don't know the first step."*
>
> – Veterinary technician/Producer participant

The lack of communication and collaboration between stakeholders at various healthcare system levels was identified as a barrier, contributing to a limited shared understanding of responsibilities.

"There is support from groups, governments, industry, etc., but there is a lack of consensus and collaboration between these in their messaging and impact."

– Veterinary clinician/Academic/Industry/Producer Organization participant

"Lack of awareness and understanding between professions. It seems like at times we are ahead and at times others are. We should all be on the same page, consistently."

– Government/Human sector participant

"Engaging more stakeholders especially environmental health professionals."

– Academic/Human sector participant

3.4.4.2. *Prescriber attitudes*

Prescriber attitudes and an overall lack of motivation to change behaviours were described as maintaining current levels of antimicrobial prescribing by supporting "*old habits or protocols for treatment*" (Veterinary clinical/Medical Association participant), or there being a "*lack of an overall driving force to get this done*" (Academic/Veterinary sector participant).

"Many field practitioners may agree that antimicrobial stewardship is important but at the end of the day they do not change their behaviors due to preference, finances, external pressures, etc." – Veterinary clinician/Industry participant

Participants working as antimicrobial prescribers described the pressures they experience, and realities of working in healthcare. Social pressures were described as the public expectation that a healthcare visit automatically results in a prescription for them or their animal. Participants felt that a prescription has become part of the social contract of healthcare for the visit to feel like it had value. Industry pressure including intensive animal production, the pharmaceutical industry, and lack of antimicrobial alternatives were all considered to contribute to AMU.

"Client pressure and outcome motivators put pressure on [the] profession."
– Industry/Human sector participant

3.4.4.3. *Economics*

Other AMS barriers were economic in nature. This theme was primarily mentioned by the veterinary sector. Market influence, or "*economics of agricultural production*" (Veterinary clinical/Medical Association participant) was highlighted as being an important barrier, which included small profit margins and a lack of economic incentives to improve AMS.

Competing priorities were also described, such as the inherent inconsistency in private veterinary clinics between selling antimicrobials for profit and supporting AMS. Producers described being in a similarly difficult position, needing to balance fear of potential disease and profit impacts when withholding antimicrobials or limiting prophylactic AMU, and supporting

AMS. One participant stated that “*Current production systems do not allow for/encourage adoption of alternative practices that may decrease/better target antimicrobial use*” (Veterinary clinician/Producer/Industry participant).

Economic limitations experienced by veterinary clients were also mentioned as limiting prescribing abilities to support AMS practices, including the cost-prohibitive nature of using diagnostic tools to optimize AMU or aid in antimicrobial selection.

> *“Because of financial constraints (of clients) veterinarians often do not have culture and sensitivity results on which to base therapeutic choices, and scheduling recheck examinations can be more difficult in veterinary than in human patients.”*
>
> – Veterinary clinician/Academic participant

Further, the lack of cost-effective antimicrobial alternatives, and limited financial capacity to make structural changes to reduce infection rates to limit the need for antimicrobials (i.e., improvements in biosecurity or animal husbandry) were identified as important barriers. Labor constraints (i.e., time and capacity of employees) and a lack of educated personnel were also identified as reducing the ability to make improvements that support AMS.

> *“A lack of cost-effective, efficient methods to address reduced use of antimicrobials is also a barrier.”*
>
> – Veterinary clinician/Government participant

3.4.5. Drivers of AMS

Regarding drivers of AMS, there was emergence of 3 main themes: 1) leadership to guide change, 2) education to support optimizing AMU, and 3) research to identify best practices and opportunities for action (Figure 3.3). Whereas lack of progress in these themes presented as AMS barriers, their mention as drivers was accompanied by some examples of existing programs or support. However, the overarching theme in response to the question about existing AMS support was the general lack of support participants felt to improve AMS practices.

Examples of existing AMS leadership and guidance included regulations and professional prescribing guidelines. Additionally, examples of easily accessible educational opportunities and resources to support and drive AMS practices were provided by participants, including CE opportunities, conferences and websites. "*Guidelines and CE from professional organizations*" (Veterinary Clinician/Medical Association participant) were described as important sources of information for prescribers.

Research to better understand AMU best practices and to identify areas for AMU reduction were described as AMS drivers. Active AMU/AMR surveillance programs identifying usage trends and changes in prevalence of important resistant pathogens were also deemed important. Although participants provided some examples of existing AMS drivers, many responses indicated that there was not enough AMS support.

> *"There are many programs and information available to help guide decision making, lots of CE efforts. However, the lack of specific information in some instances (ex. limited guidelines in equine practice) and lack of awareness among clinicians are remaining barriers."*
>
> – Veterinary Clinician

> *"Written strategies exist or are being developed. More work needs to happen to promote the concepts within them."*
>
> – Veterinary Clinician/Medical Association participant

3.4.6. Cross-Cutting Themes

Across participant responses to multiple questions, there was emergence of 2 cross-cutting themes: 1) a One Health understanding of AMS, and 2) blame placed on others for the lack of AMS success. Although the transdisciplinary nature of AMR was acknowledged in responses, that also translated to blame being placed on others, including other sectors.

3.4.6.1. *One Health*

Whereas questions centered around how participants perceived AMS, as well as related drivers and barriers of AMS, the One Health concept was pervasive in responses. Some descriptions of AMS included 2 sectors (primarily human and animal health), whereas others included human, animal, and environmental sectors, or specifically the term 'One Health.'

> *"Responsible and judicious use of antimicrobial products to preserve human, animal and environmental health and welfare."*
>
> – Veterinary clinician

> *"Practicing and educating prudent use of antimicrobials since health of all forms of life is inter-related."*

> – Academic/Human sector participant

The One Health theme was a pervasive response to the question “Who should take responsibility in promoting antimicrobial stewardship?” (Figure 3.4). Although participants indicated they believed there should be a top-down approach (i.e., government-led AMS support), they also described that everyone needs to be involved, because “*It’s One World, One Health*” (Academic/Human sector participant).

> “*I think that anyone with knowledge/expertise in antimicrobial resistance should promote antimicrobial stewardship.”*
>
> – Academic/Human sector participant

> *“Everyone has a role in antimicrobial stewardship. The lead for stewardship programs should be multidisciplinary and include health system leadership.”*
>
> – Pharmacist/Human sector participant

3.4.6.2. *Blame*

Another cross-cutting theme that emerged was blame. Participants placed blame for the lack of current AMS success on others within their profession, as well as on other sectors. Existing industry structures and overall cultural norms were also blamed for the lack of AMS success. Some participants (8%; 6/80) did not agree that their colleagues viewed AMS as important (Table 3.1), or claimed others had a “*lack of awareness and regard for the issue*” (Government/Agriculture sector participant).

"We all have a part to play in stewardship, but not all may be putting it as a priority in the profession."

– Academic/Veterinary sector participant

"I feel we are falling behind as compared to human AMS."

– Academic/Veterinary sector participant

Additionally, blame was placed on patients and clients by prescribers for pressuring them for antimicrobial prescriptions, limiting their ability to maintain AMS practices. Prescribers also described receiving blame from patients or clients if treatments were unsuccessful.

"Client pressure and outcome motivators put pressure on the profession."

– Industry/Human sector participant

There was also blame placed on prioritization of human health over health of other species.

"It is not just about safeguarding certain antimicrobials for human use - need to consider impact on [the] rest of [the] species on [the] planet too."

– Veterinary clinician/Academic/Industry/Government participant

Although a perceived lack of AMS support emerged as a barrier across sectors, it also emerged in response to questions regarding existing support. Participants stated that they did not have enough support in AMS activities, and that more support was required for meaningful progress.

"More needs to be offered at the level of producers and general public."

– Veterinary clinician

In addition to the perceived lack of AMS support being described in qualitative responses, it was also evident in the Likert scale responses where ~25% of participants claimed that they did not have adequate AMS support (Table 3.1). Participants expressed that overall, *"We have some support. But not enough."* (Producer/Producer Organization participant).

3.5. DISCUSSION

This study described the presence of a 'status quo' of antimicrobial prescribing and use in the Canadian context, maintained by described barriers to improving AMS. Participants felt personal responsibility in AMS, but ~25% of participants did not feel they had adequate support to improve AMS. A total 80% of participants believed AMS barriers existed in their profession; the few participants indicating AMS barriers did not exist in their profession were from the veterinary sector or was a participant with an undefined profession. Human sector participants suggested that the certainty regarding the existence of AMS barriers ("I don't know" versus

“Yes”) increased with time spent in the profession, which may reflect barriers individuals experience over time as they consider AMS in their profession.

Skepticism regarding AMU in animals and the subsequent impact on AMR in humans is common in the veterinary sector (Etienne et al., 2017; Golding et al., 2019; McCubbin et al., 2022). However, our results indicated there was overall agreement among participants that AMS in livestock was important for humans, especially among veterinarians and veterinary technicians, but less so regarding the converse. Regardless, transmission of human AMR pathogens to animals has been identified, as well as broader impacts of human AMU and its contributions to environmental contamination and AMR are important (McCubbin et al., 2021; UNEP, 2023).

This perceived species hierarchy in AMR is reiterated in descriptions of AMS practices in livestock, where the main goal is maintaining safe food systems for humans, instead of solely focusing on animal health. In that regard, a focus on animal health to maintain human health reflects the global focus of public health where livestock AMS efforts are required to preserve antimicrobials important for human health (Official Journal of the European Union, 2019; PHAC, 2021), but there are not necessarily policies in place to ensure the reverse. However, animal health and welfare should be prioritized, highlighted by veterinary sector participants as a moral responsibility of care and reflected in the literature (Jansen et al., 2010; Golding et al., 2019; McCubbin et al., 2022).

Many participants viewed the concept of AMS to be synonymous with responsibility in terms of contributing to the AMS education of others and food safety, and most importantly, preservation of antimicrobial efficacy. However, there is an inherent contradiction in combining aims of preventing and managing bacterial infections in a risk-averse manner through antimicrobial treatment and preservation of antimicrobial efficacy for future infections (e.g., increased antimicrobial prophylaxis for COVID-19 patients during the pandemic) (Pelfrene et al., 2021; Kariyawasam et al., 2022). The desire to use antimicrobials to avoid potential negative clinical outcomes through practices such as prophylaxis, or 'future discounting' was described by UK producers and veterinarians working in a variety of livestock industries (Golding et al., 2019). Motivation to limit AMU existed but is contradicted by concern for potential animal welfare or production impacts when antimicrobials are withheld (Golding et al., 2019). Furthermore, human hospital personnel described antimicrobial prescribing being influenced by professional liability (Black et al., 2019).

As a prescriber or antimicrobial user, it is difficult to assign specific negative impacts to AMU in general, or providing preventative or prophylactic antimicrobials, when impacts of increasing AMR are not immediate or clearly visible. This concern for harmful immediate impacts by withholding antimicrobials, coupled with the intangible consequences of antimicrobial misuse and the pressure put on prescribers, could contribute to an overall lack of motivation to change prescribing practices.

Unfortunately, Canadian investment in AMR has been stagnant in the past decade (Rogers Van Katwyk et al., 2020). Participants noted that it may be necessary to rethink our current health and agricultural systems to further support AMS. One important consideration is the access and cost of timely diagnostics in both the human and animal contexts, as well as the cost of other infection prevention and control measures to limit the need for antimicrobials. Further, in the current private veterinary clinic model, there is financial reliance on selling products to clients, including antimicrobials. It will be a challenge to shift our current health and agricultural systems to further support AMS from an economic perspective, although that could increase sustainability.

Specifics of how to alter each production system or healthcare context to support AMS would need to be investigated further in collaboration with stakeholders within each context. This should also include economic considerations that support sustainability of production industries as well as contribute to shared goals with pharmaceutical industries to support prolonging efficacy of antimicrobial products. As described by participants, substantial health system changes may be required to further entrench AMS priorities, including reconsidering animal production systems to improve biosecurity and reduce the need for AMU while remaining profitable, or improving market support for novel antimicrobial research and development (Hollis, 2021).

Lack of overall leadership and stakeholder collaboration was described as an AMS barrier. Collaboration between leaders in AMS and key stakeholders at all levels in healthcare is required to effectively drive AMS efforts (Garraghan, 2022). However, prescribers' resistance to other healthcare provider recommendations and a lack of continuity of care were identified as AMS barriers by acute care hospital personnel in Nova Scotia (Black et al., 2019). Although a top-down approach of AMS governance was identified by participants as required for AMS improvement, they also described a need for collaboration at all levels of antimicrobial prescribers and end-users. Co-development of AMS goals and protocols within healthcare teams can serve to involve all relevant healthcare team members in the AMS discussion (Black et al., 2019). Opportunity to influence change is a characteristic of successful implementation (Nilsen et al, 2020).

Increased public involvement and communication could also help limit the public pressure on prescribers for prescriptions, and limit overall antimicrobial misuse. To support efforts in AMS stakeholder communication, education in AMS efforts is integral to success; however, it should not be the sole focus of an intervention (Satterfield et al., 2020).

Understanding the role of the environment in the AMR ecosystem has been identified as an important knowledge gap (McCubbin et al., 2021). Participants identified the environmental component in AMS collaboration as lacking and that more engagement should be sought. Expanded communication and collaboration across sectors are required with a One Health approach, and essential to overall AMR mitigation success.

The cross-cutting theme of blame highlights the occasional divisions within and between sectors. Blame can contribute to feelings of apathy regarding stewardship efforts (Golding et al., 2019). ‘Other blaming’ is a common theme that emerges in AMS research, where some stakeholders feel reluctance of other stakeholders to act renders their efforts to be pointless (Golding et al., 2019; Farrell et al., 2021; Gunasekara et al., 2022). Antimicrobial prescribers or users could feel that their AMS efforts are being negated or diluted by the overprescribing or use of others (Golding et al., 2019). To combat feelings of apathy towards stewardship, increased transparency and accountability, or collaboration in general could help make people feel like they are working towards the same goal (Golding et al., 2019).

Finally, when asked who should take responsibility for promoting AMS, the most common response was that everyone shares responsibility in AMS efforts. The One Health concept was evident in responses, with responsibility being placed on antimicrobial prescribers and users in all sectors, as well as government, industry, professional associations, researchers, diagnosticians, and educators. Although the One Health understanding of AMR was clear and responsibility was placed on all sectors, so was blame for lack of success. However, if the barrier of poor communication and collaboration can be improved to develop a national and global sense of collective AMS responsibility, meaningful progress may be made.

The goal of the qualitative analysis was to describe responses from Canadian participants. Study design limitations included small sample sizes for the human healthcare (n = 15) and environmental sectors (n = 2) regarding quantitative responses which could have led to the overrepresentation of veterinary sector specific responses. Limitations also include potential bias for increased awareness, or belief of AMS importance and emergence of the One Health theme due to participating in an AMS-focused One Health conference (n = 74). Further, the virtual nature of the questionnaire limited the ability to explore participants perspectives deeper, compared to an open-ended study design conducted in person. Regardless, the study design allowed for convenient questionnaire distribution and could contribute to critical discussion of AMS barriers due to assured anonymity. Despite study limitations, results presented highlighted various themes and key components of AMS in a One Health framework to address AMR in Canada.

3.5.1. Conclusions

Participants across sectors viewed AMS in Canada as important, with personal and professional responsibility and sustainability of AMU representing major themes across sectors. The described sense of responsibility can be capitalized on to prioritize AMS as "*a target to be achieved*" (Veterinary clinician/Academic participant) across sectors and professions in pursuit of a shared goal. Participants clearly identified the importance of One Health in AMS, placed blame on others and acknowledged there was more that they could do personally to improve

AMS in their profession. Both sector-specific and cross-sectoral AMS drivers and barriers were identified, highlighting the diverse needs of required AMS improvements in Canada.

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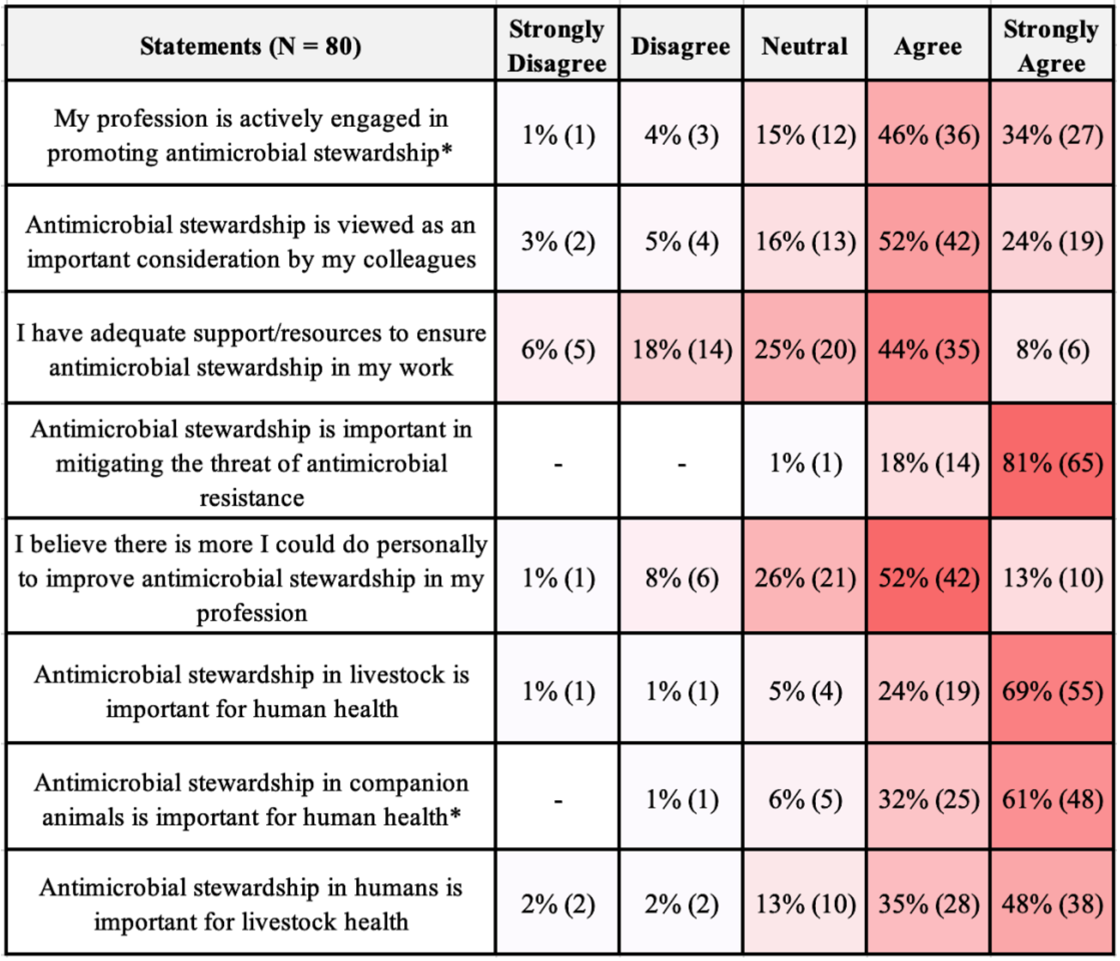
Table 3.1. Participant responses to Likert scale statements regarding antimicrobial stewardship displayed on a heat map to indicate frequency of responses from least common (white) to most common (red).



Statements (N = 80)	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
My profession is actively engaged in promoting antimicrobial stewardship*	1% (1)	4% (3)	15% (12)	46% (36)	34% (27)
Antimicrobial stewardship is viewed as an important consideration by my colleagues	3% (2)	5% (4)	16% (13)	52% (42)	24% (19)
I have adequate support/resources to ensure antimicrobial stewardship in my work	6% (5)	18% (14)	25% (20)	44% (35)	8% (6)
Antimicrobial stewardship is important in mitigating the threat of antimicrobial resistance	-	-	1% (1)	18% (14)	81% (65)
I believe there is more I could do personally to improve antimicrobial stewardship in my profession	1% (1)	8% (6)	26% (21)	52% (42)	13% (10)
Antimicrobial stewardship in livestock is important for human health	1% (1)	1% (1)	5% (4)	24% (19)	69% (55)
Antimicrobial stewardship in companion animals is important for human health*	-	1% (1)	6% (5)	32% (25)	61% (48)
Antimicrobial stewardship in humans is important for livestock health	2% (2)	2% (2)	13% (10)	35% (28)	48% (38)

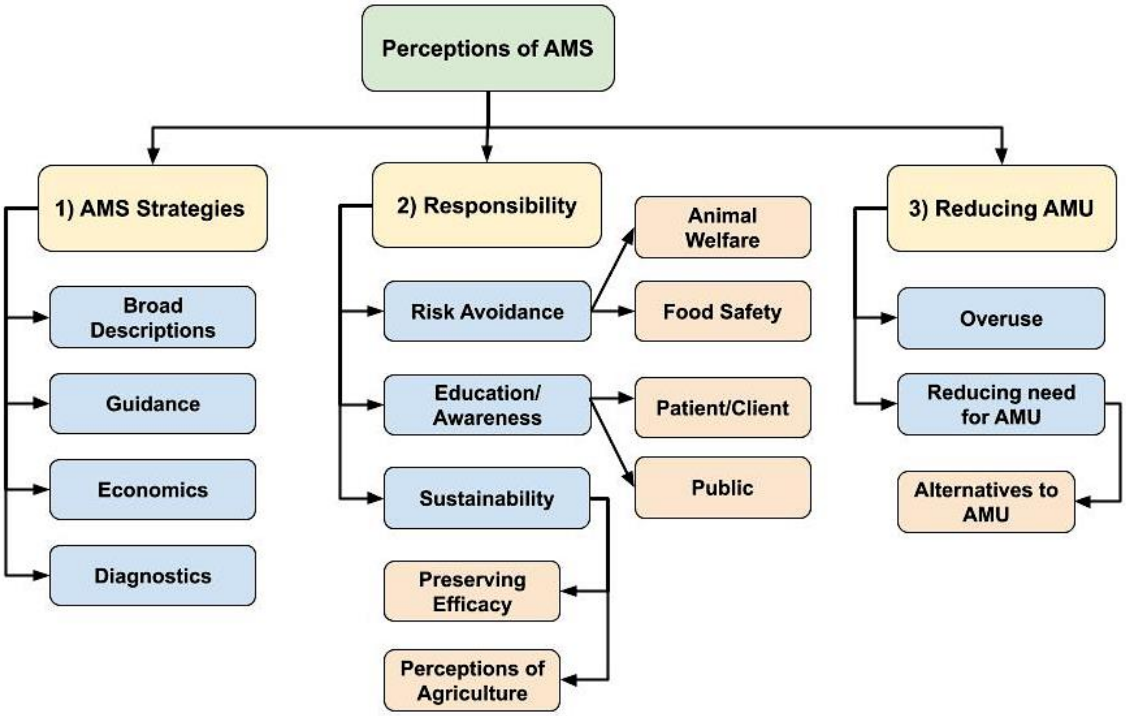
*N = 79

Table 3.2. Participant responses (n = 79) to questions about antimicrobial stewardship drivers and barriers within different professions.

	Do you believe there are barriers in improving antimicrobial stewardship in your profession?			Do you believe there is support in place to promote/encourage antimicrobial stewardship in your profession?		
Sector	**Yes**	**I don't know**	**No**	**Yes**	**I don't know**	**No**
Veterinary* (n = 59)	49	5	5	42	8	8
Human health (n = 15)	11	4	-	11	4	-
Agriculture (n = 2)	2	-	-	1	-	1
Human health & Veterinary (n = 2)	1	1	-	1	1	-
Undefined (n = 1)	-	-	1	1	-	-

*N = 58 responses for "Do you believe there is support in place to promote/encourage antimicrobial stewardship in your profession?"

Figure 3.1. Flowchart of identified hierarchical themes across participant responses to the open-ended questions: 1) "What does antimicrobial stewardship (AMS) mean to you in your profession?" (n = 74), and 2) "What does antimicrobial stewardship mean to your profession as a whole?" (n = 73).

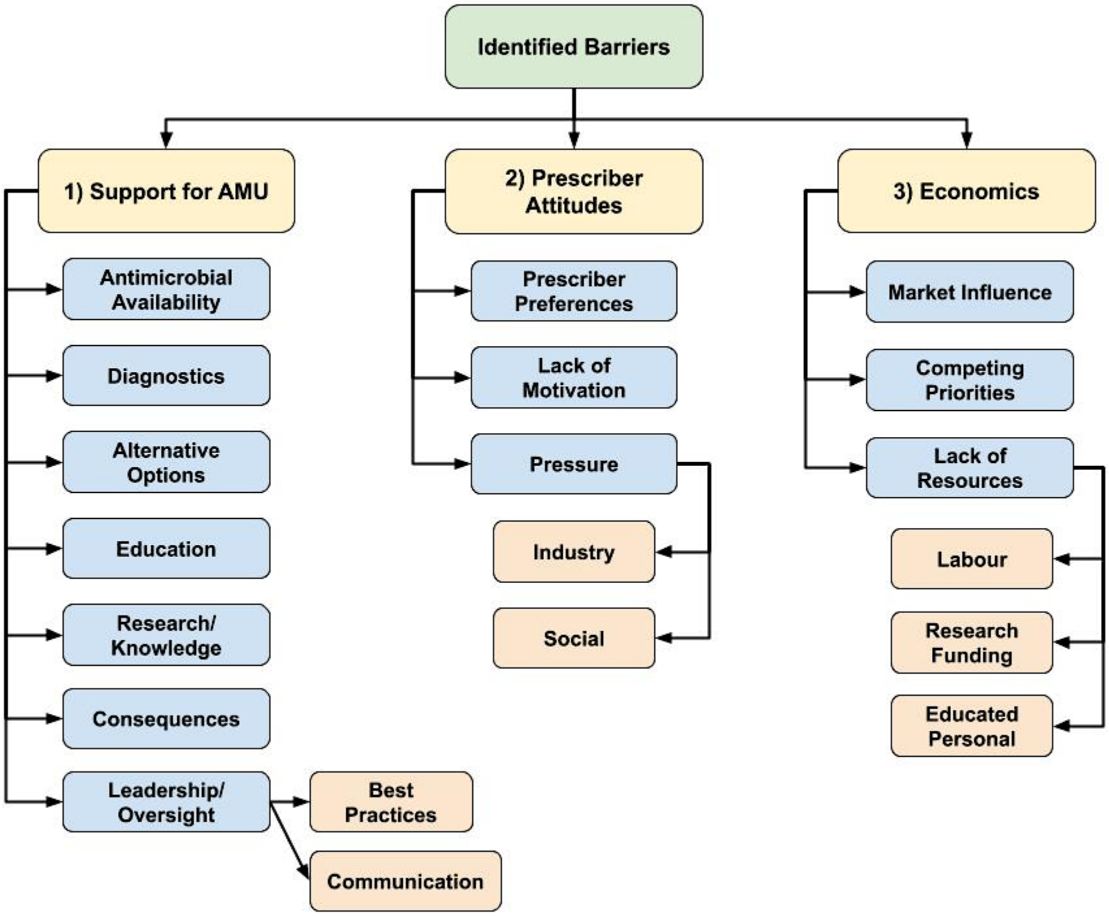


1) AMS strategies or considerations in antimicrobial prescribing and use

2) Responsibility to maintain health and preserve antimicrobial effectiveness

3) Reducing antimicrobial use (AMU) as a goal of AMS efforts

Figure 3.2. Flowchart of identified hierarchical themes across participant responses to the open-ended questions about antimicrobial stewardship barriers: “What is preventing antimicrobial stewardship in your profession?” (n = 63) posed to participants who responded, ‘yes’ to “Do you believe there are barriers in antimicrobial stewardship in your profession?”

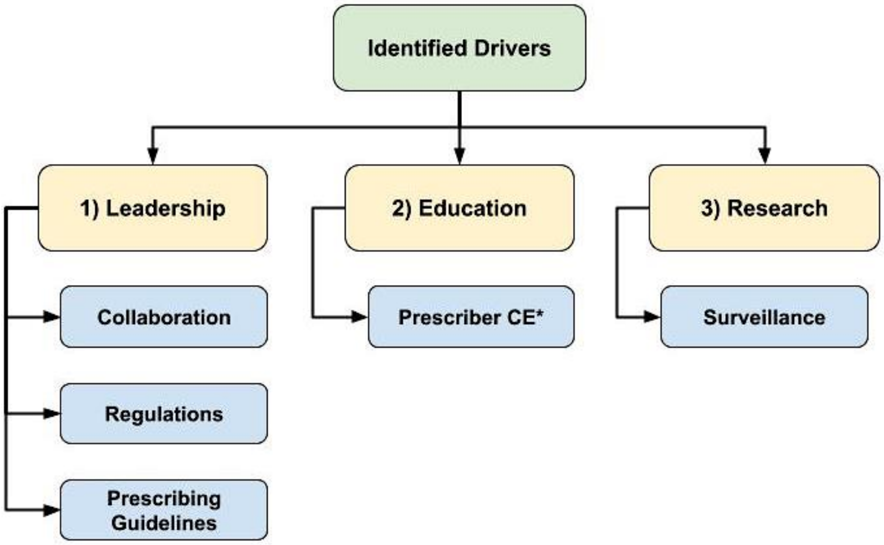


1) Lack of various prescribing and antimicrobial use (AMU) support mechanisms

2) Shift in prescriber attitudes to drive change

3) Stronger economic considerations to support shifting prescribing practices

Figure 3.3. Flowchart of identified hierarchical themes across participant responses to the open-ended questions regarding antimicrobial stewardship drivers: “What is currently in place that helps promote antimicrobial stewardship in your profession?” asked to participants who responded ‘yes’ (n = 56) to “Do you believe there is support in place to promote/encourage antimicrobial stewardship in your profession?”



1) Leadership to guide change

2) Education to support optimizing antimicrobial use

3) Research to identify best practices and opportunities for action

*CE = Continuing Education

Figure 3.4. Word cloud of the most common responses (n = 67 participants) to the question "Who should take responsibility in promoting antimicrobial stewardship?"

CHAPTER 4: Selective use of antimicrobials in dairy cattle at drying off

4.1. ABSTRACT

Administering intramammary antimicrobials to all mammary quarters of dairy cows at drying off, i.e., blanket dry cow therapy (BDCT), has been a mainstay of mastitis prevention and control. However, as udder health has considerably improved over recent decades, with reductions in intramammary infection prevalence at drying off and the introduction of teat sealants, BDCT may no longer be necessary on all dairy farms, thereby supporting antimicrobial stewardship efforts. This narrative review summarizes available literature regarding current dry cow therapy practices and associated impacts of selective dry cow therapy (SDCT) on udder health, milk production, economics, antimicrobial use, and antimicrobial resistance. Various methods to identify infections at drying off that could benefit from antimicrobial treatment are described for selecting cows or mammary quarters for treatment, including utilizing somatic cell count thresholds, pathogen identification, previous clinical mastitis history, or a combination of criteria. Selection methods may be enacted at the herd, cow, or quarter levels. Producers' and veterinarians' motivations for antimicrobial use are discussed. Based on review findings, SDCT can be adopted without negative consequences for udder health and milk production, and concurrent teat sealant use is recommended, especially in udder quarters receiving no intramammary antimicrobials. Furthermore, herd selection should be considered for SDCT implementation in addition to cow or quarter selection, as BDCT may still be temporarily necessary in some herds while they optimize mastitis control. Costs and benefits of SDCT vary among herds, whereas impacts on antimicrobial resistance remain unclear. In summary, SDCT is

a viable management option for maintaining udder health and milk production while improving antimicrobial stewardship in the dairy industry.

4.2. INTRODUCTION

Intramammary (IMM) administration of antimicrobials to all quarters of all dairy cows at drying off, termed blanket dry cow therapy (BDCT), is a key component of the National Mastitis Council (NMC) Recommended Mastitis 10-point Control Program (NMC, 2020). This program is the successor to the 5-point mastitis control plan originally focused on prevention and treatment of contagious intramammary infections (IMI) (Neave et al., 1969; Ruegg, 2017). Consequently, it is the most widely used dry cow therapy (DCT) approach in many countries (Bertulat et al., 2015; United States Department of Agriculture [USDA], 2016; Bauman et al., 2018). In contrast, selective DCT (SDCT) involves selecting only cows or mammary quarters with existing IMIs to be treated with IMM antimicrobials at drying off (Cameron et al., 2015; Scherpenzeel et al., 2016a; Lhermie et al., 2018).

The majority of antimicrobial use (AMU) on dairy farms is for mastitis treatment and prevention (Saini et al., 2012a; Stevens et al., 2016; Ruegg, 2017), and DCT uses long-acting antimicrobials (Rowe et al., 2020a, 2021a). Due to pressure to reduce overall AMU, including in food production animals, and to phase out preventive antimicrobial treatments, SDCT is being considered in lieu of BDCT to improve prudent AMU in the dairy industry (Rajala-Schultz et al., 2021; Santman-Berends et al., 2021). Reducing livestock-associated AMU has the potential to reduce prevalence of antimicrobial resistance (AMR), with expected benefits for both animal and public health. In addition to reducing overall AMU, the dairy industry signals it is engaged in antimicrobial stewardship and promoting sustainability (Barkema et al., 2015). Since the introduction of a mandatory ban on BDCT in the Netherlands, DCT AMU has declined by 36%, and overall IMM AMU (including treatments during lactational) declined by 15% between 2013 and 2017 (Santman-Berends et al., 2021).

A large proportion of producers have adopted BDCT, owing to the demonstrated efficacy of treating existing IMIs and mitigating the risk of new IMI development, which is highest at the beginning of the dry period and at the start of the subsequent lactation (Neave et al., 1950; Smith et al., 1985; Bradley and Green, 2001; Nitz et al., 2021). Dry period IMI incidence is associated with several factors including milking cessation, accumulation of milk in the udder, potential milk leakage, teat end condition, environmental hygiene and delay or absence of keratin plug formation (Williamson et al., 1995; Dingwell et al., 2004; Pyörälä, 2008; Dufour et al., 2019; Vilar and Rajala-Schultz, 2020). Furthermore, around calving, immunosuppression occurs, hormone concentrations change, and colostrum formation may lead to milk leakage due to opening of teat orifices (Oliver and Sordillo, 1988; Pyörälä, 2008; Dufour et al., 2019), increasing new IMI risk.

Although SDCT has been done in Scandinavian countries for decades (Niemi et al., 2020, 2021), it has only recently been considered in national policies in many other countries. This change has been motivated and justified by or due to changes in mastitis epidemiology, including considerable decreases in IMI prevalence at drying off (du Preez and Greeff, 1985; Pantoja et al., 2009; Rowe et al., 2019), reduced prevalence of contagious mastitis pathogen with bacteria such as *Streptococcus agalactiae* and *Staphylococcus aureus* (Cameron et al., 2014; Scherpenzeel et al., 2014; Ruegg, 2017), and reductions in bulk milk somatic cell count (SCC) (Hillerton et al., 1995; Ekman and Østerås, 2003; Agriculture and Horticulture Development Board Dairy, 2017).

In addition, reliable and affordable diagnostics have been developed, and teat sealants (TS) are now available. With these improvements, there is an opportunity, or arguably an obligation, to reduce or perhaps completely phase out prophylactic AMU in the dry period to reduce AMR and its impacts on health and welfare (Rajala-Schultz et al., 2011).

Research regarding udder health impacts of SDCT has included various approaches to selection methods for SDCT (e.g., SCC thresholds and bacteriological culture), including level of selection (i.e., herd, cow, quarter), and whether TS are used in SDCT protocols. As a consequence, comparing studies is complicated. Therefore, it is important to know which selection methods were used, as well as effectiveness of these criteria in relation to udder health and production. Consensus regarding appropriate herd and cow selection criteria for SDCT has not been achieved, perhaps in part because of insufficient comparable scientific research, differences in regulations, the different structures of the dairy industry, attitudes of key stakeholders towards DCT, and pathogen distributions among countries and regions (Erskine et al., 1988; Bradley et al., 2007; Olde Riekerink et al., 2008; Lam et al., 2017). Due to differences among regions in availability and formulations of DCT products, the primary focus of this narrative review will be selection criteria used in antimicrobial administration decision-making and associated udder health and production outcomes rather than specific antimicrobial products, when antimicrobials are part of the dry cow management strategy.

Furthermore, parenteral in addition to IMM administration of DCT was also considered, whereby parenteral antimicrobials are administered in combination with or in lieu of IMM antimicrobials. Despite evidence that systemic antimicrobial administration can be effective against IMI (Bolourchi et al., 1995; Janosi and Huszenicza, 2001; Contreras et al., 2013), IMM antimicrobial DCT is far more common and remains the focus of this review.

Clearly, SDCT is a management practice for which farm-specific benefits and risks are difficult to quantify. Therefore, a comprehensive review of SDCT implementation and subsequent farm-level outcomes is required to appropriately evaluate SDCT as a management strategy to enhance antimicrobial stewardship. This narrative review aims to summarize current drying off practices and their results, specifically referring to antimicrobial treatment of existing IMI at drying off and prevention of new IMI during the dry period, to provide an overview of trends worldwide, including associations with udder health, production, economics, and AMR. Discussion of SDCT and BDCT comparisons are limited to field trials excluding those studies comparing BDCT and no antimicrobials. A scoping review was conducted to identify available SDCT and BDCT comparisons in the literature available as of December 2021, country-specific SDCT practices, and relevant literature pertaining to TS use, DCT-associated AMR, as well as producer and veterinary AMU motivations. The literature search was limited to those articles available in English.

4.2.1. Dry Cow Therapy Practices

Adoption of DCT and selection methods vary considerably among countries (Table 4.1) (Ekman and Østerås, 2003; Vilar et al., 2018). In North America, BDCT is practiced widely, on 80 and 84% of surveyed operations in the United States and Canada, respectively (USDA, 2016; Bauman et al., 2018), whereas in Nordic European countries and the Netherlands, routine prophylactic AMU at drying off is not permitted (Scherpenzeel et al., 2016b; Rajala-Schultz et al., 2021; Santman-Berends et al., 2021). Further, veterinary prophylactic AMU, other than in exceptional cases, has been forbidden in the European Union since January 28, 2022 (Official Journal of the European Union, 2019). In New Zealand, SDCT has been recommended since the

1990s (McDougall 2003; Blackwell and Lacy-Hulbert 2013), although veterinarians may prescribe BDCT (Bryan and Hea, 2017). In some countries, regulatory violations can result in monetary fines for dairy farmers, whereas veterinarians could either temporarily or permanently lose their licenses with repeat offenses, although loss of license is rare (Rajala-Schultz et al., 2021). In all Nordic countries, cow or quarter bacteriologic diagnosis prior to DCT AMU is encouraged or at least the herd mastitis pathogen profile and antimicrobial susceptibility profile should be known (Rajala-Schultz et al., 2021). In the Netherlands, veterinary guidelines for selection of cows eligible for antimicrobial DCT primarily based on SCC levels at drying off were developed by the Royal Dutch Veterinary Association, although most farmers, in consultation with their veterinarian, use specific selection methods for their own herd (Santman-Berends et al., 2016). Selection criteria must optimize sensitivity and specificity for IMI identification while remaining feasible, both logistically and financially.

4.2.2. Herd Characteristics and SDCT

Optimization of herd screening for SDCT eligibility and management changes required prior to SDCT implementation have not been fully evaluated. Despite some general guidelines, robust data to direct herd-level selections are lacking. Regardless, before implementation of SDCT, a review and optimization of herd and udder general hygiene and health characteristics should be undertaken, including bulk milk SCC (BMSCC) thresholds (e.g., < 250K cells/mL), clinical mastitis (CM) incidence, and factors that influence these, e.g., hygienic drying off practices, and/or mastitis pathogen profiles (Schukken et al., 1993; Berry et al., 1997; Cameron et al., 2014; Bradley et al., 2018), etc. It is important that major pathogen IMI prevalence at drying off and new major pathogen IMI incidence in the dry period are minimized. Additional considerations include adequate record keeping (i.e., CM cases, antimicrobial treatments, etc.), so that producers know if cows have had CM during lactation, or additional negative health consequences (i.e., CM recurrence, culling, etc.). Such record keeping also enables identifying whether a SDCT protocol was successful based on (i.e., maintained milk production and BMSCC, and no increase in major pathogen IMIs). As herd selection criteria were not always stated, external validity of SDCT studies also needs to be considered, and DCT approaches may differ based on herd characteristics. For example, in Finland, BDCT adoption was greater in larger herds and those using automated milking systems (Vilar et al., 2018).

When BDCT was banned in the Netherlands, only minor negative outcomes followed (slight increase in percent of cows with high SCC, and new high SCC), providing evidence that most herds are capable of initiating SDCT without major negative udder health consequences (Santman-Berends et al., 2021). A Finnish analysis of dairy herd improvement association (DHIA) records over 5 years compared herd milk production and SCC among farms implementing various DCT approaches (SDCT, BDCT, or no DCT) (Niemi et al., 2020). The authors stated it was possible to maintain low herd average BMSCC and high milk production while employing SDCT. As SCC, production, and management skills vary greatly amongst herds (Niemi et al., 2020); therefore, udder health management is likely crucial to successfully implement SDCT, to limit overall IMI risks.

In studies on DCT, herd characteristics were variable and often unreported (Table 4.2). Herd characteristics that may contribute to improved SDCT outcomes include a relatively low BMSCC, low contagious mastitis prevalence (absence of *Streptococcus agalactiae* and controlled *Staphylococcus aureus* IMI) (Cameron et al., 2014; Bradley et al., 2018), hygienic drying off practices (i.e., minimizing risk of introducing bacteria into the teat canal, dry and clean bedding after drying off, etc.) (McDougall et al., 2009), good record keeping, veterinary support and ongoing monitoring for potential unintended consequences are regarded important criteria for successful implementation of SDCT. Although most herds can adopt SDCT without major udder health consequences (Santman-Berends et al., 2021), herds with deficiencies in any of these criteria should improve mastitis management before considering adopting SDCT to improve overall mastitis management and optimize SDCT implementation.

4.3. SELECTION OF COWS

The IMM administration of antimicrobials at drying off is associated with higher bacteriological cure rates compared to no DCT (Halasa et al., 2009a; Winder et al., 2019a); therefore, failure to treat quarters infected with major pathogens has negative udder health consequences (Østerås and Sandvik, 1996; Winder et al., 2019a). Consequently, the main challenge for SDCT implementation is deciding which cows or quarters should be treated with antimicrobials or could be left untreated. For prudent AMU, the objective is to accurately identify cattle likely to have a major pathogen IMI that would potentially benefit from antimicrobial treatment. If antimicrobials are applied preventively, cows or quarters at high risk of acquiring a new major pathogen IMI during the dry period, would need to be identified. However, teat sealants are also an effective IMI preventative, in lieu of antimicrobials (Winder et al., 2019b; Kabera et al., 2021). Identification of IMIs can be done using a variety of methods, including: SCC at cow- or quarter-level, pathogen identification-based methods, or other diagnostic procedures such as the California Mastitis Test (CMT), milk leukocyte differential (MLD), conductivity testing, lactate dehydrogenase (LDH), and *N*-acetyl-β-D-glucosaminidase.

A vast body of literature regarding selection using various SCC thresholds, bacteriological culture results, and their associated outcomes, is summarized in Table 4.2.

4.3.1. Quarter versus Cow-Level Selection

Selection protocols can be employed at the cow- or quarter-levels. Previous meta-analyses concluded that the success of SDCT protocols depended on whether they were implemented at cow- or quarter-levels (Robert et al., 2006a; Halasa et al., 2009b). This can be explained partly by interdependence of udder quarters (Barkema et al., 1997; Robert et al., 2006b; Paixão et al., 2017), meaning an IMI in 1 quarter is a risk factor for IMI development in other quarters of the same cow. Therefore, without TS, quarter-level decisions could contribute to negative udder health outcomes (i.e., increased IMI prevalence). More recent studies with inclusion of TS had success (i.e., no negative udder health impacts compared to BDCT) with cow- and quarter-level selection (Winder et al., 2019b; Rowe et al., 2020a; Kabera et al., 2021).

When using DHIA SCC reports as a basis for SDCT, only cow-level selection is possible, as composite milk samples are used, unless further quarter-level diagnostics are employed. However, a distinct advantage of quarter-level selection is the potential for additional AMU reduction. For example, with the inclusion of TS, no negative udder health consequences were observed with a DCT AMU reduction of 22% using a cow-level culture-based method (Cameron et al., 2014), whereas a similar quarter-level SDCT protocol resulted in an AMU decline of 58% (Kabera et al., 2020). Rowe et al. (2020a), however, stated either a culture-guided quarter-level SDCT protocol or a cow-level algorithm guided (SCC and CM history) SDCT protocol reduced AMU by 55%. To summarize, selection level (quarter versus cow) depends on information available (i.e., composite milk samples versus information at quarter level), but SDCT can be successfully enacted at either level with a strong recommendation to use TS to protect quarters not receiving IMM antimicrobials.

4.3.2. Pathogen Detection-Based Selection

Intramammary infection is defined based on culture of mastitis pathogens or detection of pathogen nucleic acid by polymerase chain reaction (PCR) testing (Cameron et al., 2014; Vasquez et al., 2018; Vilar et al., 2018). Various mastitis pathogen detection-based SDCT protocols, e.g., rapid on-farm culture, PCR techniques, or laboratory culture methods, at regional diagnostic facilities and veterinary clinics, have been studied (Cameron et al., 2014; Rowe et al., 2020a). However, their overall uptake in commercial herds is unknown (available information described in Table 4.1).

Pathogen detection-based SDCT methods aim to provide a direct diagnosis of IMI detection and thus more accurately identify cows that are infected and truly need antimicrobials, while also reducing negative udder health impacts associated with untreated IMIs with targeted antimicrobial therapy against known infections. Sensitivity and specificity for diagnosing IMI are higher for pathogen detection-based methods compared to SCC-based approaches (Rowe et al., 2020b). Sensitivities, specificities, and positive and negative predictive values for IMI identification at drying off are summarized in Table 4.3.

On-farm culture-based selection protocols (e.g., Petrifilm (Cameron et al., 2014, 2015; Kabera et al., 2020) or rapid culture (Minnesota Easy 4Cast plate, University of Minnesota, St. Paul; Patel et al., 2017; Rowe et al., 2020a) can be effectively used to select cows for SDCT (Table 4.2). However, culture-based selection has disadvantages compared to use of SCC thresholds, including additional time, labor, and materials (Crispie et al., 2004; Vasquez et al., 2018, Rowe et al., 2021b). The goal of using a culture-based method is to collect milk samples from cows and culture them within a short interval, either on-farm, or through a veterinary clinic or other laboratory facility. However, costs are variable. For example, on-farm culture costs were estimated at $4 US/cow (composite milk sample) (Rowe et al., 2021b), in addition to costs associated with training and maintaining skilled labor to perform cultures and interpret results. Further, culture-based methods may be less practical on smaller farms, due to expiration dates of consumables and lack of skilled labor. Costs associated with regular testing of milk for SCC (e.g., monthly DHIA testing) are also substantial, and could exceed costs for conducting culture-based selection if used exclusively for SDCT. However, based on available literature (Table 4.2) pathogen detection-based SDCT methods can be enacted without significant negative udder health impacts.

4.3.3. SCC-Based Selection

A cow composite milk SCC > 200K cells/mL is commonly used as an indicator of subclinical mastitis (Dohoo and Leslie, 1991). Although SCC is not perfectly correlated with IMI status, it is a practical and often easily accessible parameter to assess udder health for herds on a routine DHIA testing program (Schukken et al., 2003). However, some countries consider SCC thresholds other than > 200K cells/mL or consider primiparous and multiparous cows separately (Table 4.2). Differential SCC (i.e., differentiating proportions of specific leukocyte types) has also been evaluated as an effective proxy for IMI status (Schwarz et al., 2019; Halasa and Kirkeby, 2020); however, application of differential SCC in practice is currently limited, and its value for SDCT has yet to be evaluated.

When establishing an optimal SCC threshold for SDCT selection, it is important to consider that lowering the threshold will increase the sensitivity of diagnosing an existing IMI, but concurrently increase the proportion of false-positives (lower specificity and lower positive predictive value) and therefore result in more DCT AMU (Pantoja et al., 2009; Scherpenzeel et al., 2016a). Furthermore, pathogens vary in their effects on SCC after establishing an IMI and in their ability to be identified at drying off through use of SCC records (Rowe et al., 2021c).

The ideal SDCT protocol will have an optimal sensitivity to identify cows with a major pathogen IMI that will benefit from antimicrobial treatment, but also be specific enough to limit the use of antimicrobials in udders or quarters unlikely to benefit from treatment. In the absence of a perfect diagnostic test, a balance must be struck between limiting untreated infected animals and unnecessary antimicrobial treatments; this balance may depend on the goal of AMU reduction (i.e., optimizing udder health versus limiting livestock-associated AMU for improving public health) (Scherpenzeel et al., 2016a; Rowe et al., 2021c).

Commonly, SCC-based SDCT protocols may include additional selection criteria such as CM history (no CM or ≤ 1 CM case during lactation, or no CM in a specific interval (e.g., last 3 months)) (Rajala-Schultz et al., 2011; Vasquez et al., 2018; Rowe et al., 2020a). Although inclusion of CM history may not add any additional benefit to selection criteria (McDougall et al., 2021a; Rowe et al., 2021c), these data may be readily accessible and could improve selection, specifically in herds with higher lactational CM incidence (Rowe et al., 2021c).

A threshold of >200K cells/mL is a conventional cut-off value for diagnosing an IMI, but sensitivity can be increased by considering more than a single SCC report (Torres et al., 2008; Lipkens et al., 2019) or lowering the threshold (McDougall et al., 2021a). Some authors suggested that SCC < 200K cells/mL during the last 3 months before drying off provides the best balance of sensitivity and specificity for SCC-based identification of cows without IMIs at drying off, using bacteriological culturing as the gold standard (Torres et al., 2008; Lipkens et al., 2019). However, in a comparison of 4 SCC-based SDCT algorithms (Table 4.3), Rowe et al. (2021c) reported higher sensitivity through consideration of all SCC tests during lactation compared to the last 3 months, although all algorithms had poor agreement with IMI status. Nevertheless, these algorithms had high negative predictive values for major pathogens which may account for their success in the field (Rowe et al., 2021c).

It is becoming evident that various selection methods can be effective: SDCT protocols based on either SCC or pathogen-detection can identify cows that would benefit from antimicrobial DCT to varying degrees. Apart from test characteristics, the choice of a particular selection method for SDCT may also include factors such as cost and ease of implementation for the producer and farm workers. In summary, despite no perfect selection method, there are various methods that can be effectively employed in a SDCT protocol.

4.3.4. Other Diagnostic Tests

Other diagnostics that promote decision making for IMI identification, such as CMT (Poutrel and Rainard, 1981; Bhutto et al., 2012; Swinkels et al., 2021), MLD (Gonçalves et al., 2017; Denis-Robichaud et al., 2019) electrical conductivity (Manning et al., 2019), LDH (Rowe et al., 2020b), and *N*-acetyl-β-D-glucosaminidase (Hassan et al., 1999), have been evaluated for use in SDCT protocols. Although these diagnostics have been evaluated for their ability to identify IMIs, their success depends on diagnostic thresholds and subjective interpretations (Poutrel and Rainard, 1981; Godden et al., 2017).

Few published studies have evaluated the effectiveness of selection criteria based on these tests when used in SDCT protocols when compared to BDCT, or another method for selection of cows or quarters for SDCT (Poutrel and Rainard, 1981; Denis-Robichaud et al., 2019; Swinkels et al., 2021). Instead, the major focus has been the addition of these diagnostics to either bacteriological diagnosis or SCC threshold methods to increase sensitivity/specificity or to specifically detect infected quarter(s) once a cow has been diagnosed with an IMI (Rindsig et al., 1978; Cameron et al., 2014; Gonçalves et al., 2017).

In a small study (n = 83 cows) electrical conductivity was deemed not to be an accurate measure of IMI identification for SDCT (Manning et al., 2019), whereas Rowe et al. (2020b) stated LDH had poor agreement with IMI status at drying off. When using a CMT-based SDCT protocol, approximately 80% of major pathogen IMIs and only 23% of minor pathogen IMIs were identified, whereas 13% of uninfected quarters were false-positives (Poutrel and Rainard, 1981). More recently, both cow- and quarter-level CMT-based SDCT maintained udder health (CM incidence, major pathogen cure rates, milk yield in the first 100 days in milk [DIM], and decreasing AMU 31 to 55% (Swinkels et al., 2021)) with internal TS use in all quarters of all cows. Based on these study findings, perhaps CMT could be used to guide SDCT treatment decisions in high SCC cows, and that antimicrobial DCT in low-SCC cows does not improve udder health, regardless of CMT results (Swinkels et al., 2021). However, as these findings have not been replicated, further evidence is needed.

In a recent MLD-based SDCT study, CM incidence rate, moderate and severe CM incidence rate, SCC, milk production and odds of AMU for CM in the first 100 DIM did not differ compared to BDCT (Denis-Robichaud et al., 2019). However, with a modest sample size (n = 328 cows), the evidence to support using an MLD-based selection method is still limited.

Although *N*-acetyl-β-D-glucosaminidase has been suggested as a proper diagnostic tool to detect IMIs, Hassan et al. (1999) deemed high activity of *N*-acetyl-β-D-glucosaminidase was not an accurate IMI identification method, as only 29.7% of quarters with high *N*-acetyl-β-D-glucosaminidase activity had a mastitis pathogen detected by culture, compared to 14.5% in the normal activity group.

Although the use of CMT and MLD-based SDCT protocols are promising, until more research describing the accuracy and utility of these cow-side diagnostic methods is available, pathogen detection or DHIA SCC threshold-based selection methods provide more reliable information than currently available cow-side diagnostics.

4.4. TEAT SEALANTS

To prevent new IMIs in the dry period, it is important to reduce the likelihood of udder pathogens entering the teat canal and proliferating in the udder. Up to 50% of teats remain open 10 days after drying off (Williamson et al., 1995), and 23% are open for even 6 weeks into the dry period (Dingwell et al., 2004), considerably increasing the risk of pathogens entering the teat canal. Teat sealants were developed to offer protection against new IMIs by adding a physical barrier with more reliability than relying solely on keratin plug formation (Krömker et al., 2014; Biggs, 2017). Further, most IMIs during the dry period are caused by environmental bacteria (Crispie et al., 2004; Dingwell et al., 2004; Green et al., 2005), and TSs may provide greater IMI protection compared to IMM antimicrobial DCT alone for environmental bacteria (Huxley et al., 2002). This provides a good opportunity for reducing prophylactic AMU by providing another means of preventing IMIs, although TS use does not replace other measures to prevent dry period IMIs.

Both internal and external TSs are available. External TSs are an external coating on the teat end typically applied using a dipping cup. However, they can be difficult to apply correctly, are ineffective long-term, and require frequent reapplication (Crispie et al., 2004; McDougall et al., 2009; Biggs et al., 2016). In contrast, internal TSs consist of supposedly inert substances infused into the teat canal and teat cistern, ideally forming a physical barrier that remains in the distal teat cistern during the dry period but are stripped out the first milking after calving (Meaney, 1976; Bhutto et al., 2011). An internal TS plug was confirmed at first milking in 83% (ranging from 45-100% by herd) of treated quarters (Kabera et al., 2018). Based on positive research findings, the National Mastitis Council recommended TS application as part of dry cow management (NMC, 2006).

Internal TS use without concurrent AMU in cows identified as noninfected at drying off has been successful, with no difference compared to BDCT for CM incidence in the dry period (Huxley et al., 2002) and during the first 120 DIM (Cameron et al., 2014; Rowe et al., 2020a), risk of new IMI during the dry period (Bradley et al., 2010; Cameron et al., 2014), and at calving (Patel et al., 2017), SCC, and milk production in the subsequent lactation (Cameron et al., 2015). Internal TS reduces new dry period IMI risk by 52% compared to no treatment and by 23% compared to IMM antimicrobials in cows entering the dry period without an IMI (Dufour et al., 2019). External TS was evaluated in 2 SDCT studies, and was also successful compared to BDCT, with no differences for SCC (Denis-Robichaud et al., 2019), linear score, new IMI risk (Vasquez et al., 2018), milk production, culling, or CM incidence (Vasquez et al., 2018; Denis-Robichaud et al., 2019).

If administered with IMM antimicrobials, TS may increase IMI protection (Godden et al., 2003; Bradley et al., 2011) and was associated with decreased SCC compared to IMM antimicrobials alone (Golder et al., 2016). Specifically, concurrent administration of TS and IMM antimicrobials (with antibacterial activity especially against Gram-positive bacteria (e.g., cloxacillin)), may improve protection against Gram-negative bacteria later in the dry period (Bradley et al., 2011). However, other studies (Woolford et al., 1998; Huxley et al., 2002; Cook et al., 2005) suggested no increased IMI protection with combined internal TS and IMM antimicrobials in low-SCC cows. In studies conducted with low-SCC cows, there was no difference in IMI protection between internal TS only and cows treated with a combination of internal TS and IMM antimicrobial (Cameron et al., 2014; Patel et al., 2017; Kabera et al., 2020).

In a meta-analysis (1974-2020), if internal TS was administered to untreated, healthy quarters or cows at drying off, there was no difference between BDCT and SDCT regarding the risk of IMI incidence during the dry period and at calving, and early lactation CM risk, milk yield, and SCC (Kabera et al., 2021). However, without an internal TS, new IMI dry period risk and harboring an IMI at calving was higher with SDCT versus BDCT (Kabera et al., 2021).

Furthermore, mechanisms of action of internal TS may also include antimicrobial activity, in addition to physical blocking of the teat canal (Notcovich et al., 2020). Specifically, bismuth subnitrate, a component of TS, is associated with reduced bacterial growth of major mastitis causing pathogens, with the extent of inhibition varying among bacterial species (Notcovich et al., 2020). Further, a small German study (n = 50 cows), described no difference in IMI protection of a bismuth subnitrate-free TS between experimentally treated and control (untreated) cows (Kiesner et al., 2015). Impacts of this potential growth inhibition on udder health and SDCT need to be studied.

Low SCC cows (< 200K cells/mL for the entire preceding lactation) receiving only internal TS had higher mean daily milk production but slightly higher lactational SCC (34,001 cells/mL with IMM antimicrobials versus 41,523 cells/mL for no IMM antimicrobials) compared to concurrent antimicrobial and internal TS use in the subsequent lactation (McParland et al., 2019). However, no other studies detected a positive effect of TS use on milk production.

Despite numerous studies documenting overall internal TS benefits both in healthy quarters untreated with antimicrobials (Winder et al., 2019b: Kabera et al., 2021), and in combination with IMM antimicrobials (Godden et al., 2003; Bradley et al., 2011; Golder et al., 2016), some research suggests the possibility of negative TS and IMM antimicrobial interactions. Internal TS use in combination with IMM antimicrobials limited antimicrobial penetration to teat canal lining and potentially impaired effectiveness of eliminating chronic bacterial infections within this udder niche (Derakhshani et al., 2018). Furthermore, IMM oil-based antimicrobials have been theorized to undermine internal TS retention through affecting the viscosity of TS (Bradley et al., 2010; specific combination of Cepravin Dry Cow, Intervet Schering-Plough Animal Health, Milton Keynes, UK and OrbeSeal Pfizer Animal Health, Sandwich, UK), where TS presence at calving improved when used alone compared to in combination with IMM antimicrobial (Kabera et al., 2018). Although specifics of TS and IMM antimicrobial interactions are unclear, it is evident that TS should at a minimum be administer in non-antimicrobial treated quarters as part of a SDCT protocol (Cameron et al., 2015; Winder et al., 2019b; Kabera et al., 2021).

4.5. IMPACTS OF SELECTIVE DRY COW THERAPY

4.5.1. Udder Health

If SDCT programs are successful, IMI dynamics (i.e., new IMI, bacteriological cures) during the dry period will be similar to BDCT, resulting in equivalent IMI prevalence at calving. If this equivalence is achieved, udder health and performance in the subsequent lactation should be equivalent to BDCT. Based on the findings presented in Table 4.2, the majority of recent clinical trials concluded SDCT can be implemented in commercial dairy herds without negative consequences for udder health (Bradley et al., 2010, Cameron et al, 2014, 2015; Vasquez et al., 2018; Rowe et al., 2020a, c; Kabera et al., 2020, Swinkels et al., 2021). This conclusion was supported by recent meta-analyses concluding udder health was similar for BDCT and SDCT, provided that SDCT protocols used on-farm culture systems (Minnesota Easy 4Cast plate or Petrifilm) or SCC-based selection, and internal TS was administered to untreated healthy quarters or cows (Winder et al., 2019b; Kabera et al, 2021).

When considering studies presenting negative impacts of SDCT (Table 4.2), explanations can often be derived through careful assessment of study methods. Scherpenzeel et al. (2014) used SCC thresholds of < 150K and < 250K cells/mL for primiparous and multiparous cattle, respectively, and reported increases in SCC at calving and 14 DIM and higher CM incidence after introducing SDCT in low-SCC cows. In addition, Rajala-Schultz et al. (2011) reported low-SCC cows treated with antimicrobials had 16% lower SCC (approximately 35,000 cells/mL) than untreated low-SCC cows in the subsequent lactation. However, herd selection was not described, and TS was not administered in either study (Rajala-Schultz et al., 2011; Scherpenzeel et al., 2014). Further, Scherpenzeel et al. (2014) employed a split-udder design, where exclusion of TS acts as a risk factor for IMI development in other quarters (Barkema et al., 1997; Robert et al., 2006b; Paixão et al., 2017). Zecconi et al. (2020) reported a slight increase in new IMI after calving with SDCT; however, one factor may be that only 3 of 5 included herds used TS, although results from all herds were combined, potentially overestimating negative effects of SDCT when TS are applied.

Vasquez et al. (2018) reported bacteriologic cure remained slightly higher for cows entering the dry period with an IMI and receiving IMM antimicrobials, whereas Huxley et al. (2002) reported no significant differences between SDCT and BDCT for CM incidence, CM severity, or bacteriological cure of existing IMI. The only difference noted was that quarters receiving TS acquired fewer major pathogen IMIs (Huxley et al., 2002). On a larger scale, the BDCT ban in the Netherlands resulted in significant DCT AMU reduction (36%) without major negative udder health impacts (Santman-Berends et al., 2021). However, a small but significant increase in high test-day SCC (> 150K cells/mL – primiparous, > 250K cells/mL – multiparous) (+0.41%) and a new high test-day SCC (either at first test after calving, or a high SCC report after low SCC at previous test day during lactation; +0.06%) (Santman-Berends et al., 2021). The only notable health impact was an increase in the probability of belonging to a herd with > 25% of multiparous cows with a new high SCC test when lactation started (odds ratio [OR] = 1.23) (Santman-Berends et al., 2021). Results may have been affected by concurrent national dairy industry changes (e.g., increasing herd sizes with removal of chronic high SCC cows). Furthermore, impact of TS use is unknown, as this study included higher-level national surveillance data but excluded individual farm drying off practices (Santman-Berends et al., 2021). However, Vanhoudt et al. (2018) stated that between 2013 to 2015, TS sales in the

Netherlands increased by 73%. Regardless, this provided further evidence that most herds can enact SDCT without negative udder health consequences.

To summarize, in consideration of cow udder health, SDCT is a viable option for producers, with consistent reports of no negative impact on SCC after calving (Cameron et al., 2015; Kabera et al., 2020; Rowe et al., 2020a), IMI elimination, new IMI risk (Cameron et al., 2014; Patel et al., 2017; Vasquez et al., 2018; Kabera et al., 2020; Rowe et al., 2020c), and presence of IMI at calving (Rajala-Schultz et al., 2011; Cameron et al., 2014; Patel et al., 2017; Rowe et al., 2020c). With appropriate consideration of selection criteria and other mastitis control procedures (i.e., TS, good overall hygiene) to reduce IMI, SDCT can be implemented without negative consequences for udder health.

4.5.2. Milk Production

As IMIs reduce milk production (Deluyker et al., 1993; Hadrich et al., 2018), increases in SCC or CM incidence through failure to identify infected cows/quarters in a SDCT program could adversely impact milk production and farm profitability. High SCC and CM could occur due to persistence of unidentified IMIs not treated at drying off, or development of new IMI or CM during the dry period. Although selection criteria and specific udder health impacts differed among studies studying SDCT impacts (Table 4.2), based on available literature, many reported no difference between BDCT and SDCT with respect to milk production in the subsequent lactation (Cameron et al., 2015; Vasquez et al., 2018; Kabera et al., 2020; Rowe et al., 2020a). However, most studies reporting no effect on milk production included either internal TS (Cameron et al., 2015; Kabera et al., 2020; Rowe et al., 2020a) or external TS (Vasquez et al., 2018; Denis-Robichaud et al., 2019) in their SDCT protocols, whereas Rajala-Schultz et al. (2011) excluded TS use and did not report negative milk production impacts.

Interestingly, in an Irish study, low SCC cows (< 200K cells/mL throughout lactation) that received only internal TS had increased mean daily milk yield (0.67 kg) over the entire lactation, compared to low SCC cows receiving both internal TS and IMM antimicrobials (McParland et al., 2019). However, no other studies indicated similar findings for milk production. Various studies demonstrate variable effects of TS versus combination treatments with TS and IMM antimicrobials on milk production, and authors speculated that pathogen profiles may influence effects of SDCT versus BDCT including TS on milk production (McParland et al., 2019).

Based on available literature, with selection criteria sensitive enough to identify most infected cows at drying off and TS administration to prevent new IMI, negative milk production consequences can be avoided. However, further research is needed to better define relationships among SDCT, TS, and milk production.

4.5.3. Economics

Producer DCT decision-making is likely influenced by financial costs and benefits as well as udder health impacts (Friedman et al., 2007; Scherpenzeel et al., 2016b; Poizat et al., 2017). Huijps and Hogeveen (2007) suggested that CM after calving, culling probability, dry period IMI rate, antimicrobial costs, production losses, and hourly labor rates had the greatest impacts on DCT costs. However, a major limitation with some economic comparisons of SDCT and BDCT is that the studies included SDCT-associated increases of CM incidence (Huijps and Hogeveen, 2007; Scherpenzeel et al., 2016a), SCC (McNab and Meek, 1991; Scherpenzeel et al., 2016a; Lhermie et al., 2018) or decreased milk production in the subsequent lactation (McNab and Meek, 1991). Such assumptions were based on earlier literature assuming negative health impacts associated with SDCT implementation that are no longer relevant, as recent literature suggests no difference between CM incidence or milk production for SDCT and BDCT (McParland et al., 2019; Kabera et al., 2020; Rowe et al., 2020a). It should also be noted that TS is not always included in the economic model (Huijps and Hogeveen, 2007; Scherpenzeel et al., 2016a, 2018a), although its importance for preventing new IMIs during the dry period has been established (Dufour et al., 2019; Winder et al., 2019b; Kabera et al, 2021). Therefore, structural limitations are introduced through model development that inherently put SDCT herds at an economic disadvantage when assumptions are made regarding health and production parameters that do not reflect current literature. Furthermore, economic evaluations are country or region specific, due to variations in costs or milk prices, as the latter differ between countries with or without a supply managed system (Huijps and Hogeveen, 2007), whether low-SCC incentives are offered, as well as other regional differences.

Most DCT economic evaluations are limited to evaluation of AMU at drying off compared to no DCT (McNab and Meek, 1991; Berry et al., 1997; Yalcin and Scott, 2000) or blanket TS use instead of IMM antimicrobials (Berry et al., 2004; Lhermie et al., 2018). Economic comparisons of BDCT and SDCT are presented in Table 4.4. Although it is not possible to directly compare included studies due to differences in included parameters, modeling techniques, assumptions, year of study and currency, efforts have been made to provide a common currency (USD) and year to highlight model differences (Table 4.4).

Although some results appeared to support SDCT (Table 4.4), models were developed with the assumption that drying off IMI status would be known, and therefore testing costs were not included, assuming producers were already receiving SCC or culture data (e.g., Halasa et al., 2010). In addition, the consequences of misdiagnosing cows were ignored (Berry et al., 2004; Huijps and Hogeveen, 2007). Further, the economic model presented by Halasa et al. (2010) had meta-analyses inform the new IMI rate included in the model (with or without TS) in cows treated with IMM antimicrobials, but only a single study (Huxley et al., 2002) was used to calculate new IMI rates for cows receiving only TS (Halasa et al., 2010). Subsequently, the new IMI rate for cows receiving only TS was indicated to be higher in the model than IMM antimicrobials alone, or in combination with TS (Halasa et al., 2010). However, in the original paper of Huxley et al. (2002), authors state that compared to quarters receiving only IMM antimicrobials, quarters with only TS developed fewer new IMIs, with no difference in IMI severity, number of infected quarters, or CM cases. Therefore, these data appear misrepresented in the model. Overall, due to model assumptions, existing economic models comparing BDCT and SDCT should be interpreted with care as many factors influence economic costs and benefits of SDCT versus BDCT protocols.

Some studies include assumptions based on current literature in their model (Patel et al., 2017; Rowe et al., 2021b), assuming no inherent udder health disadvantages for SDCT cows were present. In the study by Patel et al. (2017), assumptions were made regarding incubator costs attributed to each cow, as authors assumed a large herd size (800 cows), that producers would also use the culture system for lactational IMI identification (in addition to SDCT), and its cost would be amortized over 5 years. Therefore, actual culturing costs per cow may be higher for SDCT. Regardless, a successful AMU reduction of 48% was possible with additional economic benefits (Patel et al., 2017), and no negative udder health impacts were observed.

Meanwhile, Rowe et al. (2021b) stated that SDCT was more economically beneficial than BDCT, but specifically that SCC-based SDCT was more economically beneficial than culture-guided SDCT (mean costs savings/cow of $7.85 versus $2.14 USD, respectively). However, DHIA SCC testing was assumed to be an already occurring cost, and therefore no additional testing costs were included. Furthermore, economic impacts varied considerably among herd economic conditions. In a sensitivity analysis, the authors identified that the economic advantages of SDCT would be substantially reduced in situations where its implementation increased clinical and subclinical mastitis after calving (Rowe et al., 2021b). Although economic benefits of SDCT were higher in herds with lower CM incidence and BMSCC, all herd types can have reduced AMU at drying off without economic losses (Scherpenzeel et al., 2018a).

Overall, economic impacts of SDCT will likely differ among herds and management systems due to varying pathogen profiles, selection criteria, costs for antimicrobial treatments, and the level of AMU reduction achieved (Huijps and Hogeveen, 2007; Cameron et al., 2014; Scherpenzeel et al., 2018a). Therefore, it would be useful to have general agreement on economic model development and coefficient inclusion, such as routine mastitis management strategies (i.e., pre- and post-dipping, culling of recurrent high SCC cows, bedding management, etc.), as well as the ability to adapt economic analysis to farm-specific scenarios, to enable producers to predict expected costs or benefits (Huijps and Hogeveen, 2007). Therefore, economic models need to consider costs associated with evaluating current mastitis management practices on these farms, implementation of new management practices as required, then application of SDCT. Models must also be updated with data supported by literature and be contextually specific, while minimizing structural limitations introduced through model development.

A partial budgeting tool that can be adapted to a variety of herd contexts for individual producers to compare economic impacts of various DCT approaches is available at https://dairyknow.umn.edu/research/udder-health/selective-dry-cow-therapy-cost-calculator/. Further economic evaluations specific to different industry contexts are needed to fully inform producers and provide tools to increase SDCT uptake.

4.5.4. Additional Considerations

Various factors impact drying off decision making and dry cow management, including social determinants of AMU, product availability, and physical environment the cows inhabit, all of which have changed over time (Biggs et al., 2016). Further, IMM administration is not completely risk-free and provides an opportunity for injection of bacteria into the teat canal (Leelahopongsathon et al., 2016). Therefore, hygienic drying off practices and other management decisions are also important for overall dry cow wellbeing and for limiting IMI risks. Other factors influencing drying off decisions for individual cows include but are not limited to: parity, teat end condition, milk production level at drying off (abrupt cessation of milking versus gradual reduction), nutrition, body condition score, dry cow and calving area hygiene, culling chronically infected cows, DIM at drying off, and dry period duration (Barkema et al., 1999; Dingwell et al., 2003, 2004; Green et al., 2007; Henderson et al., 2016; Rajala-Schultz et al., 2018; Nitz et al., 2021) as well as limiting lactational IMI to reduce drying off IMI prevalence. Although these other management strategies, and lactational IMI prevention, are important in overall dry cow management, an in-depth discussion of them is outside the scope of this review.

4.6. ANTIMICROBIAL RESISTANCE

As AMR is a major public health concern, AMU reduction in livestock is an important area of focus (World Health Organization, 2015; Wall et al., 2016; World Bank, 2017). Selection pressure imposed by AMU in dairy cows could result in emergence, maintenance, and horizontal transfer of AMR genes (Oliver et al., 2011). Although most AMU on dairy farms is udder health related (Oliver and Murinda, 2012; Sani et al., 2012a; Stevens et al., 2016; Ruegg et al., 2017) and BDCT has been propagated for decades, prevalence of AMR among udder pathogens of dairy cows in developed dairy nations is relatively low (Call et al., 2008; Bengtsson et al., 2009; Cameron et al., 2016).

Regardless, increased AMR levels would adversely affect animal health and welfare as well as dairy farm profitability and sustainability, and is of public health concern. As reductions in livestock-related AMU is expected to result in a decrease or at least a leveling off in production-system-associated AMR (Tang et al., 2017; Nóbrega et al., 2020), SDCT represents an important area for consideration to reduce AMU in the dairy industry.

The impacts of widespread SDCT adoption and reduced AMU on AMR development and spread is not fully understood, as studies considering direct relationships between antimicrobial DCT and AMR are limited. However, associations between DCT AMU and AMR on dairy farms have been observed. Specifically, penicillin and ampicillin resistance of *Staph. aureus* were associated with penicillin-novobiocin AMU for DCT, and ampicillin-intermediate or -resistant *Escherichia coli* were associated with DCT AMU of cloxacillin, penicillin-novobiocin combination, cephapirin (Saini et al., 2012b, 2013), cefquinome, and framycetin (Schubert et al., 2021). Cephalosporin DCT administration was associated with reduced susceptibility of fecal coliforms to cephalothin and streptomycin (Mollenkopf et al., 2010). Conversely, IMM administration of antimicrobials were not associated with increased AMR prevalence among non-*aureus* staphylococci (NAS) species (Nóbrega et al., 2018; Stevens et al., 2018). Although organic dairy herds had lower antimicrobial MIC among NAS species and streptococci isolated from milk, compared to herds using antimicrobial DCT, differences in MIC levels were below clinical breakpoints, meaning differences in bacteriological cure rates would not necessarily be observed (McDougall et al., 2021b).

Broader farm impacts of DCT AMU should also be considered. Antimicrobial residues may be present in colostrum fed to newborn calves, although levels are expected to be low (European Food Safety Agency [EFSA] Panel on Biological Hazards et al., 2016). The EFSA Panel on Biological Hazards concluded that the risk of fecal shedding of AMR bacteria in newborn calves fed colostrum will not increase when dams receive antimicrobial DCT if the time between drying off and calving is longer than the antimicrobial withdrawal period.

In a recent small (n = 2 farms) observational study, there was lower fecal shedding of AMR bacteria in calves on farms employing SDCT (Tetens et al., 2019). Specifically, compared to SDCT, BDCT was associated with a considerably higher ESBL-producing *E. coli* concentration in feces of 3-day-old calves (Tetens et al., 2019). As no calf was treated with β-lactams, aminoglycosides, or fed waste milk before testing, authors stated these differences were most likely associated with DCT methods. The external validity of this study must be questioned as the sample size was very small and presumed selection effects of DCT antimicrobials decreased within the next 3 weeks (Tetens et al., 2019). Although these results should be interpreted with care, broader farm impacts of DCT AMU reduction should be investigated. Specifically, the One Health approach of AMU and AMR, that incorporates human, animal, and environmental considerations, as antimicrobial and bacterial interactions are complex and are not limited to one health sector or species (McCubbin et al., 2021). The importance of One Health considerations in AMR is supported by AMU reductions in livestock production leading to a reduction in human occupation-associated AMR infections in the associated production system (Tang et al., 2017).

It is currently unknown whether widespread SDCT adoption would directly reduce AMR prevalence in mastitis pathogens, or in part, mitigate AMR development. Potential AMU reduction through widespread SDCT adoption could impact selection pressure on the microbiome. Overall, attempts to reduce AMU on dairy farms could confer benefits to producers and animal health and improve consumer perception of animal agriculture, in addition to potential reductions in AMR. In conclusion, further research to inform best practices for mitigation of AMR development in mastitis pathogens, or more broadly in the dairy industry, is needed.

4.7. ANTIMICROBIAL USE MOTIVATIONS

Even with described literature supporting SDCT adoption, it can be difficult to convince some producers and veterinarians of its importance and facilitate sustained behaviour change. It is, therefore, essential to consider various drivers and barriers to SDCT adoption to significantly increase uptake. For example, regulations and fines for ‘overuse’ can be introduced, but unintended consequences must be considered, such as illegal AMU requiring constant enforcement, and animal welfare concerns (Speksnijder and Wagenaar, 2018). Furthermore, a negative producer attitude towards regulations is associated with increased AMU (Kramer et al.,

2017) and veterinary consultation for antimicrobial decision-making and treatment for antimicrobials routinely in the producer's possession may be limited (Kramer et al., 2017; Rees et al., 2021). Another important consideration is the public perception of AMU in the dairy industry and the external pressure that this places on the industry. For example, 91% of public respondents from the United States claimed dairy industry AMU represents a threat to human health while 72% stated they would pay more for milk from cows raised without antimicrobials (Wemette et al., 2021).

Some research has been conducted to improve understanding of motivations of producers (Lam et al., 2011; Jones et al., 2015; Scherpenzeel et al., 2016b) and veterinarians (Postma et al., 2016; Higgins et al., 2017a; Scherpenzeel et al., 2018b) with respect to decreasing on-farm AMU (Speksnijder and Wagenaar, 2018; Farrell et al., 2021).

4.7.1. Producers

Although cattle health and welfare influence on-farm AMU (Valeeva et al., 2007; Jansen et al., 2010; Scherpenzeel et al., 2016b), other factors with important roles for choosing antimicrobial treatments in general and dry cow AMU specifically. These can include: producer attitudes, behaviour and perceptions (Valeeva et al., 2007; Lam et al., 2011; Poizat et al., 2017); previous experience (Scherpenzeel et al., 2016b); economic considerations (Friedman et al., 2007; Scherpenzeel et al., 2016b; Poizat et al., 2017) including lack of time (Friedman et al., 2007; Farrell et al., 2021) and resources (Poizat et al., 2017); atmospheric climate; farm biosecurity (Postma et al., 2016); societal pressure (Jones et al., 2015; Lam et al., 2017; Poizat et al., 2017); risk aversion (Speksnijder and Wagenaar, 2018; Rees et al., 2021); difficulty of implementing management changes, and a moral duty to treat a sick animal (Scherpenzeel et al., 2016b; Poizat et al., 2017; Rees et al., 2021). Concern for financial consequences and uncertainty regarding mastitis recovery without AMU were among the most important factors for producers choosing BDCT over SDCT (Scherpenzeel et al., 2016b).

The existence and awareness of prudent AMU guidelines varies around the globe, with producer AMR knowledge and awareness being greater in high-income countries (Farrell et al., 2021). Skepticism has been identified regarding the degree to which agricultural AMU contributes to AMR, especially regarding human health impacts (McDougall et al., 2017; Morris et al., 2016; Etienne et al., 2017), where awareness of the relationship between AMR in humans and agriculture was low (Farrell et al., 2021). In South Carolina, 86% of producers interviewed were not concerned that livestock antimicrobial overuse could cause AMR infections in farm workers (Friedman et al., 2007). Minimal concerns regarding consequences of AMU may contribute to a lack of desire to reduce AMU (Speksnijder and Wagenaar, 2018). In contrast, in the United Kingdom, 70% of producers thought reducing AMU was a good idea (Jones et al., 2015).

Selective DCT education, training, and campaigns are important in generating change in producer attitude and behaviors regarding mastitis management (Lam et al., 2013; Farrell et al., 2021). However, successful communication of farm management improvement opportunities must acknowledge various producer attitudes, capabilities, opportunities and learning styles (Lam et al., 2011). Producers motivated to improve udder health are more likely to be impacted by a ‘central route’ of information, including providing instruction cards, treatment plans, checklists and software presenting a rational argument for change (Jansen et al., 2010). Furthermore, previous research indicated producers without initial behavioral change motivation were more likely to be impacted by a ‘peripheral route’ utilizing a subconscious or indirect method without reasoning or rational arguments that focused on a single message (e.g., wearing gloves while milking) (Jansen et al., 2010). These methods should, therefore, be combined to optimize effectiveness of AMU reduction campaigns (Jansen et al., 2010).

Crucial components of successful communication are employing a proactive approach, message personalization, providing producers with practice-based examples, and use of social environment (Lam et al., 2011). The integration of science and producers' knowledge and experience increases recommendation credibility and practicality, leading to measurable and lasting changes in AMU (van Dijk et al., 2016).

4.7.2. Veterinarians

As BDCT was endorsed by veterinarians in many countries until recently (Scherpenzeel et al., 2016b), and some continue their adamant support (Poizat et al., 2017), it is important to consider their perspective, especially as veterinarians substantially influence producers regarding AMU (Friedman et al., 2007; Lam et al., 2011; Jones et al., 2015; Speksnijder and Wagenaar, 2018; Farrell et al., 2021). Literature regarding attitudes and perceptions of veterinarians towards AMU and AMR generally indicated agreement on the importance of reducing AMU in livestock production, despite some differences.

In the Netherlands, views regarding SDCT differed among veterinarians (Scherpenzeel et al., 2018b). National policy was introduced in 2013 that determined only SDCT could be used; whereas many veterinarians agreed with this in research conducted shortly after policy implementation, others felt they were endorsing a decision not aligned with their own belief of dry-period risks (Scherpenzeel et al., 2018b). Antimicrobial prescribing behaviour of livestock veterinarians is dependent on multiple factors, including obligations to ease animal suffering, financial dependency on clients, risk avoidance, advisory skill limitations, producer economic limitations, lack of producer compliance, public health safety, and beliefs regarding degree of veterinary AMU contributions to AMR (Speksnijder et al., 2015a). Veterinarians consider economic drivers to be strongly correlated with producer compliance with veterinary recommendations (Speksnijder et al., 2015b; Postma et al., 2016).

Higgins et al. (2017a) reported most UK veterinarians interviewed (n = 20) preferred SDCT as it aligned with prudent AMU strategies. Regarding veterinary SDCT perspectives, 3 themes were identified: 1) prioritizing prudent AMU and attempting to maintain producer engagement; 2) veterinary experience level and ability to influence producer decisions; and 3) veterinary perceptions about SDCT risks and implementation difficulties, which varied greatly. With increasing experience in the field, veterinarians were less likely to consider veterinary contributions to AMR as a concern (Speksnijder et al., 2015b), whereas junior veterinarians were less likely to take a primary prescribing role or make suggestions contradicting senior colleagues (Speksnijder et al., 2015b), despite an expressed desire to assume more prescribing responsibility (Higgins et al., 2017a). As senior veterinarians have greater influence on producer AMU, they should facilitate the transition from BDCT to SDCT, where prudent to implement, and increase producer trust of their junior colleagues to further optimize AMU decisions (Higgins et al., 2017a). Furthermore, initiatives to mitigate negative veterinary perceptions of SDCT risks and improve producer perceptions of the veterinary community as a ‘united front’ of SDCT support will likely promote industry changes (Speksnijder et al., 2015b; Higgins et al., 2017a).

Changing veterinary perceptions and access to new information did not always follow a logical progression (Higgins et al., 2017b). Although new data supporting TS use were accepted by most veterinarians, research conclusions close to their own beliefs were more readily accepted. Consequently, new data on SDCT and TS may contribute to feelings of uncertainty and decreased confidence in decision-making (Higgins et al., 2017b). Advocating SDCT instead of BDCT, the longstanding industry norm, is a considerable change from an udder health perspective; it may therefore take substantial evidence to convince some veterinarians to change their beliefs regarding SDCT.

Some UK producers and veterinarians felt their personal stewardship efforts were undermined by the actions of others, including other country agricultural sectors, with specific blame on the human medical community (Golding et al., 2019). Previous research suggests increasing One Health stewardship efforts that are focused on individual knowledge and motivations may increase personal responsibility and reduce blame placed on others (Fynbo and Jensen, 2018; Johnson et al., 2018; Farrell et al., 2021) in pursuit of a common goal (Golding et al., 2019). The relationship between producers and veterinarians can either be a barrier or a facilitator of antimicrobial stewardship, depending on the dynamic, with enabling producer-veterinary partnerships fostering shared responsibility and improved stewardship efforts (Farrell et al., 2021). Promoting desired behaviour change requires end users (i.e., producers/farm workers) to perceive that their actions regarding AMR are effective and important (Fishbein and Cappella, 2006; Speksnijder and Wagenaar, 2018).

4.8. FURTHER STEPS TO IMPLEMENT SDCT

With increasing scrutiny of prophylactic AMU and calls to decrease agricultural AMU worldwide, adoption of SDCT can be expected to increase. Specifically, an industry paradigm shift is required to transition from indiscriminate antimicrobial DCT to justified AMU based on

IMI presence or risk (Biggs et al., 2016). As this shift occurs, it is worth considering how to facilitate sustained behavior change using a holistic approach. It is important to integrate priorities of all relevant stakeholders in development of any public health initiative that will be both impactful and practical (Rajala-Schultz et al., 2021). Providing benchmarks of antimicrobial prescribing to veterinarians and producers compared to their peers may allow them to contextualize their antimicrobial prescribing and use, allowing for more open conversations regarding AMU practices (Speksnijder and Wagenaar, 2018). Overall, national SDCT guideline development that considers country-specific industry differences, along with supportive veterinarians, and effective communications, would provide producers with tools to successfully implement SDCT with limited negative consequences on udder health and productivity. This should be coupled with ongoing evaluation of AMU and impacts on AMR in the dairy industry, also considering indirect costs and benefits.

4.8.1. Conclusions

Although described selection protocols and results differed, common themes emerged from the literature that present a positive argument in favor of SDCT. Producers should be provided with SDCT protocol options that reflect their access to data for the basis of antimicrobial treatment decision-making, as well as their motivation to choose one method over another. Further, sufficient evidence supports that TS should be included as an integral part of an SDCT protocol (Winder et al., 2019b: Kabera et al., 2021). If SDCT recommendations are practical and based on producer situations, uptake will likely increase. Furthermore, ongoing producer and veterinary education is essential to increase antimicrobial stewardship in the dairy industry (Farrell et al., 2021) and increased personal responsibility in AMR mitigation is required to help facilitate required behaviour change (Fishbein and Cappella, 2006). Also, proper evaluation mechanisms should be in place to evaluate impacts of introduced SDCT protocols. In summary, SDCT protocols can be enacted in developed dairy countries without negative udder health and production impacts and will substantially reduce DCT-associated AMU, potentially reducing the impact on AMR.

4.9. References

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Table 4.1. Summary of most recent reported country-specific antimicrobial dry cow therapy (DCT) and teat sealant (TS) practices.

Country	First author, year	Drying off practices		DCT Regulations
		Antimicrobials	TS	
Austria	Wittek, 2018 N = 1,657 herd records	- 31.3% dried off using antimicrobials - 68.7% dried off without antimicrobials	- Unknown	None
Canada	Bauman, 2018 N = 374 participants	- 84% BDCT[a]	- Unknown	None
Finland	Vilar, 2018 N = 715 participants	- 13% BDCT, 78% SDCT[b], 9% no DCT - Drying off microbiological milk testing was most common selection method (81.9%) of SDCT farms (also conducted on 64.2% of BDCT farms) - Milk from all cows examined on 33.9% of SDCT farms; significantly more frequent on pipeline farms (51.9%) than parlor (25.4%) or automatic milking systems (22.7%) - CM[c] history and high SCC[d] (61.3%) second most common criteria - 71.5% of SDCT farms treated up to 25% of cows - BDCT higher with automatic milking systems, larger farms, and with increasing milk production	- Larger herds more likely to use internal TS[e], 44.5% of TS farms applied it to up to 1/4 of cows and 34.6% to all cows - Differences between internal TS with automatic milking system (49.0%), milking parlor (40.7%) or pipeline (24.8%) - Internal TS alone or in combination with antimicrobial DCT on 35% of farms	Nordic countries do not permit routine prophylactic AMU[f] at drying off
France	Poizat, 2017 N = 24 participants	- 58.3% BDCT - 41.7% SDCT	- Some use it, details not specified	None
Germany	Bertulat, 2015 N = 93 participants	- 79.6% BDCT, SDCT not mentioned by any producer, 9.7% did not use DCT - Bacteriological examination of milk before drying off on 31.0% of farms, with bacteriological examinations of all cows on	- Internal TS used by 33.3% of farms - Farms using antimicrobial DCT 2.8x more likely to use internal TS	None

		6.6% of farms, whereas 24.4% were for selected cases, e.g., high-yielding cows - 64.9% of all antimicrobial DCT conducted without bacteriological examination	- 22.6% of farms used internal TS and antimicrobials	
Ireland	More, 2017 N = ~ 85% of all sales (2003-2015)	- Estimated national coverage of DCT (2003-2015), increased by 2.9 - 3.2% (each year from 2003 to 2015), reaching ~100% coverage during last 6 years of study period	- 64-67% of teat sealant of total numbers of antimicrobial tubes sold (2011-2015)	None
The Netherlands	Santman-Berends, 2016 N = 224 herds, 220 for TS use	- 16 (7.1%) treated ≤ 25% of cows with antimicrobials at drying off - 26 (11.6%) treated 26 – 50% of cows - 27 (12.1%) treated 51 – 75% of cows - 155 (69.2%) treated ≥ 76% of cows	- 60 herds (27.2%) indicated 'Yes' (>90% of cows) 47 (21.4%) said 'Sometimes' (11-89% of cows) and 113 (51.4%) said no (<10% of cows)	Preventive AMU in animal husbandry prohibited since 2013
United States	USDA, 2016 N = 1,261 herds	- 93.0% treated with IMM[g] antimicrobials at drying off, no DCT used on 9.2% of farms - BDCT used in 94.2% of farms with > 500 cows versus 77.5% < 100 cows	- Internal TS used in some cows on 36.9% - 33.9% used internal TS on all cows, 14.0% used external TS	None
United Kingdom	Fujiwara, 2018 N = 146 participants	- Drying off IMM antimicrobials used on 95.9% of farms	- 82.2% using antimicrobials with TS - TS used by 84.9% of farms, with 86.3% using internal TS, 3.2% using external, and 9.5% using both	None

[a]BDCT = blanket dry cow therapy
[b]SDCT = selective dry cow therapy
[c]CM = clinical mastitis
[d]SCC = somatic cell count
[e]TS = teat sealant
[f]AMU = antimicrobial use
[g]IMM = intramammary

Table 4.2. A summary of reported blanket and selective dry cow therapy (DCT) comparisons primarily using somatic cell counts or pathogen identification-based selection methods, limited to field studies (controlled trials), sorted by publication year.

First author, year	Region/ Country	Herd BMSCC[a]	Cow Selection	Selection Level	Teat Sealant	Outcome
Somatic Cell Count Based Selection						
Rindsig, 1978 - 232 cows - 1 herd	University of Illinois, United States	Not listed	- CMT[b] ≥ 2 in any quarter, or SCC (membrane filter-DNA procedure) > 500K cells/ml antimicrobial treated - Controlled trial	Cow-level	No	- Similar quarter IMI[c] elimination rate (*S. aureus*, *Strep. agalactiae*, other streptococci, and Gram-negative rod) in BDCT[d] (85.4%) and SDCT[e] (88.2%) - New quarter IMIs slightly higher in SDCT (6.5%) compared to BDCT (3.1%) - Lower CM[f] incidence with BDCT (4.6%) compared to SDCT (7.8%) - Lower SCC[g] with BDCT
Østerås, 1991 - 703 cows - 291 herds	Norway	Not listed	- > 100K cells/mL in last 2 SCC tests, and positive CMT or major pathogen in 1+ quarters at first screening (1-6 weeks before drying off) - Random groups: Group A = control (no treatment); Group B = placebo (infected quarters treated); Group C = only treated infected quarters; Group D = IMM AMU in infected quarters every 2nd day for 6 days at drying off	Quarter-level (except if ≥ 3 quarters infected, all treated) Drying off CM treated with antimicrobials (groups B/C/D)	No	- Quarter-based SDCT using samples taken 1-6 weeks before drying off provided inadequate diagnostics for SDCT (i.e., culture results before drying off were not well correlated to drying off culture results) - When using long-acting IMM[h] antimicrobials, all quarters of an infected cow should be treated whereas treating only infected quarters may be possible with short-acting IMM antimicrobials

Østerås, 1994 - 684 cows - 288 herds	Norway	Not listed	- Cows > 100K cells/mL in last 2 tests, and mastitis present (positive CMT) or bacteriological finding of major pathogen in 1+ quarters at first screening (45 ± 32 days before drying off) - Random groups: Group A = control (no treatment), Group B = placebo, Group C = long-acting AMU in each infected quarter, Group D = short acting AMU, every 2nd day for 8 days in infected quarters	Quarter-level (except if ≥ 3 quarters infected, all treated) CM treated at drying off with antimicrobials (groups B/C/D)	No	- More healthy cows in treatment groups (C+D) than control groups (A+B) and more cows with major pathogens in control groups mid-lactation - More healthy quarters with short than long-acting AMU[i] in mid-lactation, and for cows with major pathogens both before and at drying off (higher cure rate than long-acting AMU) - In quarters with *Staph. aureus* IMIs both before and at drying off, no difference between groups at calving - Short acting AMU had significantly fewer new IMI (*Staph. aureus* or *Strep. dysgalactiae*) in untreated healthy quarters in cows with < 3 infected quarters - Differences between long-acting AMU and controls were present at calving but decreased later in lactation to a level that was not significant
Osterås, 1996 - 608 cows - 268 herds	Norway	Not listed	- Refer to Østerås et al. (1994)	Refer to Østerås et al. (1994)	No	- No effect on culling rate - Control cows had higher incidence of CM, higher SCC, and lower mean milk yield per lactation
Bradley, 2010 - 839 and 810 cows - 6 herds	Somerset and Wiltshire, England	<250K cells/mL	- Uninfected (last 3 SCC < 200K cells/mL, no CM within that period) → TS alone or with antimicrobials - All other animals: infected -→ antimicrobial alone or with internal TS	Quarter-level	Internal TS	- Combination treatment (TS[j] and AMU) in infected cows increased likelihood of being pathogen free after calving and decreased likelihood of developing CM in first 100 DIM[k] compared to AMU alone - No difference between TS alone and in combination with AMU in uninfected cows, except for IMI prevalence at calving with coagulase-positive staphylococci and *Streptococcus* spp. combined

						- No significant differences in cure rates and new IMI rates for major or minor pathogens - In uninfected cows, no significant difference in CM; however, combination treated quarters were more likely to develop CM caused by *E. coli* or an enterobacterial pathogen
Rajala-Schultz, 2011 - 723 cows - 4 herds	Ohio, United States (2 herds were institutional)	Mean BTSCC = 162k – 340k cells/mL	- Low risk cows randomly assigned to antimicrobial DCT or no DCT if; 1) < 200K cells/mL and no CM, 2) if CM during 1st 90 DIM, but < 100K cells/mL for rest of lactation	Cow-level	No	- No significant difference between milk yield or IMI at calving of treated and untreated low risk cows during following lactation - Treated low risk cows had 16% lower SCC than untreated cows during following lactation - Milk yield and SCC effects were variable in different herds
Scherpenzeel, 2014 - 1657 cows - 97 herds	Netherlands	BMSCC = 41k – 387k cells/mL (mean 184k)	- Primiparous < 150K cells/mL - Multiparous < 250K cells/mL - No CM present	Split-udder	No	- SCC at calving and 14 DIM significantly higher without AMU - CM incidence rate 1.7 times higher without AMU - Highest CM incidence rate occurred during first 21 DIM - Dry period→ CM 3.7 times higher odds to acquire CM without AMU
Vasquez, 2018 - 565 cows - 1 herd	New York, United States	Mean BMSCC = 201k cells/mL	- Low-risk = < 200K cells/mL at last test, mean < 200K cells/mL over last 3 tests, no CM at drying off and ≤ 1 CM case during lactation, randomly assigned to AMU	Cow-level	External TS, all cows	- No statistical differences for new IMI risk, milk production, linear scores, culling events, or CM events - Cows treated with antimicrobials had slightly higher IMI cures than cows that did not receive antimicrobials
McParland, 2019 - 654 cows - 3 herds	Cork, Ireland (Research herds)	BMSCC < 200k cells/mL, exceeded only in Jan and	- SCC < 200K cells/mL, and no CM (lowSCC) in previous lactation randomly assigned to internal TS alone or antimicrobials and TS	Cow-level	Internal TS, all cows	- Cows with internal TS alone → higher daily milk yield (0.67 kg/day) over lactation compared and higher SCC (not considered problematic) in early, up to mid, and throughout lactation compared to low SCC cows with internal TS and antimicrobials

		Feb (n = 2)	(high SCC = >200K cells/mL or CM during lactation)			- No difference → weekly SCC of cows with internal TS alone and high SCC cows - Odds of internal TS alone cows having bacteria present in foremilk across lactation was 2.7 and 1.6 times the odds of low SCC cows with internal TS and antimicrobials and of high SCC cows, respectively
Zecconi, 2020 - 516 cows - 5 herds	Lombardy, Italy	BMSCC 175k – 220k cells/mL	- AMU if SCC at last test before drying off > 100K cells/mL (primiparous), > 200K cells/mL (multiparous)	Cow-level	Internal TS, all cows (3 herds)	- TS significantly increases bacteriological cure, significantly decrease new IMI rate - New IMI rate significantly lower in negative untreated cows compared with treated cows - Proportion of negative (49.1 versus 49.3%), transient (24.8 versus 27.3%), or harboured IMI (26.1 versus 23.5%) were very similar at drying-off and after calving, respectively - SDCT increases risks for IMI after calving
Pathogen Identification-based Selection						
Browning, 1990 - 1044 cows - 12 herds	Victoria, Australia	Mean BMSCC = 100K – 400K cells/ml	- Laboratory culture-negative cows at drying off randomly allocated to receive treatment (all quarters) or no treatment - Infected cows randomly allocated to all quarters treated or infected quarter only treatments	Cow/Quarter-level	No	- New IMI rate during dry period nearly 4 times higher for infected cows with quarter treatment compared to other treatment groups - Significantly higher *Staph. aureus* IMI rate in infected cow-level treatment group in early lactation compared to the uninfected, all treated group, but no overall difference for total pathogens between groups - Significantly higher *Strep. uberis* rate infected quarter-level treatment group, both at calving and mid-lactation, compared with the infected cow-level treatment - No significant difference in CM incidence, but in early lactation different between groups
Browning, 1994 - 1044 cows	Refer to Browning et al. (1990)	Not listed	- Refer to Browning et al. (1990)	Cow/Quarter-level	No	- Quarter SDCT resulted in a higher new dry period IMI rate - No significant difference; however, teat-level selected cows had more infected quarters at calving

- 12 herds						- No difference in IMI prevalence by mid-lactation - Low initial IMI prevalence→ no difference between strategies - Medium initial IMI prevalence→ new IMI rate with selective quarter therapy was higher than other strategies
Cameron, 2014 - 729 cows - 16 herds	Prince Edward Island and Québec, Canada	BMSCC < 250K cells/mL	- Cultured cows: SCC < 200K cells/mL on last 3 tests and no CM in same period - Randomly assigned to BDCT (with TS) or SDCT - SDCT based on Petrifilm on-farm culture: culture (+) = antimicrobials and TS, culture (-) = TS only	Cow-level	Internal TS, all cows	- No difference observed between groups for quarter-level cure risk, new IMI risk over the dry period and at calving, and CM risk in first 120 DIM
Cameron, 2015 - 729 cows - 16 herds	Refer to Cameron et al. (2014)	BMSCC < 250K cells/mL	- Refer to Cameron et al. (2014)	Cow-level	Internal TS, all cows	- No difference for natural logarithm of SCC or milk production over first 180 DIM
Patel, 2017 - 56 cows - 1 herd	University of Minnesota, United States	Not listed	- Cows without CM at drying off randomly assigned to BDCT (TS and AMU) or SDCT. SDCT = rapid culture system, culture (-) = TS, culture (+) = TS and AMU	Quarter-level	Internal TS, all cows	- No difference in IMI risk after calving, bacteriological cures, or new IMI
Kabera, 2020	Québec, Canada	BMSCC < 250K cells/mL	- Petrifilm on-farm culture (culture (+) = infected, culture (-) = healthy)	Quarter-level	Internal TS	- No significant difference for new IMI or persistence of existing IMI over dry period, CM incidence, mean SCC, or mean daily milk production during first 120 DIM

- 568 cows - 9 herds			- SDCT groups; (1) AMU - infected, TS - healthy, (2) AMU and TS - infected, TS - healthy - BDCT groups; AMU alone or AMU and TS			
Comparison of Pathogen Identification and SCC-based Selection						
Rowe, 2020a - 1211 cows - 7 herds	California, Iowa, Minnesota, New York, and Wisconsin, United States	BMSCC < 250K cells/mL	- Comparison between BDCT, culture based SDCT (quarter-level) and algorithm based SDCT (cow-level) - Culture SDCT - treating quarters culture (+) - Algorithm SDCT cows, AMU if: any SCC > 200K cells/mL or ≥ 2 CM cases during lactation	Both cow and quarter-levels	Internal TS, all cows	- Both culture or algorithm based SDCT programs unlikely to increase CM risk or test-day $\log_e$SCC, risk of removal from herd and test-day milk yield. IMI dynamics (IMI cure risk, new IMI risk) and IMI prevalence post-calving similar between BDCT, culture based SDCT, and algorithm based SDCT.

[a] BMSCC = bulk milk somatic cell count
[b] CMT = California mastitis test
[c] IMI = intramammary infection
[d] BDCT = blanket dry cow therapy
[e] SDCT= selective dry cow therapy
[f] CM = clinical mastitis
[g] SCC = somatic cell count
[h] IMM = intramammary
[i] AMU = antimicrobial use
[j] TS = teat sealant
[k] Days in milk

Table 4.3. Summary of reported sensitivities and specificities for intramammary infection (IMI) identification at drying off using somatic cell count (SCC) thresholds or culture results for selective dry cow therapy protocols from composite milk samples, sorted by publication year.

First author, year	Gold standard for IMI used	Method	Sensitivity % (95% CI[a])	Specificity % (95% CI)	Positive Predictive Value % (95% CI)	Negative Predictive Value % (95% CI)
Torres, 2008 (Cow IMI prevalence 32.3%)	- Culture/isolation of the same pathogen from paired samples (≥100 cfu[b]/mL)	SCC < 100K cells/mL and no CM (Major pathogens only)	84.2 (78.8-88.8) (88.4)	35.1 (30.5-39.8) (31.0)	40.4 (35.9-45.0) (not described)	80.9 (74.6-86.4)
		SCC < 200K cells/mL and no CM	69.8 (63.2-75.8)	50.6 (45.7-55.4)	42.5 (37.3-47.7)	76.2 (70.8-81.1)
		SCC < 200K cells/mL (no CM in lactation) or < 100K cells/mL (CM < 90 DIM) (Major pathogens only)	69.4 (62.9-75.4) (79.1)	63.3 (58.5-67.9) (56.9)	49.7 (43.9-55.4) (not described)	79.8 (75.1-83.9)
		SCC < 300K cells/mL and no CM	62.2 (55.4-68.6)	55.3 (50.4-60.1)	42.1 (36.7-47.6)	73.7 (68.5-78.4)
Pantoja, 2009 (Cow IMI prevalence 34.6%)	- ≥ 300 cfu/mL colonies of same type - 3+ dissimilar colony types = contaminated	< 50K cells/mL	94	37	18	98
		< 100K cells/mL	88	52	21	97
		< 150K cells/mL	76	60	22	95
		< 200K cells/mL	64	66	22	93
		< 250K cells/mL	51	72	21	91
		< 300K cells/mL	49	76	23	91
Cameron, 2013 (Cow IMI prevalence 43.4%)	- ≥ 100 cfu/mL of any pathogenic organism of interest cultured, ≥ 200 cfu/mL for NAS[c] - 3+ dissimilar colony types = contaminated	Petrifilm on-farm culture negative (SCC< 200K cells/mL)				
		>5 colonies	85.2 (78.5-90.5)	73.2 (66.4-79.3)	70.9	86.6
		>10 colonies	71.8 (63.9-78.9)	86.1 (80.4-90.6)	(not described)	(not described)
		SCC < 200K cells/mL	34.1 (27.8-40.5)	94.4 (87.0-100)	97.3	19.0

Kiesner, 2016 (Cow IMI prevalence 85.6%) Only organic herds	- ≥ 100 cfu/mL of major contagious pathogens[d] - ≥ 500 cfu/mL of any other pathogen - 2 most numerous colony types identified	SCC < 100K cells/mL	70.5 (64.5-76.7)	80.5 (67.6-93.4)	95.6	31.5
		SCC < 100K cells/mL + CM	72.9 (66.9-78.9)	78.0 (64.2-91.3)	95.1	32.6
		SCC < 100K cells/mL + Parity	78.5 (73.0-84.0)	61.0 (45.2-77.0)	92.3	32.4
		SCC < 100K cells/mL + CMT > 1	78.5 (73.0-84.0)	50.0 (33.6-66.3)	90.3	28.1
		Selection by farmers	36.3 (4.0-69.4)	91.6 (75.0-100)	96.7 (86.6-100)	20.0
Patel, 2017 (Quarter IMI prevalence of 34.8%)	- ≥ 100 cfu/mL of any pathogenic organism of interest (except NAS set at ≥200 cfu/mL and *Bacillus spp*. ≥500 cfu/mL) - 3+ dissimilar colony types = contaminated	Rapid on farm culture[e] (quarter-level)	82.4 (73.3-91.4)	73.2 (65.5-80.9)	62.2 (52.2-72.2)	88.6 (82.5-94.7)
Lipkens, 2019 (Cow IMI prevalence 55.8%)	- ≥ 300 cfu/mL colonies of same type - 3+ dissimilar colony types = contaminated (exception of NAS)	SCC at last test before drying off ≥50K	86.0 (82.8-89.3)	28.7 (24.5-33.0)	22.6 (18.7-26.5)	89.5 (86.6-92.3)
		≥100K	68.6 (64.3-72.9)	52.4 (47.7-57.1)	25.9 (21.8-30.0)	87.3 (84.2-90.4)
		≥150K	58.1 (53.5-62.7)	64.2 (59.8-68.7)	28.2 (24.0-32.5)	86.4 (83.2-89.6)
		≥200K	41.9 (37.3-46.5)	74.4 (70.3-78.4)	28.3 (24.1-32.6)	84.1 (80.7-87.5)
		≥250K	36.0 (31.6-40.5)	79.2 (75.4-82.9)	29.5 (25.3-33.8)	83.6 (80.2-87.1)
		≥500K	20.9 (17.1-24.7)	93.8 (91.6-96.1)	45.0 (40.4-49.6)	83.0 (79.5-86.5)
		Geometric mean of last 3 SCC tests ≥50K	82.4 (78.8-85.9)	32.5 (28.1-36.9)	23.0 (19.0-26.9)	88.3 (85.3-91.3)
		≥100K	67.1 (62.6-71.5)	59.5 (54.9-64.1)	28.8 (24.5-33.1)	88.1 (85.0-91.1)
		≥150K	49.4 (44.7-54.1)	71.6 (67.3-75.8)	29.8 (25.5-34.1)	85.3 (81.9-88.6)
		≥200K	37.6 (33.1-42.4)	79.3 (75.5-83.1)	30.8 (26.4-35.1)	83.9 (80.4-87.4)

		≥250K	32.9 (28.5-37.4)	85.3 (82.0-88.7)	35.4 (30.9-39.9)	83.9 (80.4-87.4)
		≥500K	12.9 (9.8-16.1)	95.4 (93.4-97.4)	40.7 (36.1-45.4)	81.8 (78.1-85.4)
		Sum of last 3 SCC tests ≥50K	89.4 (86.5-92.3)	20.1 (16.3-23.9)	21.5 (17.6-25.3)	88.6 (85.6-91.6)
		≥100K	76.5 (72.5-80.5)	44.5 (39.9-49.2)	25.2 (21.1-29.3)	88.6 (85.6-91.6)
		≥150K	68.2 (63.9-72.6)	57.2 (52.5-61.8)	28.0 (23.8-32.2)	88.1 (85.0-91.1)
		≥200K	57.6 (53.0-62.3)	66.7 (62.2-71.1)	29.7 (25.4-34.0)	86.6 (83.4-89.8)
		≥250K	49.4 (44.7-54.1)	72.4 (68.2-76.6)	30.4 (26.1-34.8)	85.4 (82.1-88.7)
		≥500K	27.1 (22.9-31.2)	87.6 (84.5-90.7)	34.8 (30.4-39.3)	83.1 (79.6-86.6)
Rowe, 2020b[f] (Quarter IMI prevalence of 25%)	- ‘Significant growth’ of any pathogen - NAS with <200 cfu/mL and *Bacillus spp.* <500 cfu/mL considered ‘non-significant growth’ - 3+ dissimilar colony types = contaminated	SCC > 200K cells/mL or 2+ CM cases during lactation	66 (61-71)	47 (44-50)	30 (27-33)	80 (77-83)
		(Major pathogens only)	(72 (57-84))	(44 (42-47))	(4 (3-5))	(98 (97-99))
		Rapid on farm culture - Producer	72 (67-76)	55 (52-58)	35 (32-39)	85 (83-88)
		(Major pathogens only)	(75 (59-86))	(49 (46-52))	(4 (3-5))	(99 (97-99))
		Quarter-level samples	72 (67-76)	61 (58-64)	39 (35-42)	87 (84-89)
		(Major pathogens only)	(75 (59-86))	(53 (51-56))	(4 (3-6))	99 (98-99))
		Rapid on farm culture - Technician	76 (72-81)	52 (49-55)	35 (32-38)	87 (84-89)
		(Major pathogens only)	(72 (57-84))	(45 (42-48))	(4 (3-5))	(98 (97-99))
		Quarter-level samples	73 (68-77)	63 (60-66)	40 (36-44)	87 (85-89)
		(Major pathogens only)	(70 (54-82))	(54 (52-57))	(4 (3-6))	(98 (97-99))
McDougall, 2021a[g] (Cow IMI prevalence 7.2%, major pathogens)	- Single *Staph. aureus* colony present, or 2+ colonies of other species[h] - 2 colony types = mixed, 2+ types = contaminated	Last SCC report (>108K cells/mL)	86	71	20	98
		Maximum SCC (>152K cells/mL)	82	74	20	98
		Average SCC (>105K cells/mL)	76	80	24	98
Rowe, 2021c	- MALDI-TOF mass spectrometer, cows with 1+	Primiparous - SCC <150K cells/mL at last test, Multiparous - SCC <50K cells/mL at last test	53 (47-58)	52 (47-57)	50 (45-55)	54 (51-58)
		(Major pathogens only)	(62 (56-68))	(52 (47-57))	(20 (17-24))	(88 (84-90))

(Cow IMI prevalence 47.8%)	infected quarters classified as positive for IMI - NAS with less than <200 cfu/mL and *Bacillus spp.* <500 cfu/mL considered not infected	Primiparous - SCC <120K cells/mL all tests, Multiparous - SCC <150K cells/mL at all tests, no CM during whole lactation (Major pathogens only)	69 (63-74) (70 (64-76))	44 (38-49) (39 (33-45))	53 (49-57) (18 (15-22))	61 (56-65) (87 (83-90))
		SCC <200K cells/mL for each of last 3 tests, no CM between third last test and drying off (Major pathogens only)	37 (32-43) (44 (37-52))	75 (69-79) (71 (66-76))	57 (52-62) (23 (19-28))	56 (53-60) (87 (84-89))
		SCC <200K cells/mL all tests, <2 CM cases during whole lactation (Major pathogens only)	56 (50-63) (59 (51-66))	56 (50-62) (59 (51-66))	54 (50-58) (19 (16-23))	58 (54-63) (87 (83-90))

[a]CI = Confidence Interval

[b]cfu = colony forming units

[c]NAS = non-*aureus* staphylococci

[d]*Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, and *Trueperella pyogenes*

[e]Minnesota Easy 4 Cast Plate

[f]All tests conducted 2 days before drying off

[g]Identification for treatment instead of identification to leave cows untreated, major pathogens only

[h]*Staphylococcus aureus*, *Streptococcus dysgalactiae*, *Streptococcus uberis*, *Streptococcus* spp. (i.e., streptococci other than *Strep. uberis* or *Strep. dysgalactiae*), *Escherichia coli*, or *Klebsiella* spp.

Table 4.4. Summary of reported economic comparisons of blanket dry cow therapy (BDCT) and selective dry cow therapy (SDCT), sorted by publication year.

First author, year	Method	Assumptions[a]	Drying off AMU[b]	Costs (USD/cow)[c]
Hogeveen, 2005 (EUR/cow)	- Stochastic Monte Carlo model	- SDCT had higher IMI[d] rate at drying off, reduced cure rate, new IMI in dry period, IMI at calving and mastitis after calving - No TS[e] use or labour costs - Selection methods not described (assumed to have SCC[f] reports and CM[g] history) - Assumed sensitivity (95%) and specificity (60%)	48.9%	No DCT: 81.18 BDCT: 43.18 SDCT: 57.00
Huijps, 2007 (EUR/cow)	- Stochastic Monte Carlo model - Pathogen-specific IMIs (*Strep. agalactiae*, *Strep. dysgalactiae*, *Strep. uberis*, *Staph. aureus*, and *E. coli*)	- Unclear assumptions for SDCT selection and sensitivity/specificity - No TS use - SDCT had higher IMI rate at calving, CM rate, and increased production losses - CM occurring during dry period and not cured was not included - Labour costs included	35%	No DCT: 7.36-76.79 (mean 23.71) BDCT: 19.13-47.97 (mean 28.12) SDCT: 8.76-53.01 (mean 24.74)
Halasa, 2010 (EUR/100 cow herd)	- Stochastic bio-economic model, milk quota applied, with pathogen-specific IMIs (*Strep. dysgalactiae*, *Strep. uberis*, *Staph. aureus*, and *E. coli*) 1) BDCT; 2) BDCT and TS; 3) SDCT (at least 1 SCC > 200K cells/mL last 3 before drying off, or CM case during lactation),	- Milk production recording assumed to happen every 4 weeks - Sensitivity 96%, Specificity 100% - PPV[h] = 100%, NPV[i] = 98% - No testing costs, assumed as standard management practices (SCC and CM records) - Labour costs included	29%	BDCT: 146.66 BDCT (with TS): 152.97 SDCT (AMU or TS): 154.04 SDCT (with TS): 157.24

	unselected cows had TS only; 4) SDCT and all TS			
Scherpenzeel, 2016a (EUR/100 cow herd)	- Deterministic model based on field data (Scherpenzeel et al., 2014) to predict outcomes for 7 SDCT scenarios - Based on last SCC (cells/mL) before drying off, with primiparous (P) and multiparous (M) treated separately for some scenarios 1) BDCT, 2) 50K overall, 3) 100K overall, 4) 150k overall, 5) 150K (P), 50K (M), 6) 150K (P), 100k (M), 7) 150K (P), 200K (M), and 8)150K (P), 250K cells/mL (M)	- Model informed by Scherpenzeel et al. (2014)[j], where SDCT cows had a significant increase in SCC at calving and CM risk - No TS use - Labour costs included - SCC testing costs not included	(1) 3.15[k] (2) 2.48[k] (3) 1.94[k] (4) 1.56[k] (5) 2.09[k] (6) 1.83[k] (7) 1.37[k] (8) 1.27[k]	BDCT (1): 63.93 SDCT (2): 62.36 SDCT (3): 65.44 SDCT (4): 66.33 SDCT (5): 61.69 SDCT (6): 65.84 SDCT (7): 66.52 SDCT (8): 67.87
Patel, 2017 (USD/cow)	- Partial budget analysis informed by group study results culture guided SDCT at quarter level	- Assumed large herd (800 cows) - Culture system used for lactational CM and paid over 5-years - 2 IMM antimicrobial tubes/cow for SDCT group compared to 4 in BDCT group, no TS costs included (applied to both groups) - Sensitivity 82.4%, specificity 73.2%, NPV 88.6%, PPV 62.2% - Labour costs included	48% reduction	SDCT: 3.09 (Net return)
Scherpenzeel, 2018a (EUR/cow)	- Linear programming model - 9 cow groups considered with 4 SCC classes of primiparous (P) (cells/mL (0-50K; 51K-100K; 101K-150K); and >150K, and 5 classes of multiparous (M) (0-50K; 51K-100K; 101K-150K; 151K-250K; and >250K cells/mL)	- Model informed by previous study (Scherpenzeel et al., 2014), where SDCT cows had a significant increase in SCC at calving and CM risk and literature data for high SCC cows dried off with AMU (Barkema et al., 1998) - No TS use - Labour costs included	100% 50% 75%	BDCT in low (57.89), average (60.70), and high (65.51) BMSCC SDCT: 57.75 (low bulk tank SCC) SDCT: 60.70 (average bulk tank SCC)

	- BMSCC (cells/mL) ranged from low (<150K), average (≥150K but <250K), and high (≥250K but <400K)	- SCC testing costs not included	85%	SDCT: 65.51(high bulk tank SCC)
Rowe, 2021b (USD/cow)	- Partial budget model using Monte Carlo simulation (first 30 DIM[l] considered) - BMSCC (90K-230K cells/mL); herd size (850-5,700) - Culture-guided (quarter-level) treating only culture positive (Minnesota Easy 4Cast plate) - Algorithm-guided SDCT (cow-level) if cow had an SCC test > 200K cells/mL or 2+ CM cases in current lactation	- Based on data from 1,275 cows (7 herds) across the USA randomized to BDCT, culture-guided SDCT, or algorithm-guided SDCT (Rowe et al., 2020a,c) - No differences in dry period IMI dynamics and after calving udder health - Internal TS in all cows (no costs included) - No SCC testing costs, assumed as standard management practice	55% reduction (mode of distribution) (Quarter-level, both SDCT methods)	Culture-guided SDCT – cost savings of 2.14 (−2.31 to 7.23 for 5th and 95th percentiles) compared to BDCT (75.5% of iterations ≥$0.00) Algorithm-guided SDCT – cost savings of 7.85 ($3.39–12.90) compared to BDCT (100% of iterations ≥$0.00)
Hommels, 2021 (USD/cow)	- Logistic regression models developed using DHIA data and individual dairy herds in California to predict SCM[m] (set 1) and CM incidence risk (set 2) in next lactation for 96 last test-day SCC categories - Linear programming used to optimize DCT costs in 3 simulated herds (Set 1) of 1,000 cows with various BMSCC levels (low - 121,009–164,710 cells/mL, medium -188,782–222,688 cells/mL, and high - 257,941–373,702 cells/mL)	- Set 1- assumed to use BDCT with internal TS - Set 2 - all 6 dairy herds used BDCT with internal TS (assumed TS used when antimicrobials were not) - Assumed risk ratio based on Scherpenzeel et al. (2018a) (higher SCM/CM incidence when only TS used versus AMU and TS) - Internal TS in all cows (no costs included) - No extra labor, culling, AMU, or SCM milk quality loss - Assumed 80% of discarded milk substituted for milk replacer - No SCC testing costs included	P/M[n] 22/89% 30/88% 38/89%	Low BMSCC – SDCT: 37.3, BDCT: 38.0, No DCT: 42.9 (total costs of mastitis around the dry period (TCMD) Medium BMSCC – SDCT: 38.1, BDCT: 38.8, No DCT: 43.7 TCMD High BMSCC – SDCT: 39.3, BDCT: 39.9, No DCT: 45.2 TCMD

[a] Not all model assumptions included in table, only those relevant to interpretation of model differences

[b] AMU = antimicrobial use

[c] Published results were converted from EUR to USD/cow when required using mean conversion rate for publishing year (https://www.macrotrends.net/2548/euro-dollar-exchange-rate-historical-chart), and all studies with publishing years before 2021 were calculated with inflation rates to standardize them, from August of their publishing year to August of 2021 (https://www.bls.gov/data/inflation_calculator.htm)

[d] IMI = intramammary infection

[e] TS = teat sealant

[f] SCC = somatic cell count

[g] CM = clinical mastitis

[h] PPV = positive predictive value

[i] NPV = negative predictive value

[j] For full list of bulk tank and CM incidence combinations, see Scherpenzeel et al. (2018a); Tables 2 and 3

[k] Expressed as Animal Daily Dose (ADD)

[l] DIM = days in milk

[m] SCM = subclinical mastitis

[n] P/M = Primiparous/Multiparous

CHAPTER 5: Antimicrobial and teat sealant use and selection criteria at drying off on Canadian dairy farms

5.1. ABSTRACT

Infections with antimicrobial resistant pathogens are a major threat to human and animal health worldwide. Further, reduction of livestock-associated antimicrobial use (AMU) is often identified as an area of focus. Selective dry cow therapy (DCT) warrants consideration as an important way to decrease AMU on Canadian dairy farms. In addition, teat sealants (TS) are a non-antimicrobial alternative for prevention of intramammary infection during the dry period. Therefore, objectives of this study were to determine how antimicrobials and TS are used at drying off on Canadian dairy farms to determine selective DCT uptake and enacted selection protocols. It was expected that these data would provide a baseline understanding of DCT practices and highlight areas for future intervention to further reduce AMU. An observational study was conducted utilizing 2 in-person questionnaires conducted between July 2019 and September 2021 on 144 participating dairy farms in 5 Canadian provinces (British Columbia = 30, Alberta = 30, Ontario = 31, Quebec = 29, and Nova Scotia = 24). Overall, 45 farms (31%) reported adopting selective DCT, 95 (66%) enacted blanket DCT, and 4 (3%) did not provide antimicrobial DCT. Farms enacting selective DCT had approximately 50% less intramammary antimicrobials used at drying off compared to blanket DCT farms. Cow somatic cell count history was the most common criterion for selective DCT decision-making, followed by previous clinical mastitis history, bacteriological culture, and milk production. A slight majority of farms (56%) applied TS to all cows at drying off, whereas 17 farms (12%) used TS selectively, and 46

farms (32%) did not use TS. Larger herds more often used TS and farms with an automatic milking system more often used TS selectively than applied to all cows. Results highlighted the variability in antimicrobial treatment and TS use protocols at drying off on Canadian dairy farms, and the potential for further antimicrobial reduction with increased adoption of selective DCT.

5.2. INTRODUCTION

Continued development of antimicrobial resistance (AMR) has increased awareness of antimicrobial stewardship in livestock industries. As the majority of antimicrobial use (AMU) on dairy farms is to either prevent or treat mastitis, including for dry cow therapy (DCT; Saini et al., 2012a; Stevens et al., 2016; Ruegg, 2017), this represents an important area for focus (McCubbin et al., 2022, De Jong et al., 2022). Blanket DCT (BDCT), i.e., intramammary (IMM) administration of antimicrobials to all cows at drying off, is the most common form of DCT in many countries to reduce the prevalence of intramammary infections (IMI) during the dry period and maintain milk production in the following lactation (Neave et al., 1969; McCubbin et al., 2022).

Decreases in bulk tank somatic cell count (SCC) over previous decades due to diminishing prevalence of IMI by contagious bacteria such as *Staphylococcus aureus* and *Streptococcus agalactiae* have made selective DCT (SDCT) possible (McCubbin et al., 2022). Particularly on dairy farms with low bulk tank SCC (<250,000 cells/mL), instead of administering antimicrobials to all cattle at the end of lactation, only cows most likely to benefit should receive antimicrobial treatment at drying off (Cameron et al., 2013; Scherpenzeel et al., 2016; Lhermie et al., 2018). Recent studies provided evidence that with careful consideration of selection criteria and dry cow management, SDCT farms do not appear to be at a disadvantage compared to BDCT farms regarding significant udder health or production impacts (Rowe et al., 2020; Kabera et al., 2021a; McCubbin et al., 2022). Increases in mean SCC and incidence of clinical mastitis (CM) could occur due to unidentified IMIs persisting if not addressed at drying off, or development of new dry period IMI in the absence of prophylactic AMU. However, these unintended udder health consequences are uncommon (McCubbin et al., 2022). Limiting the incidence of IMI during the dry period and early lactation depends on overall dry cow management; however, according to recent meta-analyses, success of SDCT protocols depends on administration of teat sealants (TS) to at least cows not receiving antimicrobials at drying off (Winder et al., 2019; Kabera et al., 2021a).

Depending on the selection protocol, SDCT can decrease AMU at drying off by 55% (Rowe et al., 2020) or as high as 95% (Kabera et al., 2021b). Further, there is an association between AMU reductions in livestock industries and subsequent reductions in AMR prevalence in the associated production system (Tang et al., 2017; Nóbrega et al., 2020). Therefore, SDCT is a desirable alternative to BDCT in herds with a relatively low bulk milk SCC, with potential economic benefits for producers as well as AMR mitigation (McCubbin et al., 2022). Although the relationship between IMM AMU and subsequent development of AMR varies by bacterial species and antimicrobial treatment, broader impacts of reducing AMU in livestock should not be overlooked (McCubbin et al., 2022).

With mandatory bans of BDCT in Nordic European countries and the Netherlands (Santman-Berends et al., 2021; McCubbin et al., 2022), plus new European regulations banning veterinary prophylactic AMU (other than in exceptional cases) in the European Union (Official

Journal of the European Union, 2019), the dairy industry is shifting towards SDCT and limited prophylactic AMU in general. In Canada, there are currently no regulations restricting BDCT and current adoption of SDCT is not well characterized.

Previous descriptions of DCT practices on Canadian dairy farms focused on BDCT uptake (88 and 84%; Dufour et al., 2012 and Bauman et al., 2018, respectively) rather than SDCT and antimicrobial treatment decision-making. Further, adoption and details of TS use on Canadian dairy farms are unknown. Therefore, our objective was to characterize SDCT uptake and TS use on Canadian dairy farms including selection criteria considered at drying off. Improved understanding of current SDCT practices should identify opportunities for targeted AMU reduction.

5.3. MATERIALS AND METHODS

This study was reviewed and approved by the University of Calgary Conjoint Faculties Research Ethics Board (REB19-0353) and is reported using STROBE-Vet guidelines (O'Connor et al., 2016).

5.3.1. Farm Selection

This study was part of the Canadian Dairy Network for Antimicrobial Stewardship and Resistance (CaDNetASR), a surveillance system aimed to increase understanding of AMU and AMR in Canadian dairy through collection of fecal and bulk milk samples, AMU audits, as well as reviews of farm and veterinary records (Fonseca et al., 2022). A purposive sample of dairy farms inside FoodNet Canada Sentinel Sites was identified through local veterinary clinics to gain producer consent before they were contacted by the study team (Government of Canada, 2013). Farm participation was voluntary. Further details regarding program design, sample size, and farm enrollment have been reported (Fonseca et al., 2022).

Farms were enrolled in 5 provinces. Farms were considered eligible if they participated in both the proAction® Initiative (a national mandatory certification quality assurance program for Canadian dairy farms) and in Canada's milk recording program, Lactanet (Guelph, ON, Canada), raised their own replacement heifers, had a minimum milking herd size of 50 cows (except Nova Scotia, with a minimum herd size of 40 milking cows), and were willing to share their veterinary clinic drug purchase data (Fonseca et al., 2022).

5.3.2. Data Collection

Two questionnaires were administered by regional fieldworkers during annual farm visits on the 144 farms enrolled in the CaDNetASR program between July 2019 and September 2021. The first questionnaire was conducted in 2019 and a follow-up questionnaire to get additional information and clarity was conducted in 2020. Questionnaires were conducted in-person during CaDNetASR farm visits and focused on antimicrobial DCT and TS administration at drying off and decision-making regarding application of these treatments (Appendix II). Producers were contacted by regional fieldworkers via phone or in person to address missing data or when further clarification was needed. Farms were assigned to the SDCT or selective TS use group if producers reported that selection criteria were considered when assigning either IMM antimicrobials or TS use, whereas antimicrobial and TS coverage was asked as a herd-level estimate (i.e., percent of cows per herd that receive either IMM antimicrobials or TS at drying off). Questionnaires were developed in consultation with the CaDNetASR team and administered in either English or French, based on producer preference.

When available, individual-level milk production data (24-h milk yield and 305-d lactational yield; n = 130 herds) and individual-level SCC data (lactational and 30 days in milk [DIM]) (n = 128 herds) were retrieved from Lactanet (with producer permission) for all cows present on participating farms for the entire 2020 calendar year. Cow-level dairy herd improvement (DHI) data were used to create the following herd-level variables: mean 24-h milk yield, mean 305-d lactational milk yield, mean lactational geometric SCC, and mean geometric SCC of the first 30 DIM.

5.3.3. Statistical Analyses

Data analyses were conducted using STATA (version 15.1, StataCorp LLC, College Station, TX). Univariable logistic regression models were used to assess associations between dichotomous outcome variables (SDCT vs. BDCT, TS use vs. no use, selective vs. blanket TS on farms that use TS) and farm-level estimates for udder health (mean 24-h milk yield, mean 305-d lactational milk yield, mean lactational SCC, and mean SCC in the first 30 DIM), province, milking system and farm size. Continuous variables were checked for linearity in their log odds (Hosmer et al., 1989) and categorized, if needed. Antimicrobial and teat sealant coverage were calculated as the reported % of cows per farm receiving IMM antimicrobials or TS at drying-off.

For continuous outcome variables (antimicrobial coverage on SDCT farms and TS coverage on selective TS farms), the same variables were checked for their associations (farm-level estimates for udder health, province, milking system, and farm size). Normality was assessed before fitting linear regression models. In TS coverage models, province was dichotomized to East (Ontario, Québec, and Nova Scotia) and West (British Columbia and Alberta) to achieve sufficient observations in each group and lactational milk production was condensed to 2 categories (≤11,000 and > 11,000 kg). Farms reporting multiple milking systems (n = 3) were excluded from the univariable analysis for the milking system comparison and the multivariable analysis.

For each outcome, all variables associated with outcome variables in the univariable analysis ($P \leq 0.25$) were entered into multivariable logistic regression models to assess effect modification and confounding. If removal of a variable resulted in a relative change of >25% in any effect estimate or an absolute change of >0.10 and if the effect estimate had a value between−0.40 and 0.40, it was considered a confounder and was retained in the model (Noordhuizen et al., 2001). Statistical significance was accepted when $P \leq 0.05$.

5.4. RESULTS

Based on producer responses, SDCT and selective TS application were defined as farms with a maximum of 97% IMM antimicrobial herd coverage and 98% TS herd coverage (i.e., percent of cows on that farm receiving IMM antimicrobials or TS at drying off), respectively. These limits were assigned because 1 farm with 98% antimicrobial coverage was self-described as BDCT as the 2% left untreated ‘dried themselves off.’ Regarding TS use, 2 farms reported 98% TS coverage but were included as selective TS farms as specific selection criteria were reported.

5.4.1. Study Farms

Both questionnaires were completed for all 144 participating dairy farms across 5 Canadian provinces (British Columbia = 30, Alberta = 30, Ontario = 31, Quebec = 29, and Nova Scotia = 24). A summary of reported selection criteria for SDCT and selective TS use is presented in Table 5.1. Median number of lactating cows was 106 (range 40 – 560 cows), mean 24-h milk yield was 36.0 kg (range 20 – 48 kg; n = 130), and median SCC was 182,326 cells/mL (range 60,321 – 485,222 cells/mL; geometric mean: 54,503 cells/mL; n = 128). Lactating cows were housed in a free stall (n = 86; 60%) or tie stall (n = 58; 40%). The most common milking system was a parlour (n = 65; 45%), followed by pipeline (n = 44; 31%) and automatic milking systems (n = 37; 26%). Some producers indicated > 1 housing type (n = 9) and/or milking system (n = 3).

There were 16 farms (11%) that did not have DHI SCC data available for analysis, whereas 14 herds (10%) did not have milk yield data available for analysis. Herds that did not have DHI data available for analysis were from all provinces (British Columbia = 5, Alberta = 2, Ontario = 5, Quebec = 2, Nova Scotia = 2), but were primarily automatic milking system herds (n = 9 for SCC data, n = 7 for milk yield data). Farms with a combination of milking systems were excluded from analyses (n = 3).

5.4.2. Antimicrobial Use at Drying Off

Of the 144 farms, 140 (97%) used antimicrobial DCT and 4 farms (3%) reported not using any antimicrobials at drying off. Overall, 45 (31%) farms enacted SDCT (Table 5.2). On SDCT farms, mean IMM antimicrobial coverage at drying off was 49.8% (median = 50%) of the cows (range 3 – 97%; Figure 5.1).

Of producers implementing SDCT (n = 45; 31%), 39 (87%) reported using cow SCC history as part of the criteria for SDCT antimicrobial treatment allocation (Table 5.1). Thresholds for SCC were used to allocate IMM antimicrobials to cows above the SCC threshold (Table 5.1). Of the 39 farms using SCC history, the most common SCC threshold was 200,000 cells/mL (n = 13; 33%); however, the range of thresholds reported was from 40,000 to 500,000 cells/mL. Additionally, 2 producers reported that although they considered SCC in their SDCT decision-making, there were no consistent SCC details (i.e., thresholds, timeframe, etc.) that were considered across cows. Other decision-making factors included CM history (n = 34; 76%), bacteriological culture (n = 11; 24%), and milk production (n = 7; 16%).

The timeframe considered for SCC thresholds ranged from the previous 2 weeks to the entire preceding lactation, with the latter being the most common (n = 12: 31%). Farms considering CM history in their SDCT protocol (n = 34; 76%) reported considering the timeframe of CM event (n = 22; 65%), number of CM events (n =16; 47%), and causal bacteria (n = 13; 38%). Low milk production at drying off was a decision-factor for not treating a cow with antimicrobials at drying off (n = 7; 16%), whereas parity was a consideration (n = 3; 7%), with cows in their second or greater lactation being administered IMM antimicrobials at drying off.

Most of the 11 farms (24%) using bacteriological culture data as part of their selection process received culture results from their veterinary clinic (n = 6; 55%); the level of bacteriological information producers received included was specific bacterial genus and species (n = 9; 82%) (Table 5.1). Two farms also received antimicrobial sensitivity data along with bacteriological culture results. Of the 11 farms considering bacteriological culture data in the SDCT decision-making, 10 (91%) also applied TS to all cows, whereas 1 farm did not use any

TS. All farms using bacteriological culture data also reported considering SCC data in their SDCT considerations.

There were no differences among farms practicing SDCT or BDCT regarding geometric mean lactational SCC and geometric mean SCC in first 30 DIM, mean 24-h milk yield (≤30, 30 – 35, 35 – 40, >40 kg) and mean 305-d lactational milk yield (≤10,000, 10,000 – 11,000, 11,000 – 12,000, and >12,000 kg), province, milking system, or number of milking cows (Table 5.3). No comparisons were made between farms using DCT (n = 140) and those who did not (n = 4) due to the small sample size of the latter farm group.

Mean geometric SCC (lactational and the first 30 DIM), milk production (lactational and 24-h milk yield), and province were not associated with antimicrobial DCT coverage on SDCT farms (Table 5.4). Herds with automatic milking systems tended to have higher antimicrobial DCT coverage (P = 0.10) than other milking system types. Further, after accounting for effect modification and confounding in a multivariable analysis, no significant associations were present.

5.4.3. Teat sealant use

More than half of farms, 56% (n = 81), administered TS to all cows at drying off, whereas 12% (n = 17) selectively applied TS at drying off, and 32% (n = 46) did not use TS at all. Of the 17 farms that selectively applied TS, mean herd TS coverage at drying off was 54% (range: 5 – 98%; Figure 5.1). On these farms, SCC was the most important criterion for TS allocation (n = 11; 65%), followed by CM history (n = 9; 53%) (Table 5.1). Use of internal TS was most common (n = 85; 87%), whereas 9 farms (9%) used external sealants. Four of these 9 farms used both internal and external sealants and administered both TS products to all cattle at drying off. One producer used high production at drying off as a decision-factor to allocate TS to cows, whereas 2 other producers reported low milk production was a consideration to receive TS only compared to IMM antimicrobials.

When considering antimicrobial DCT and TS uptake simultaneously (Table 5.2), 63% of producers (n = 60) that practiced BDCT also applied TS at drying off (56% to all cows and 7% selectively). Of the farms practicing SDCT, 84% (n = 38) also used TS at drying off (62% to all cows and 22% selectively).

Two farms used opposite selection criteria, meaning cows would either receive IMM antimicrobials or TS, whereas 3 farms either provided IMM antimicrobials with TS, or nothing, leaving some cows untreated. Five farms did not appear to have a relationship between their antimicrobial and TS selection criteria, apparently using various section criteria for both antimicrobials and TS. Overall, 18 producers reported leaving part or all of their herd without IMM protection, ranging from 1 to 100% of the herd (n = 4 producers who did not implement DCT), with a median of 47.5% cows left without any additional IMM protection.

There were no differences in geometric mean SCC (lactational), mean milk yield (24-h and 305-d lactational), province, or milking system between farms using TS and those who were not (Table 5.5). However, farms with higher geometric mean SCC in the first 30 DIM tended to have a lower likelihood to use TS (P = 0.08). Use of TS increased with increasing herd size (i.e., per 100 milking cows), but was confounded by province in the final multivariable model (odds ratio [OR]: 2.43; 95% confidence interval [CI]: 1.33 – 4.41). When comparing blanket TS use to selective TS use (Table 5.6), automatic milking system farms were less likely to use blanket TS (OR: 0.19; 95% CI: 0.05 – 0.73), but there was no association with mean SCC (lactational and first 30 DIM), milk yield (24-h and 305-d lactational), farm size, or province. However, the few selective TS farms (n = 17) did not enable exploration of any potential effect modification or confounding in a multivariable analysis.

On selective TS farms (Table 5.7), based on linear regression, farms in the west had a higher TS coverage compared to farms in the east (mean deviation of 50 percent points; 95% CI: 20.97 – 78.31). Western farms (Alberta and British Columbia) had a mean TS coverage of 86%, whereas Eastern farms (Ontario, Québec, and Nova Scotia) had a mean TS coverage of 36%.

5.5. DISCUSSION

Approximately 1/3 of Canadian farms used various SDCT selection criteria. It was noteworthy that herd-level SCC, milk production, farm size, province, and milking system were not different between farms using SDCT and those using BDCT. Although study methodology cannot indicate causality, describing currently enacted SDCT protocols on Canadian dairy farms experiencing no negative udder health consequences contributes to a growing body of contextual literature supporting SDCT as a successful DCT management strategy. Qualitative research regarding drivers and barriers of SDCT could increase understanding of how to improve uptake on Canadian dairy farms.

Producers most commonly used cow-level SCC data to select cows receiving IMM antimicrobials at drying off, which is possible on most dairy farms as approximately 65% of Canadian producers use DHI services (Lactanet, 2020; Government of Canada, 2021). Although access to DHI SCC data provided the option to enact SCC-based SDCT, not all producers with access to these data used them for SDCT. Further, automatic milking systems can provide frequent SCC data that could inform SDCT protocols, and 3 producers indicated they considered this information in their DCT decision-making.

Approximately 3/4 of reported SCC thresholds utilized on participating herds were between 100,000 – 200,000 cells/mL. The common SCC cut-off value to indicate subclinical mastitis is 200,000 cells/mL (Dohoo and Leslie, 1991); a lower SCC threshold could increase the sensitivity of the selection criteria, but it could also decrease specificity, with a higher proportion of cows unnecessarily receiving IMM antimicrobials at drying-off (Pantoja et al., 2009; Scherpenzeel et al., 2016; Rowe et al., 2021).

Different SCC thresholds reported for making antimicrobial DCT decisions at drying off could accomplish various goals, i.e., increasing threshold sensitivity versus decreasing AMU as much as possible and accepting a slightly higher risk of missing a cow with an IMI (Scherpenzeel et al., 2016; Rowe et al., 2021). Therefore, some producers may be more conservative in their AMU decision-making, whereas others may be more willing to substantially reduce AMU. Regardless, motivation to use very high SCC thresholds (300,000 – 500,000 cells/mL; Table 5.1) by 2 producers in our study sample were unclear.

The approximately 35% of Canadian dairy herds without DHI data have options if they wish to initiate SDCT. For example, some of these producers use an automatic milking system that may have their own SCC-based outputs, whereas producers that do not have access to SCC data could use a culture-based SDCT method. A variety of other diagnostics tools have been suggested as part of SDCT decision-making (i.e., California mastitis test [CMT], milk leukocyte differential, conductivity testing, lactate dehydrogenase [LDH], and *N*-acetyl-β- d-glucosaminidase) (Denis-Robichaud et al., 2019; Swinkels et al., 2021; McCubbin et al., 2022). However, only 1 producer mentioned considering CMT results, while other producers specifically referenced conductivity (n = 1) or LDH (n = 1) as their automatic milking system outputs considered (Table 5.1).

Despite research supporting bacteriological culture-based SDCT (Cameron et al., 2015; Patel et al., 2018; Kabera et al., 2020), uptake among included producers was low, especially for on-farm culture systems (n = 2 producers). Therefore, there could be a gap in producer desire to use bacteriological culture and actual uptake of this practice, perhaps due to a lack of skilled labour, the cost-prohibitive nature of culture, or other extenuating circumstances. Producers may also prefer the convenience of having culture done by trained personnel off-site, or they lack the time and/or trained personnel to conduct bacteriological culture on-farm. Research into overall drivers and barriers of SDCT practices can also further elucidate SDCT protocol choice, as well as identify areas of opportunity to increase SDCT uptake based on producer context and preference.

Described factors impacting culture-based selection method uptake could contribute to SCC-based SDCT protocols being the most commonly implemented SDCT protocol in Canadian dairy herds. However, as both SCC and bacteriological culture-based methods can be successfully implemented (Rowe et al., 2020a; McCubbin et al., 2022), either approach can reduce on-farm AMU, with the choice based on producer preference and access to data for decision-making.

Mean herd antimicrobial coverage on SDCT farms of 50% highlighted an achievable and safe level of AMU reduction (compared to BDCT) in the Canadian dairy industry, as there were no identified udder health or production differences between selective and BDCT herds. This was similar to the estimate of a potential 55% AMU reduction described by Rowe et al. (2020) for the United States, but lower than the 66% estimate from a meta-analysis incorporating a variety of SDCT protocols, including selection at both cow and quarter-levels (Kabera et al., 2021a). Therefore, we inferred that a higher percentage of reduction is possible and could represent a significant reduction of AMU for the dairy industry if SDCT uptake increases. However, AMU reduction not only depends on the selection protocol used, but also on overall herd health parameters such as bulk milk SCC and udder pathogen distribution in addition to attitudes and capabilities of producers and farm workers.

Descriptions of TS use and selection criteria used to make decisions for TS allocation at drying off are lacking in the literature. Descriptions are primarily limited to the percent of the herd receiving TS at drying off rather than the reasons for selection of those cows (McCubbin et al., 2021). Therefore, we introduced the idea of selective TS use, independent of SDCT, as producers in our study have indicated that they occasionally use different selection criteria, or only enact selective TS use while using BDCT.

Based on descriptive data regarding TS use and decision-making, current practices do not always align with best management. For example, simultaneous use of internal and external TS (n = 4) has not been previously identified in the literature in Canadian dairy herds and is not documented to provide any additional benefit to using only 1 form of TS. Further, there is strong evidence supporting TS use as part of a SDCT protocol (Bradley et al., 2011; Golder et al., 2016; McCubbin et al., 2022), especially in cows not receiving IMM antimicrobials at drying off (Winder et al., 2019; Kabera et al., 2021a).

Further, some producers allocated TS to cows above certain SCC thresholds rather than below (Table 5.1) which raises concerns that producers are using them for curative rather than as a preventative purpose. For example, the farm using BDCT and only providing TS to all cows with a mean SCC > 200,000 cells/mL on the last 3 DHI tests.

Although TS provide additional physical IMI protection by limiting bacteria entering the teat canal (Krömker et al., 2014), mean SCC (lactational and first 30 DIM) was not significantly different between herds using versus not using TS in their DCT protocols. However, the outcomes are difficult to interpret, as the majority of cows not receiving TS were given IMM antimicrobials at drying off (median = 100%, range 0 – 100%).

There may be additional benefit by providing IMM antimicrobials and TS concurrently, but the benefits are unclear in low SCC cows (McCubbin et al., 2022). However, there are clear benefits of TS use at drying off for cows not receiving IMM antimicrobials to provide additional IMI protection during the dry period (Winder et al., 2019; Kabera et al., 2021a). On 3 farms enacting both SDCT and selective TS use, the same selection criteria were used for both products; therefore, cows received IMM antimicrobials and TS concurrently leaving a portion of the herd without any (antimicrobial or TS) IMI protection. Overall, 18 producers (13%) reported leaving part or all of their herd without IMM protection. Optimizing IMI prevention represents an important area of focus in SDCT and dry cow management overall.

Farms with automatic milking systems were more likely to enact selective TS use compared to other milking systems, whereas TS use in general was more common in larger herds. The same trend of larger herds being more likely to use TS was also observed in Finland, although they reported TS use in general was more common on automatic milking system farms but did not distinguish between blanket and selective TS application (Vilar et al., 2018). In a recent study on 5 automatic milking system dairy farms in Ontario, Canada, only 1 reported had blanket TS use, whereas the others did not use TS (Padua et al., 2021). Internal TS needs to be completely stripped out after calving so that the residues do not cause problems with the robotic system (Lely, 2022). Therefore, producers with automatic milking system farms may be more conscious of conserving TS use to only those cows they think require it, resulting in more selective TS use protocols on these farms.

Behaviour change related to on-farm AMU and antimicrobial stewardship is influenced by a multitude of both internal (i.e., knowledge, belief, motivations, etc.) and external factors (i.e., economics, access to diagnostics or antimicrobial alternatives, farm situation and infection status, social pressures, etc.) (Poizat et al., 2017; Speksnijder and Wagenaar, 2018; McCubbin et al., 2022). Attitudes of producers regarding antimicrobial stewardship and udder health on Canadian dairy farms could be improved by enhancing understanding of farmers' knowledge regarding benefits of TS use to prevent IMI in the dry period and early lactation. However, education is only 1 part of a larger picture of facilitating successful and sustained behaviour change.

For example, there was success changing behaviour and reducing AMU in the dairy industry in The Netherlands, when the RESET Mindset model was used, which includes **R**ules and regulations, **E**ducation and information, **S**ocial pressure, **E**conomics, and **T**ools (Lam et al., 2017). The RESET Mindset model, or other behaviour change models could be employed to facilitate industry change and adoption of TS use aligned with best practices.

A variety of factors influence AMU on dairy farms, and DCT-related AMU in particular (McCubbin et al., 2022). However, in recent research from the UK, the main themes that accounted for AMU behaviours on dairy farms included: 1) knowledge and understanding of disease treatment; 2) sense of duty to animal care and wellbeing; and 3) autonomy of treatment practice (Rees et al., 2021).

Research conducted in Alberta, Canada, identified that producers were skeptical of a link between AMU in dairy cattle and AMR in humans, and valued their AMU decision-making autonomy (Ida et al., 2022). Further, Albertan producers believed their knowledge and experience were undervalued by consumers and policymakers and expressed concerned that AMU policy will be based on misguided consumer concerns (Ida et al., 2022). Understanding the context of on-farm AMU decision making is important to consider in any AMU reduction recommendations and establishing long-term uptake by producers.

Associations have been identified between certain antimicrobials used at drying off and development of AMR in some bacterial pathogens (Mollenkopf et al., 2010; Saini et al., 2012b, 2013; Schubert et al., 2021), but not others (Nóbrega et al., 2018; Stevens et al., 2018). Although specific implications of widespread IMM AMU for DCT are unclear (McCubbin et al., 2021), the association with reducing livestock-associated AMU (Tang et al., 2017; Nóbrega et al., 2021) underscores the need to act. Therefore, by facilitating open transdisciplinary communication within the industry regarding AMU and highlighting the importance of AMR mitigation while concurrently taking producer experience and concerns into consideration, may increase selective AMU practices and improve overall antimicrobial stewardship in the industry.

Farms included in this study were a convenience sample with voluntary participation, which may have artificially increased the number of farms engaging in antimicrobial stewardship practices (i.e., SDCT), a selection bias that could impact external validity. Further, small sample sizes for some subsets (i.e., farms not practicing DCT, or those practicing selective TS use), could have limited study power to identify a significant difference in included parameters. That more automatic milking system herds compared to other milking systems did not have DHI data available for analysis likely was attributed to the availability of milk yield and sometimes SCC data through the automatic milking system. Finally, dry cow management practices beyond antimicrobial and TS use (i.e., housing, diet, bedding, etc.) were outside the scope of this study.

5.5.1. Conclusions

Selective DCT was used on 31% of the dairy farms studied, whereas 56% enacted blanket TS use at drying off. Adoption of SDCT on Canadian dairy farms encompassed a wide variety of SDCT protocols and TS use considerations, with approximately 50% DCT-associated AMU reduction compared to BDCT. Due to the high proportion of producers not using TS (32%), there is an opportunity for increasing IMI prevention in the dry period through increasing inclusion of TS as part of a SDCT protocol to further improve udder health in the dry period and early lactation and decrease reliance on IMM antimicrobials. The identified decreased use of BDCT in recent years and opportunities for further AMU reduction presents a positive image for antimicrobial stewardship in the Canadian dairy industry by identifying that AMU reduction is ongoing and SDCT could have substantial use reduction impacts.

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Table 5.1. Number of farms and reported selection criteria for selective dry cow therapy (DCT) and selective teat sealant (TS) use protocols.

	No. farms	
Criteria	Selective DCT	Selective TS
SCC[a]	39	11
SCC thresholds (1,000 cells/mL)		
> 40	1	
> 50	1	
> 100	6	2
> 150	9	1
> 200	13	1
> 225	1	
> 250	4	
> 300	1	
> 500	1	
< 100		1
< 150		1
< 200		2
< 300		1
SCC time frame*		
Entire lactation	12	4
Past 8-9 mo	3	
Past 6 mo	3	1
Past 3-4 mo	13	2
Past 1-2 mo	5	1
Last two wk	1	
All SCC records except first		1
CM[b] events	34	9
Time frame		
Current lactation	15	4
Past 6 mo		1
Past 3 mo	3	2
Past month	2	
At dry-off	1	
Previous lactation	1	
Number of CM events		
1 CM in same lactation		1
> 1 CM in same lactation	3	
> 2 CM in same lactation	5	3
> 3 CM in same lactation	2	
> 1 CM in same month	1	
> 2 CM in same month		2
1 CM in previous lactation	1	
> 1 CM in previous lactation	1	

> 2 CM in previous lactation	1	
Any previous CM case	2	1
Bacteria		
Suspected bacteria	3	1
Confirmed bacteria	10	3
Milk bacteriological culture	11	
Location		
Veterinary clinic	6	
Provincial/regional lab	5	
On-farm	2	
Results provided		
Growth/no growth	7	
Gram-positive/Gram-negative	5	
Specific bacteria	9	
Antibiotic sensitivity	2	
Other cow history		
Milk production at drying off	7	2
Age	3	
Automated Milking System outputs	3	1
Season/climate	2	
Housing	1	1
Genetics	1	
Milk leakage	1	
California Mastitis Test	1	

[a] SCC = somatic cell count

[b] CM = clinical mastitis

*Producers reported timeframe considerations both in terms of months and number of DHI reports. Reference to a specific number of DHI records has been transformed into months to be more comparable based on provided data regarding how many times a year they received SCC data.

Table 5.2. The variety of combinations of teat sealant use methods (blanket, selective, no use) and antimicrobial dry cow therapy (DCT) methods (blanket, selective, no use) on Canadian dairy farms (n = 144).

	Teat sealant use n (%)			
	Blanket	Selective	None	Total
Blanket DCT				
British Columbia	10 (56)	-	8 (44)	18
Alberta	12 (60)	1 (5)	7 (35)	20
Ontario	14 (70)	2 (10)	4 (20)	20
Québec	9 (43)	3 (14)	9 (43)	21
Nova Scotia	8 (50)	1 (6)	7 (44)	16
Total Blanket DCT	53 (56)	7 (7)	35 (37)	95
Selective DCT				
British Columbia	5 (45)	1 (10)	5 (45)	11
Alberta	4 (40)	4 (40)	2 (20)	10
Ontario	8 (80)	2 (20)	-	10
Québec	5 (71)	2 (29)	-	7
Nova Scotia	6 (86)	1 (14)	-	7
Total Selective DCT	28 (62)	10 (22)	7 (16)	45
No DCT				
British Columbia	-	-	1 (100)	1
Ontario	-	-	1 (100)	1
Québec	-	-	1 (100)	1
Nova Scotia	-	-	1 (100)	1
Total no DCT	-	-	4 (100)	4
Total	81	17	46	144

Table 5.3. Results of univariable analyses between farm dry cow therapy (DCT) strategies (selective versus blanket), farm characteristics and DHI data with blanket DCT as the outcome variable (n = 140).

			P-value	
	Odds Ratio	95% CI[a]	Category	Variable
Lactational geometric SCC[b] (cells/mL)[c]	1.00	0.99 – 1.01	-	0.93
Geometric SCC first 30 DIM[d] (cells/mL)[c]	0.99	0.98 – 1.01	-	0.99
No. milking cows (per 100 cows)	1.11	0.77 – 1.59	-	0.58
24-h milk yield (kg)				0.19
≤30	Ref			
30 – 35	3.87	1.05 – 14.28	0.04	
35 – 40	1.87	0.55 – 6.33	0.32	
>40	1.93	0.57 – 6.54	0.29	
305-d lactational milk yield (kg)				0.24
≤10,000	Ref			
10,000 – 11,000	2.35	0.79 – 6.98	0.13	
11,000 – 12,000	0.86	0.30 – 2.50	0.79	
>12,000	1.53	0.57 – 4.08	0.40	
Province				0.88
British Columbia	Ref			
Alberta	1.22	0.42 – 3.55	0.71	
Ontario	1.22	0.42 – 3.55	0.71	
Québec	1.83	0.59 – 5.72	0.30	
Nova Scotia	1.22	0.43 – 5.72	0.57	
Milking system[e]				0.34
Parlour	Ref			
Pipeline	1.52	0.63 – 3.70	0.35	
Automated milking	0.73	0.30 – 1.76	0.49	

[a] CI = confidence interval
[b] SCC = somatic cell count
[c] N = 125
[d] DIM = days in milk
[e] N = 137

Table 5.4. Results of univariable linear regression analyses between the outcome of antimicrobial coverage (i.e., proportion of cows per herd receiving intramammary antimicrobials at drying off) and farm characteristics, DHI data and on selective DCT farms (n = 45).

			P-value	
	Coefficient	95% CI[a]	Category	Variable
Lactational geometric SCC[b] (cells/mL)[c]	0.09	-0.32 – 0.51	-	0.65
Geometric SCC first 30 DIM[d] (cells/mL)[c]	-0.11	-0.45 – 0.24	-	0.54
No. milking cows (per 100 cows)	-4.78	-14.35 – 4.78	-	0.32
24-h milk yield (kg)[b]				0.16
≤35	Ref			
35 – 40	-15.21	-39.78 – 9.36	0.22	
>40	3.93	-20.64 – 28.49	0.75	
305-d lactational milk yield (kg)				0.73
≤10,000	Ref			
10,000 – 11,000	7.97	-19.74 – 35.68	0.57	
11,000 – 12,000	2.34	-22.55 – 27.23	0.85	
>12,000	12.31	-11.72 – 36.33	0.31	
Province				0.35
British Columbia	Ref			
Alberta	10.68	-14.72 – 36.08	0.40	
Ontario	18.38	-7.02 – 43.78	0.85	
Québec	-6.96	-35.07 – 43.78	0.15	
Nova Scotia	-2.68	-30.78 – 25.43	0.62	
Milking system[e]				0.10
Parlour	Ref			
Pipeline	15.55	-6.63 – 37.73	0.16	
Automated milking	20.85	0.45 – 41.25	0.05	

[a] CI = confidence interval
[b] SCC = somatic cell count
[c] N = 42
[d] DIM = days in milk
[e] N = 43

Table 5.5. Results of univariable analyses between farm teat sealant (TS) use strategies (TS use versus no use), farm characteristics and DHI data with TS use as the outcome variable (n = 144).

			P-value	
	Odds Ratio	95% CI[a]	Category	Variable
Lactational geometric SCC[b] (cells/mL)[c]	0.98	0.96 – 1.00	-	0.11
Geometric SCC first 30 DIM[d] (cells/mL)[c]	0.98	0.97 – 1.00	-	0.08
No. milking cows (per 100 cows)	1.85	1.15 – 2.95	-	0.004
24-h milk yield (kg)				0.33
≤30	Ref			
30 – 35	1.62	0.49 – 5.42	0.43	
35 – 40	3.0	0.86 – 10.23	0.08	
>40	1.75	0.53 – 5.74	0.36	
305-d lactational milk yield (kg)				0.94
≤10,000	Ref			
10,000 – 11,000	1.34	0.47 – 3.77	0.58	
11,000 – 12,000	1.11	0.36 – 3.35	0.85	
>12,000	1.05	0.39 – 2.78	0.92	
Province				0.14
British Columbia	Ref			
Alberta	2.04	0.71 – 5.89	0.19	
Ontario	4.55	1.37 – 15.05	0.01	
Québec	1.66	0.58 – 4.75	0.34	
Nova Scotia	1.75	0.58 – 5.32	0.32	
Milking system[e]				0.32
Parlour	Ref			
Pipeline	0.59	0.26 – 1.38	0.23	
Automated milking	0.55	0.23 – 1.35	0.19	

[a] CI = confidence interval
[b] SCC = somatic cell count
[c] N = 128
[d] DIM = days in milk
[e] N = 141

Table 5.6. Results of univariable analyses between farm teat sealant (TS) use type (blanket versus selective), farm characteristics and DHI data with blanket TS use as the outcome variable (n = 98).

			P-value	
	Odds Ratio	95% CI[a]	Category	Variable
Lactational geometric SCC[b] (cells/mL)[c]	0.99	0.96 – 1.01	-	0.41
Geometric SCC first 30 DIM[d] (cells/mL)[c]	0.99	0.96 – 1.02	-	0.65
No. milking cows (per 100 cows)	1.31	0.74 – 2.32	-	0.34
24-h milk yield (kg)				0.78
≤30	Ref			
30 – 35	0.48	0.48 – 4.68	0.52	
35 – 40	0.67	0.07 – 6.47	0.73	
>40	0.93	0.09 – 9.67	0.95	
305-d lactational milk yield (kg)				0.47
≤10,000	Ref			
10,000 – 11,000	0.43	0.08 – 2.41	0.34	
11,000 – 12,000	0.33	0.06 – 1.96	0.22	
>12,000	0.82	0.14 – 4.99	0.83	
Province				0.46
British Columbia	Ref			
Alberta	0.21	0.22 – 2.04	0.18	
Ontario	0.37	0.04 – 3.61	0.39	
Québec	0.19	0.02 – 1.80	0.15	
Nova Scotia	0.47	0.04 – 5.73	0.55	
Milking system[e]				0.05
Parlour	Ref			
Pipeline	0.43	0.11 – 1.75	0.24	
Automated milking	0.19	0.05 – 0.73	0.02	

[a] CI = confidence interval

[b] SCC = somatic cell count

[c] N = 86

[d] DIM = days in milk

[e] N = 96

Table 5.7. Results of univariable linear regression analyses between teat sealant (TS) coverage (i.e., proportion of cows per herd receiving TS at drying off) and farm characteristics, DHI data and on selective TS use farms (n = 17).

			P-value	
	Coefficient	95% CI[a]	Category	Variable
Lactational geometric SCC[b] (cells/mL)[c]	0.55	-0.62 – 1.72	-	0.33
Geometric SCC first 30 DIM[d] (cells/mL)[c]	0.22	-0.78 – 1.23	-	0.64
No. milking cows (per 100 cows)	16.14	-1.86 – 34.13	-	0.08
24-h milk yield (kg)[e]				0.79
≤35	Ref			
35 – 40	15.67	-32.56 – 62.89	0.50	
>40	7.5	-45.86 – 60.85	0.77	
305-d lactational milk yield (kg)[e]				0.22
≤11,000	Ref			
>11,000	21.5	-14.52 – 57.52	0.22	
Province[e]				0.002
East	Ref			
West	49.64	20.97 – 78.31	0.002	
Milking system[c]				0.23
Parlour	Ref			
Pipeline	-36.25	-68.14 – 13.64	0.14	
Automated milking	-3.82	-50.44 – 42.80	0.86	

[a] CI = confidence interval

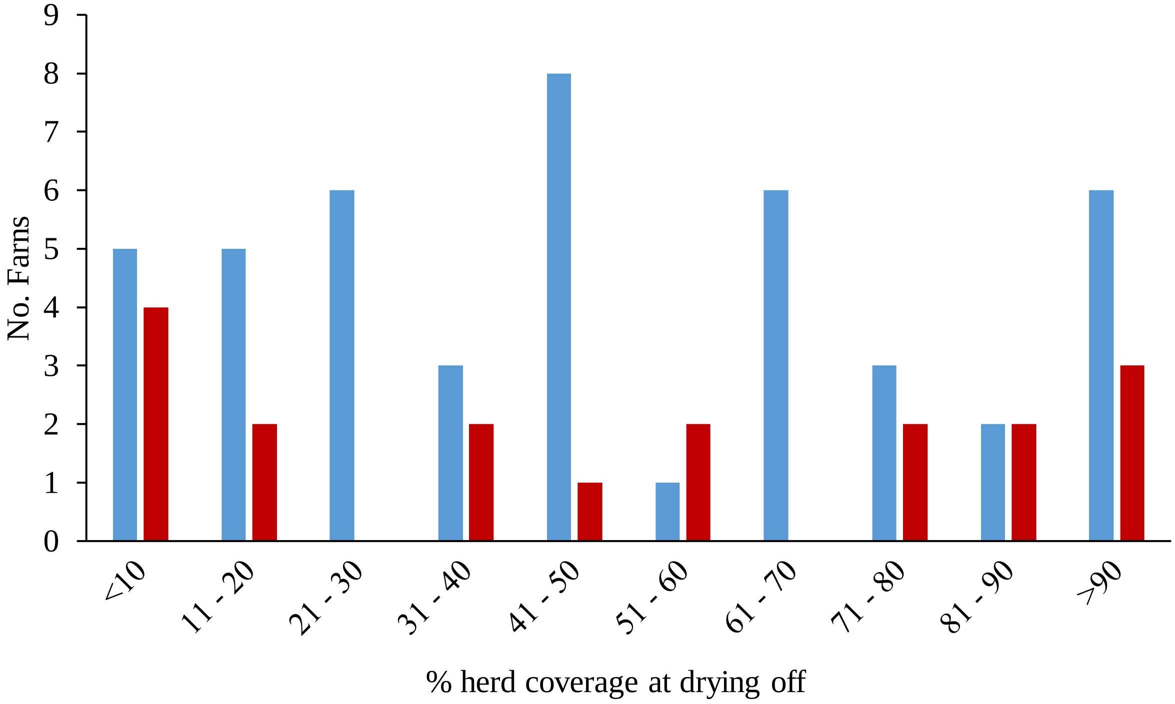
[b] SCC = somatic cell count

[c] N = 16

[d] DIM = days in milk

[e] Categories had to be condensed due to low sample size

Figure 5.1. Percentage of the herd treated intramammarily with antimicrobials (blue, n = 45) or teat sealants (red, n = 17) at drying off among farms reporting enacting selection criteria in their antimicrobial or teat sealant decision-making.



CHAPTER 6: Summarizing Discussion

Regardless of the development and uptake of certain antimicrobial resistance (AMR) mitigation efforts, development and spread of AMR is ongoing. Described gaps in the understanding of AMR in Canada and barriers of antimicrobial stewardship (AMS) emphasize the substantial improvement required before AMR mitigation can be refocused on maintenance of antimicrobial susceptibility rather than reacting to the ongoing silent pandemic threatening human and animal health worldwide. Preserving antimicrobial susceptibility represents an ongoing battle requiring a coordinated and sustained response to maintain the ability to use antimicrobials in all sectors (United Nations Environmental Programme [UNEP], 2023). Further, there is a great deal left to understand in terms of the broader ecosystem and species connections that influence AMU and AMR.

6.1. Antimicrobial Classifications for Stewardship

Programs to support AMS should have a dual focus of optimizing infection treatment and prevention, as well as risk avoidance and providing individual patients with the best outcome, but also reducing impacts of AMR in the future (Garraghan, 2022). Some resources exist to support AMS efforts, both globally and within Canada (World Health Organization [WHO], 2015; HealthCareCAN, 2016). As described, Canadian AMS resources include antimicrobial prescribing support, AMU reduction initiatives, the Pan-Canadian AMR Framework for Action, as well as supportive AMU/AMR surveillance efforts and infection prevention and control initiatives (HealthCareCAN, 2016; Public Health Agency of Canada [PHAC], 2017; Roy et al., 2020; Chicken Farmers of Canada, 2021; PHAC, 2021; Choosing Wisely Canada, 2023).

However, as stated in Chapter 3, according to Canadian stakeholders across various professions, available support is insufficient and substantial barriers to AMS still exist.

Due to the global importance of AMR, the WHO developed the ‘Global Action Plan on Antimicrobial Resistance’ (WHO, 2015). In this Action Plan, AMS is highlighted as one of the 5 steps of AMR mitigation “to optimize the use of antimicrobial medicines in human and animal health” (WHO, 2015). To provide a basis for AMS considerations, the WHO has classified antimicrobials into groups based on their relative importance for future human treatment, as well as their potential to contribute to AMR development, called AWaRe (WHO, 2019). Classifications are described as follows (WHO, 2019):

- **Access**: First and second choice antimicrobials for the empiric treatment of most common infections that should be easily accessible.
- **Watch**: Antimicrobials with higher potential for developing resistance whose use as first and second choice treatment should be limited to a small number of syndromes or patient groups.
- **Reserve**: Antimicrobials used mainly as last resort treatment options, and reserved for use only when alternatives would be inadequate or have already failed.
- **Discouraged antimicrobials**: Mostly includes antimicrobial combinations that do not have reasonable indications for use, and the potential to negatively impact AMR and patient safety.

These classifications provide clear recommendations for antimicrobial prescribing practices where global adherence could contribute to preservation of effective antimicrobial options for future use (WHO, 2019). However, as global antimicrobial consumption for both human (defined daily doses) and livestock (measure by weight) are on to the rise (Klein et al., 2018; Tiseo et al., 2020; Browne et al., 2021), there is still much to be done in the AMS realm to increase AMS efforts and preserve antimicrobial effectiveness.

In addition, Canada also has antimicrobial classifications pertaining to AMU in both humans and animals prioritizing preservation of antimicrobials for human medicine (Government of Canada, 2009):

- **Category I** (Very High Importance): Essential for treating serious human infections and no, or limited availability of alternatives.
- **Category II** (High Importance): Can be used for treating serious human infections, but some alternatives from lower classes exist.
- **Category III** (Medium Importance): Not the preferred option for treating serious human infections, and some alternative options exist.
- **Category IV** (Low Importance): Antimicrobials in this class are not used in human medicine.

Clearly, prescribing classification development does not mean that they will be used in all contexts or consistently adhered to; however, they are a required component of change management, but alone cannot be expected to achieve substantial AMS improvement. Further, the focus of described classifications on reserving antimicrobials for human infections highlights the species hierarchy in AMS considerations.

6.2. Species Hierarchy in Antimicrobial Stewardship

The majority of AMS and AMR discussions are human-centric, leaving animal welfare and our ethical responsibilities to animals in the livestock industries as a subtopic in the conversation. Although there is inclusion of animal health, the primary objective is maintaining agricultural production systems and maintaining food security while preserving antimicrobial effectiveness for human infections (Government of Canada, 2009; WHO, 2019). Further, many highly classified antimicrobials are already restricted from use in livestock (Chicken Farmers of Canada, 2021) or limited to prescription-only access (PHAC, 2021), whereas EU regulations go as far as eliminating preventative AMU for livestock, other than in exceptional cases (Official Journal of the European Union, 2019). Although regulatory AMU limitations can be an important part of AMS, the focus on limiting animal AMU to benefit human health, highlights discrepancies of value placed on other-than-human species.

There is an ‘othering’ brought into AMS discussions and regulations of ensuring antimicrobial availability for humans at the expense of other species (Connolly, 1985), where AMS definitions are influenced by species hierarchy, rather than One Health considerations. This species hierarchy also encompasses the blame commonly placed on livestock industries for excessive AMU (McCubbin et al., 2021a), contributing to the perception that livestock industries are to blame for AMR, rather than responsibility being placed on all sectors. Whereas the skepticism regarding the extent that AMR in livestock or companion animals contributes to AMR in humans (Etienne et al., 2017; Golding et al., 2019) further separates the sectors, limiting the One Health understanding on AMR and required mitigation efforts.

For essential AMS progress to be made, animal AMU and prescribing practices must be considered on par with the human sector regarding both their importance for possible AMU reduction, but also maintaining the ability to use antimicrobials appropriately when needed. The moral responsibility to treat and protect livestock animals under their care was described by veterinary sector questionnaire respondents (Chapter 3) as an important role in their profession, along with safeguarding antimicrobials for both human and animal use in the future. There are concerns regarding placing strict limitations on AMU and potential impacts on animal welfare without the ability to readily treat bacterial infections.

Therefore, any regulations limiting AMU in any sector must be accompanied by research into unintended consequences of withholding antimicrobials, as was done for selective dry cow therapy and other selective treatment practice research (McCubbin et al., 2022; de Jong et al., 2022). Additionally, proposed animal AMU reductions must be considered with accompanying structural and industry improvements needed to compensate for the lack of medicated infection control to limit unintended consequences. Even though the economic costs of some improvements could be substantial, the potential animal health and welfare impacts felt by reducing AMU without addressing some of those structural barriers identified in Chapter 3 enforces the responsibility to act, further ensuring production system safety and sustainability.

Additionally, animal AMS must be considered on par with human AMS discussions as antimicrobials are not always used or administered to the intended species. Specifically, cross-over use of antimicrobials has been documented, where antimicrobials intended for human use are provided to animals, as well as the reverse, further complicating the understanding of local drivers of AMR (McCubbin et al., 2021b), particularly in low-and-middle-income country settings (McCubbin et al., 2021b; Myers et al., 2022). However, species cross-over AMU is also reported in the United States, where people have reported taking their pet’s unfinished prescriptions (Zoorob et al., 2016), or acquiring over-the-counter fish antimicrobials for personal use (Zhang et al., 2020).

Improvements in systemic AMS barriers could allow for the required production system changes to improve animal health and welfare as well as long-term production sustainability. Additionally, acceptance of the individual value of other species outside of their role in production systems can provide a progressive baseline of ethical considerations for future discourses in AMR, and other issues of global health security. Increased acceptance of other-than-human importance could also extend to the environment, as environmental bacterial communities are impacted by human action (UNEP, 2023).

6.3. Environmental Importance in AMR

Traditionally, environmental considerations have been excluded from AMR discussions, despite substantial evidence supporting the key role of the environment in development, transmission, and spread of AMR (McCubbin et al., 2021a; UNEP, 2023). With increasing antimicrobial and genetic pollution and a lack of pollution source management, coupled with AMR in various clinical and agriculture contexts, environmental AMR risks are increasing (UNEP, 2023).

Environmental considerations in AMR in the AMR Pan-Canadian Framework for Action (2017) are currently lacking. Although the vision for the Framework is “The health of humans, animals and the environment is protected through comprehensive and coordinated action to conserve the effectiveness of antimicrobials now and into the future,” it is also stated that the Framework will first focus on human and animal AMR aspects, before incorporating the environmental aspect to reflect the One Health approach (PHAC, 2017). However, the environmental aspect must be regarded as integral to overall success.

The role of the environment in AMR development and maintenance is complex, and impacts from human and animal AMU are substantial (UNEP, 2023). Antimicrobial residues represent an important area for consideration in overall AMR mitigation. The concentration of antimicrobials excreted unmetabolized from AMU in both humans and animals varies greatly, and is influenced by drug class, formulation, route of administration, animal species, and health status (Prescott and Dowling, 2013; UNEP, 2023). Therefore, due the variety of ways that antimicrobials and genetic pollution enter the environment, and the complicated interplay among these compounds and environmental bacteria, environmental considerations must be included in AMS goals. Environmental contamination with antimicrobials can also occur when unused or expired products are not disposed of properly (Nepal et al., 2020).

Water is considered an important reservoir of resistant pathogens and genes, and an essential area for focus to limit environmental contamination (Vivid Economics, 2020; UNEP, 2023). In a technical report for the World Economic Forum assessing antimicrobial water pollution globally, on a pollution score scale from 0 – 100, Canada was in the 13 – 20 group (Vivid Economics, 2020). Although this score is better than some countries (e.g., USA and New Zealand), Canada received a higher pollution score than some European and South American countries, highlighting that improvement in environmental pollution contributing to AMR development and maintenance in the environment is possible (Vivid Economics, 2020).

Environmental inclusion in AMS efforts can take many forms, with a focus on prevention and reduction of environmental antimicrobial and genetic pollution, including governance and regulatory frameworks limiting contamination at major pollution points (i.e., pharmaceutical manufacturing plants, healthcare facilities, livestock industries, and crop production) (Vivid Economics, 2020; UNEP, 2023).

Comprehensive strengthening of environmental consideration in AMS will not only reduce the burden of AMR, but also limit environmental contamination and contributions to the ‘resistome’ (Forsberg et al., 2012; UNEP, 2023). Further, environmental AMS considerations should be strengthened in the Pan-Canadian Framework for Action (2017) and included in other national documentation outlining climate change planning and other environmental impact activities with impacts on AMR (Vivid Economics, 2020). For example, there should be research to support best practices in agricultural industries outlining manure spreading and irrigation of crops to limit AMR and genetic pollution, as these are known environmental contaminants (UNEP, 2023).

Prevention and reduction of environmental contamination are key components to overall AMR mitigation, but they should be supported by surveillance efforts to provide a baseline and continued monitoring to measure success, as well as infection prevention and control measures to further limit contributions to contamination sources. Environmental surveillance efforts should be initiated that focus on main identified sources of pollution, including waste and effluent and from healthcare facilities, pharmaceutical manufacturing plants, as well as livestock and other agricultural industries (UNEP, 2023), to increase our understanding of environmental AMR and further identify strategic areas for intervention.

6.4. One Microbiome, One Health

There has been increasing acceptance of the important role of the microbiome in health of humans and animals. Benezra et al. (2012) described the term “supraorganism” as the acceptance of us as being both composed of human cells as well as microbes, while acknowledging the microbial components far outnumber the human components. With growing support for the interconnectedness of the human microbiome with that of other species and the environment (Forsberg, et al., 2012; Wall et al., 2016; Leonard et al., 2017; Morar and Skorburg, 2018; McCubbin et al., 2021a), we must expand our understanding of self. If our microbiome can change readily through interactions with each other, other species, and the environment, this could challenge our understanding of what it means to be human. For example, Leonard et al. (2017) described that people spending more time in the coastal waters of the UK have effectively altered their microbiome to have more resistant *Escherichia coli* as part of their gastrointestinal microbial community. In this instance, if we accept the microbiome as part of us, the environment has altered their microbial composition. Through these microbiome interactions, even as one species, our health is influenced by the health of many others, further illustrating the multi-species and multi-sectoral ramifications of AMR.

The described external microbial influence could have implications to definitions of what constitutes ‘public’ in public health. Therefore, even if society is not ready to accept other species as the ‘public’ in public health, we must acknowledge the interplay among humans, animals, and the environment for any sustainable impacts to be made. By challenging the hierarchical species view initiated by early anthropologists like Lewis Henry Morgan (1877), that allows for placing human values and needs above all else, One Health provides a framework to bridge the gap between human and non-human health to shift the human-centric focus permeating the current dialogue.

6.5. AMS Change Management

There are many requirements to improve AMS overall and move towards optimal use of antimicrobial resources that range from small changes (e.g., improving public understanding of what antimicrobials are effective to treat), to larger pharmaceutical or production industry changes to decrease reliance on AMU. Therefore, further social science integration in AMR research is required to guide future research questions and discussions of existing barriers to stewardship, as well as identify and enact relevant and actionable changes for implementation.

However, there are also potential threats to AMS efforts that could either impede changes being implemented or hamper the amount of AMU reduction possible. Limited stakeholder buy-in to drive change in prescribing practices is one such challenge (Chapter 3), identified as a barrier to AMS by Canadian professionals. Further, harm reduction or risk management practices that balance the need for immediate antimicrobial treatment and the need to limit AMU, are difficult for prescribers to implement. For example, issues related to short-term adverse effects (e.g., concern for human or animal health and welfare implications without preventative AMU) may deter some sectors or prescribers from implementing stewardship guidelines (Black et al., 2019; Golding et al., 2019). There may also not be sufficient bandwidth and/or appropriate existing infrastructure to support improvement in AMS practices. Therefore, behaviour change approaches that influence prescriber and user perceptions must be considered an integral part of AMS.

There are various change management models that could provide guidance to reducing AMU, depending on the context. These models have various components but can be summarized as three phases (Errida and Lotfi, 2021). The three phases, considered the foundation for planned change management, are described by Lewin et al. (1947) as: 1) unfreezing, 2) transition, and 3) refreezing. Unfreezing represents a time where the status quo is challenged, requirement for change is emphasised, and action is taken to prepare for change. Transition involves progressing towards the required change, whereas refreezing represents the final step and takes place after implementation of the decided change, resulting in new norms, behaviors, and practices (Lewin et al., 1947; Errida and Lotfi, 2021).

Various behaviour change models can be employed in the transition phase (Oldenburg et al., 1999; Schwarzer, 2008; Errida and Lotfi, 2021). However, the specific behaviour change model used can depend on the context and motivations for change, structural limitations, social norms, among other differences. It could also be helpful to contextualize contributions of the actions of individuals to combat the blame and disconnect between sectors depicted in Chapter 3. This contextualization can be achieved using a systems approach aimed to break down components of a system, e.g., multifactorial development and maintenance of AMR, and illustrate how actions in one area impact the system as a whole (Centers for Disease Control and Prevention, 2021).

Some common characteristics of successful changes identified by stakeholders in a human healthcare setting were: 1) the opportunity to influence change, 2) being prepared for change, and 3) valuing the change (Nilsen et al., 2020). In contrast, supporting successful change in livestock industries has the additional requirement of maintaining financial success for producers (Poizat et al., 2017; Speksnijder and Wagenaar, 2018). However, which behaviour change practices are best to implement could vary greatly depending on the context, who is implementing the change, existing infrastructure, structural limitations, etc.

Having clear objectives and actions that can be easily implemented is important to ensure that AMS is prioritized (Garraghan, 2022). It can also be helpful to have measures of success in place to evaluate the implemented change, and potentially identify areas for improvement. Antimicrobial prescribing could be evaluated by an audit and feedback system to measure improvement in AMS practices (HealthCareCAN, 2016; Black et al., 2019). Although targets based on antimicrobial distribution may be easier to quantify, as in the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) system, they may not be the best measures of success. Reasons for use are not always captured nor is information about whether antimicrobials were used as intended (Otto et al., 2020; PHAC, 2022).

Besides quantification of antimicrobial prescribing and dispensing, additional AMS improvement measures of success could include: increased awareness of AMS guidelines, a decrease in perceived AMS barriers, or increased investment in AMS. Core elements of institutional AMS programs include leadership and accountability (Centers for Disease Control and Prevention, 2019; Garraghan, 2022). Unfortunately, limited AMS guidance and a lack of accountability were highlighted by Canadian professionals as impeding AMS (Chapter 3). In addition to being supported by research to identify AMS best practices, AMS champions need to lead and communicate effectively, cultivate relationships with key stakeholders, and increase the desire to drive change (Garraghan, 2022). Increasing communication and accountability between stakeholders at different governance levels and the individual prescriber level could contribute to diminishing the feeling of lack of consequences described by questionnaire participants as a barrier to improving AMS (Golding et al., 2019; Garraghan, 2022).

Reducing preventative AMU is often an important focus of livestock-associated AMS initiatives (Official Journal of the European Union, 2019; Santman-Berends, 2021). Regulations prohibiting preventative veterinary AMU do not exist in Canada. Regardless, increasing SDCT uptake represents one aspect of stewardship for immediate action that could reduce livestock-associated preventative AMU in Canada. Reducing indiscriminate AMU is part of diversifying focus within stewardship goals, and literature suggests the SDCT can be adopted on most farms without significant milk production or udder health impacts (Santman-Berends et al., 2021; McCubbin et al., 2022).

Although blanket dry cow therapy (DCT) has decreased in Canada in recent years, uptake of SDCT and specific practices have only recently been described (McCubbin et al., 2023). To explore further drivers and barriers of SDCT, qualitative research in the form of focus group discussions could serve to further identify producer and veterinary perspectives regarding SDCT or other selective use practices to identify areas of opportunity to increase uptake. Further, repeating the questionnaires included in Appendix II in a few years could identify ongoing changes in SDCT uptake and selection protocols. Measures of success for SDCT could include the proportion of Canadian dairy producers reporting that they implemented SDCT or reported antimicrobial herd coverage at drying off.

6.6. Operationalizing One Health in AMR

Implementation and operationalization of One Health in AMR comes with various challenges (Solomon, 2017). These challenges and subsequent delays in entrenching One Health as a foundation of AMR mitigation, increase the risk of failing to achieve both short- and long-term goals (Solomon, 2017). Some examples of challenges to One Health implementation include silos within governments, public health agencies, and academic institutions, as well as the lack of Canadian investment in AMR and fragmentation of existing AMS efforts (Lee et al., 2013; Rubin et al., 2014; Manlove et al., 2016; Solomon, 2017; Otto et al., 2020; Rogers Van Katwyk et al., 2020). However, AMR endangers the sustainability of the Canadian healthcare and agricultural production systems and requires substantial attention and investment (Rogers Van Katwyk et al., 2020; McCubbin et al., 2021). Overcoming challenges to operationalizing One Health requires breaking down bureaucratic and institutional silos as well as facilitating One Health collaboration by creating support structures to encourage communication across sectors and professions (Solomon, 2017).

Unfortunately, an environmental scan regarding AMR policies in Canada from 2008-2018 (Rogers Van Katwyk et al., 2020) suggested that Canadian AMR efforts have been relatively small and disjointed. Further, Canadian governments have primarily abstained from employing policy tools like regulation, legislation, and economic measures, and the lack of provincial or territorial action or action plans highlight the need for increased government coordination and collaboration (Rogers Van Katwyk et al., 2020).

Education is currently the leading strategy for AMR mitigation in Canada, aiming to reduce inappropriate AMU by increasing prescriber and end-user knowledge (Rogers Van Katwyk et al., 2019, 2020). However, there is limited evidence that long-term AMU reduction can be accomplished through public awareness campaigns alone (Cross et al., 2016; Price et al., 2018; Rogers Van Katwyk et al., 2020; Satterfield et al., 2020). Education is an important component of AMR mitigation and AMS specifically; however, it should be coupled with other context-specific initiatives supporting behaviour change (Satterfield et al., 2020). Portraying AMR as individual prescriber and end-user issue has led to the focus on education (Rogers Van Katwyk et al., 2020), but as highlighted as an AMS barrier, systemic barriers to AMS exist across health sectors that need to be addressed before substantial progress can be made. Questionnaire participants were aware of the threat of AMR, but their AMS efforts were impeded by various structural or industry limitations, further illustrating that education alone is not the key to improving AMS.

Further, as environmental considerations of AMR are complex and multifaceted, action is required at local, provincial, and national levels, and with various stakeholders (UNEP, 2023). As environmental-focused AMR programs do not currently exist in Canada (Rogers Van Katwyk et al., 2020), a legal and regulatory framework is required to address drivers of environmental AMR (UNEP, 2023). This requires inclusion of environmental concerns and action in the next Pan-Canadian AMR Framework and other related documentation limiting effluent discharge from pharmaceutical industries and hospitals, improving integrated water management, regulating manure spreading of crops to limit environmental contamination with resistant pathogens or genes, improving environmental AMR surveillance, etc. (UNEP, 2023).

Moving forward, AMR mitigation efforts must include regulatory, legislative, and economic measures (Rogers Van Katwyk et al., 2020). In addition to increased investments and coordination, political support for policy interventions that include rigorous evaluation plans is required to collectively address AMR (Rogers Van Katwyk et al., 2020).

6.7. Conclusions

Overall, this thesis describes important Canadian AMR and AMS considerations including discussion regarding requirements for improvements to be made, with a specific example of an AMS opportunity in the Canadian dairy industry. Efforts to improve AMS and overall AMR mitigation are critical to preserving society’s ability to treat infections in all sectors, maintain food security, global health security, protect the environment, and make progress towards the Sustainable Development Goals (Wall et al., 2016; UNEP, 2023). By using a One Health approach in AMS, we may be able to put aside some of our biases as a species and consider a larger picture, while challenging the human-centric dialogue that has permeated throughout the health sector. By confronting health system norms, new ideas and perceptions can be incorporated in the discussion, with potential to initiate required changes for meaningful progress to occur.

A great deal of knowledge and action are required to optimize AMU in human, animal, and environmental sectors. However, with a focus on AMS and supporting activities such as infection prevention and control as well as surveillance, while considering drivers and barriers of adopting new practices across Canadian professions, shared goals can be developed to foster collaboration and communication across sectors.

Fortunately, there are areas of AMS that can be acted on immediately with appropriate resources and action, such as improving uptake of SDCT in the Canadian dairy industry. With equitable value placed on antimicrobial susceptibility in all sectors, and a coordinated One Health response, AMS can progress past prescribing and AMU goals, towards being entrenched in society as an expectation, rather than a goal.

6.8. References

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APPENDIX

Appendix I. Questionnaire regarding antimicrobial stewardship perceptions, drivers and barriers, conducted in Qualtrics and followed full informed consent process.

Demographics *Check all that apply*
Please indicate your professional field:

Student	MSc PhD DVM MD Nursing Pharmacy Other: _______	Veterinary Medicine Public Health Medicine Community Health Animal Science Wildlife Other: ______________
Post-Doc	Veterinary Medicine Public Health Medicine Community Health Animal Science Wildlife Other: ______________	
Academic/researcher	Veterinary Medicine Public Health Medicine Epidemiology Microbiology Community Health Animal Science Wildlife Other: ______________	
Veterinary clinician	Practice owner Associate Referral hospital Emergency Shelter Government Locum Specialty clinic Laboratory	Companion animal Beef cattle Dairy cattle Equine Swine Poultry Wildlife Aquaculture Specialist: ___________ Other: ______________

Producer	Dairy Beef Swine Poultry Aquaculture Other: ___________	
Pharmacist		
Producer Organization	Specify: _________	
Industry	Pharmaceuticals Animal nutrition Other: ____________	
Government	County	Specify: ________
	Provincial Alberta British Columbia Manitoba New Brunswick Newfoundland Northwest Territories Nova Scotia Nunavut Ontario Prince Edward Island Quebec Saskatchewan Yukon	Specify: ______________
	National	Public Health Agency Canada Agriculture and Agri-Food Canada Canadian Animal Health Institute Canadian Food Inspection Agency Canadian Institutes of Health Research Health Canada NSERC Other: ____________

International	World Health Organization Food and Agriculture Organization of the United Nations World Organization of Animal Health Other: __________	
Non-Governmental Organization	Country/Province:	Specify: _________
Other: ___________		

Please indicate the country in which you work: ________________

How many years of experience do you have in your indicated field? _______________________

What does ‘antimicrobial stewardship’ mean to your profession as a whole?

What does antimicrobial stewardship mean to you in your profession?

Statements

	Strongly disagree	**Disagree**	**Neutral**	**Agree**	**Strongly agree**
My profession is actively engaged in promoting antimicrobial stewardship.					
Antimicrobial stewardship is viewed as an important consideration by my colleagues.					
I have adequate support/resources to ensure antimicrobial stewardship in my work.					

Antimicrobial stewardship is important in mitigating the threat of antimicrobial resistance					
I believe there is more I could do personally to improve antimicrobial stewardship in my profession.					
Antimicrobial stewardship in livestock is important for human health.					
Antimicrobial stewardship in humans is important for livestock health.					

Open ended

Do you believe there are barriers in improving antimicrobial stewardship in your profession?

Yes
No

What is preventing antimicrobial stewardship improvement in your profession? (if yes above)

Do you believe there is support in place to promote/encourage antimicrobial stewardship in your profession?

Yes
No

What is currently in place that helps promote antimicrobial stewardship in your profession? (if yes above)

Who should take responsibility in promoting antimicrobial stewardship?

Appendix II. Questionnaire 1. Canadian Dairy Network for Antimicrobial Stewardship and Resistance dry cow therapy and clinical mastitis questionnaire conducted in the 2019 field season.

Herd ID ____________
Date: ______________

DRY COW THERAPY

1. Do all cattle receive teat sealant at dry off?
○ Yes
○ No

2. Do all cattle receive intramammary antibiotics at dry off?
○ Yes (→ Q9)
○ No

3. Do you use SCC to select cattle to treat with antimicrobials at dry off?
○ Yes
○ No (→ Q6)

4. Which SCC record do you use?
○ Last record
○ Last two records
○ Last three records
○ SCC of the past __ months
○ Other: _____________

5. What SCC cut off do you use?
○ 150,000
○ 175,000
○ 200,000
○ 250,000
○ 300,000
○ Other: ______

6. Do you use previous mastitis history to select cattle to treat with antimicrobials at dry off?

- ○ Yes
- ○ No (→ Q8)

7. What mastitis history specifically?

- ○ Timepoint of previous clinical mastitis case
    - ○ Current lactation
    - ○ Past month
    - ○ Past two months
    - ○ Past three months
    - ○ Other: ________
- ○ Number of mastitis events
    - ○ More than ___ events in the same month
    - ○ More than ___ events in the same lactation
    - ○ More than ___ events in the previous lactation
    - ○ Other: ________
- ○ Suspected pathogen
- ○ Confirmed pathogen
- ○ Other: _____

8. Do you use additional criteria to select cattle for antimicrobial dry cow therapy?

- ○ Yes: __________________________
- ○ No

TREATMENT OF CLINICAL MASTITIS

9. Are all clinical mastitis cases treated with antimicrobials?

- ○ Yes (→ Q13)
- ○ No

10. Do you use clinical mastitis case history to select cows to treat with antimicrobials?

- ○ Yes
- ○ No (→ Q12)

11. What mastitis history specifically?

- ○ Timepoint of previous clinical mastitis case
    - ○ Current lactation
    - ○ Past month

    - ○ Past two months
    - ○ Past three months
    - ○ Other: ________
- ○ Number of mastitis events
    - ○ More than ___ events in the same month
    - ○ More than ___ events in the same lactation
    - ○ More than ___ events in the previous lactation
    - ○ Other: ________
- ○ Suspected pathogen
- ○ Confirmed pathogen
- ○ Other: _____

12. How important are these factors when deciding whether to treat a cow with mastitis with antibiotics? (Rank from 1 to 5, 1 being a very important factor and 5 being a factor that is not important)

a) Production, age, and genetics of the cow.................1 2 3 4 5
b) Severity of the symptoms 1 2 3 4 5
c) High SCC...1 2 3 4 5
what cut-off do you use? __________
d) Mastitis history 1 2 3 4 5
e) Confirmed or suspected pathogen…………...........1 2 3 4 5
f) Need for milk to fill quota..1 2 3 4 5
g) Cull cow price, price to buy a new milking cow 1 2 3 4 5
h) Protocol established with my veterinarian...............1 2 3 4 5
1) Other (Please specify): 1 2 3 4 5

13. Of the clinical mastitis cases receive antimicrobials, what proportion are receiving intramammary and/or injectable products?

____ % intramammary only

____ % injectable only

____ % intramammary and injectable

Appendix II. Questionnaire 2. Canadian Dairy Network for Antimicrobial Stewardship and Resistance dry cow therapy and clinical mastitis follow-up questionnaire conducted in the 2020 field season.

Herd ID: ____________
Date: ______________

DRY COW THERAPY

-- *This question should be asked to all farmers* --

1. **How many clinical mastitis cases did you have during the last twelve months?**
   ____

2. **Did anything in your dry cow therapy protocol or mastitis treatment protocol changed from last year?**
   ○ Yes → re-do DCT/CMT questionnaire
   ○ No

DRY COW THERAPY

-- *This question should be asked to all farmers* --

3. **How often does Lactanet test the milk samples?**
   ○ Monthly
   ○ Every two months
   ○ Every three months
   ○ Other: _____________

4. **How often does Lactanet test the milk samples for SCC?**
   ○ Monthly
   ○ Every two months
   ○ Every three months
   ○ Other: _____________

TEAT SEALANT

-- *These questions should be asked to all farmers* --

5. **Which proportion of cows receive the following at dry off, on average:** (should add up to 100%)

Teat sealant only: _____ %
Antibiotics only: _____ %

Teat sealant + antibiotics: _____ %
Nothing: _____ %

6. Do you use individual cow SCC history to select cattle who receive teat sealer at dry off?

○ Yes
○ No (→ Q9)

7. What SCC cut off do you use to select cows who receive teat sealer?

○ 150,000
○ 200,000
○ 250,000
○ 300,000
○ Other: ______

8. Which SCC record do you use to select cows who receive teat sealer?

○ Last record
○ Last two records
○ Last three records
○ SCC of the past ___ months
○ Other: _____________

9. Do you consider previous clinical mastitis cases to select cows who receive teat sealer at dry off?

○ Yes
○ No (→ Q13)

10. Specifically, what aspect(s) of a cow's clinical mastitis history do you consider? Please select all that apply.

☐ Timepoint of previous mastitis cases, i.e. how close to dry-off the case was (→ Q11)
☐ Number of mastitis events (→ Q12)
☐ Suspected bacteria
☐ Confirmed bacteria
☐ Other: _____________

11. What timeframe do you use when considering the previous clinical mastitis case (i.e. how close to dry off)?

○ Current lactation
○ Past month
○ Past two months
○ Past three months
○ Other: _____________

12. Number of mastitis events:

☐ Multiple events in the same month: ____ events

☐ Multiple events in the current lactation: ____ events
☐ Multiple events in the previous lactation: ____ events
☐ Other: ______________

13. When would you give teat sealer without antibiotics?
(if at Q2, % teat sealer only > 0%)
____

14. What type of teat sealer do you use?
(if at Q2, teat seal is being used)
○ Internal
○ External
○ Combination (→ Q15)

15. Which proportion of cows who receive teat sealer, receives: (should add up to 100%)

Internal only: _____ %
External only: _____ %
Internal + external: _____ %

CULTURING

-These questions should only be asked to farmers that have indicated that they conduct selective DCT-

16. Do you use milk culture results to decide if dry cow therapy is needed?
○ Yes
○ No (→ Q19)

17. Where do you culture?
○ On-farm
○ Lab at veterinary practice
○ Provincial/regional diagnostic laboratory
○ Other lab: ______________

18. What type of results do you get from the culture? Check all that apply.
☐ Growth/no-growth
☐ Gram-positive/Gram-negative
☐ Specific bacteria, e.g. *Staph aureus*, streptococci
☐ Sensitivity against different antibiotics

TREATMENT OF CLINICAL MASTITIS

-- These questions should only be asked to farmers that have indicated that they treat only part of the clinical mastitis cases --

19. Do you sometimes decide not to treat mastitis during lactation with antibiotics based on any of the following criteria (select all that apply):

☐ End of her lactation
☐ Chronic high somatic cell count
☐ High milk yield
☐ In first half of lactation
☐ On cull list/not-to-breed list
☐ Other: ______________

CULTURING

20. Do you culture milk samples to decide if mastitis treatment with antibiotics is needed?

○ Yes
○ No (→ Q24)

21. Where do you culture?

○ On-farm
○ Lab of the veterinary practice
○ Provincial/regional diagnostic laboratory
○ Other lab: ______________

22. What level of results (select all that apply):

☐ Growth/no-growth
☐ Gram positive/Gram negative
☐ Specific bacteria, e.g. *Staph aureus*, streptococci
☐ Sensitivity against different antibiotics

23. Do you use your culture results to (select all that apply):

☐ Decide which treatment to start
☐ Change treatment that was started
☐ Decide to stop a treatment that was started
☐ Other: ______________
☐ I don't use my culture results to start, change, or stop treatments

OTHER

-- Question for all farmers --

24. If clinical signs are still present at the end of a treatment, what do you do:

○ Continue treatment with same antibiotic
○ Switch treatment to a treatment with a different antibiotic
○ Stop treatment
○ Ask veterinarian for advice
○ Culture milk sample
○ Other: ______________