An Evaluation of a Prescription Use Only Policy for Veterinary Antimicrobials

Prepared for:
The Canadian Council of Chief Veterinary Officers (CCVO)

Prepared by:
The CCVO's Antimicrobial Use in Animal Agriculture Committee

FINAL REPORT

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Executive Summary

The objective of this report was to evaluate the rationale for and definition of a prescription use only policy for all veterinary antimicrobials and its effects on antimicrobial use (AMU) in livestock and antimicrobial resistance (AMR) in food animals, related food products and humans. Where possible, information on prescription use only in all animals was considered. This work used multiple sources of information to evaluate this policy: 1) provincial and national prescription use only policies; 2) prescription use only policy rationales as presented by a variety of organizations from around the world, including Canada; 3) analysis of the British Columbia over-the-counter (OTC) antimicrobial distribution data; 4) analysis of AMR data from the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) for animals on farm, abattoirs, retail food and humans; and 5) analysis of the CIPARS on-farm swine AMU data. This work was intended specifically to address a prescription use only policy as one piece of antimicrobial stewardship without its interaction with other measures of this concept; it did not endeavor to address prudent antimicrobial use and stewardship in general.

Evaluation of current prescription use only policies revealed that they rarely require a prescription for all antimicrobials. Health Canada changed the *Food and Drug Regulation* to include a Prescription Drug List (PDL) that has a specific list of antimicrobials that require a veterinary prescription, but does not provide a list of drugs that can be sold OTC without a prescription. The categories and volumes of distributed active OTC ingredients that fall under veterinary oversight differ dramatically between jurisdictions with different policy definitions. For example, one region in Canada requires a veterinary prescription for all AMU in livestock. The European Union requires a veterinary prescription for all veterinary drugs, but ionophore antimicrobials are considered feed additives and are exempt. The proposed voluntary introduction of increased veterinary oversight for antimicrobials in the United States is specific to those antimicrobials considered of importance to human medicine. Regardless of the policy definition, prescription use only requires veterinary oversight, but producers still maintain a significant role in the diagnosis and treatment decisions for their animals.

A common motivator for adopting a prescription use only policy is often a non-specific and non-measured concern that agricultural AMU results in AMR in human pathogens and infections. Antimicrobial use ultimately selects for AMR, and evidence exists for the transfer of AMR in animal pathogens to human pathogens and to humans in the form of resistant infections. However, quantifying the overall contribution of AMU in agriculture to human AMR and its health risk is difficult, if not impossible, given the complex epidemiology and current scientific information. Historically, other countries included a prescription use only policy within a larger policy umbrella to promote antimicrobial stewardship that would ultimately affect change and reduce agricultural AMU. As a result, the global effects of a prescription use only on AMR in humans are not certain. None of these countries evaluated the impact of a prescription use only as a stand-alone piece. Given that it was often included with other policies, it is not clear if this piece was required to affect changes in agricultural AMU.

The BC OTC AMU revealed that on a biomass basis, the majority of OTC antimicrobials distributed for livestock were Category III and IV antimicrobials (based on the Health Canada ranking of their importance to human medicine, with Category I being the most important). Generally, Category I antimicrobials are not available OTC in Canada. It is not known how a move to prescription use only would affect the quantity of use of antimicrobials in categories of higher importance, but there is a risk that it could increase as producers would have more contact with veterinarians. Though the BC OTC data represents less direct selection pressure for resistance of antimicrobials in higher categories of importance, the role of indirect selection pressure through cross and co-selection is not clear and should be considered. Antimicrobial volume use metrics are an important measure of AMU, but there is no agreement on how to apply this measure to assessing prudent or judicious use. Agreement on AMU metrics and objectives for their use are critical for implementing and evaluating AMU policy.

Canada provides a unique example with regions that contain differing prescription use only policies versus those that allow some form of OTC dispensing. Antimicrobials were classed as OTC or prescription based on Health Canada's PDL. Comparing surveillance data from these regions, where available, provided some insight into the relationships between AMR and AMU between these regions. Analysis of CIPARS surveillance data found that a region with prescription use only typically ranked significantly higher for AMR to OTC and prescription antimicrobials compared to regions that allowed OTC dispensing. More swine herds in the prescription use only region used antimicrobials on a frequency basis, but among herds that use antimicrobials, there were no consistent regional trends of quantitative AMU, with the specific exceptions of tylosin and chlortetracycline. The limitations of the AMU data (grower finisher swine only, herd-level reporting frequency data and quantitative data for in feed antimicrobials only) make it difficult to draw causal conclusions between AMU and AMR results. Data on other factors that could affect AMR (e.g., farm management, disease incidence) were not available.

The limitations of Canadian surveillance data used in this analysis make it difficult to comment with certainty on the direct effect of a prescription use only policy on AMR in humans in Canada. The fact that other countries have incorporated this with a variety of other policy changes to reduce AMU in livestock suggests that it may not be effective on its own. However, these countries did not assess the direct effect of this policy on AMU. A prescription use only policy is one of many possible tools available to encourage judicious AMU and promote antimicrobial stewardship in agriculture. Though this work found no evidence that this policy in isolation will improve antimicrobial stewardship and reduce AMR, it may be important to maintain agriculture's social license to retain access to antimicrobials for food animal production. This social license is vital to avoid further restrictive agricultural AMU policies that compromise animal health and welfare. If prescription use only is to be considered as a potential mechanism to promote antimicrobial stewardship, other pieces, which could be in the form of policy, are critical elements that should also be considered.

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Introduction

In May 2012 the Council of Chief Veterinary Officers (CCVO) created the Antimicrobial Use in Animal Agriculture Committee. Committee membership includes representatives of all provincial and territorial Agriculture or related Departments and key federal government departments including: Public Health Agency of Canada, Health Canada, and the Canadian Food Inspection Agency. The overarching goal of the Committee was to share information and provide policy recommendations to the CCVO to help in forming policy to preserve the efficacy of antimicrobials for human and animal health by promoting antimicrobials stewardship in agriculture and veterinary medicine.

In November 2012, the Committee considered a proposal for recommendation to the CCVO which included initiating Federal-Provincial-Territorial policy work toward harmonizing federal and provincial legislation to make all veterinary antimicrobials available only by veterinary prescription in Canada. The recommendation did not receive unanimous support among the Committee; therefore, in January 2013 a working group of Committee members was struck to review the proposal, study the evidence surrounding other prescription only policies and report back to the Committee who would then report to the CCVO. The CCVO provided support for the ongoing work of this group to better understand the impacts of a prescription use only policy.

The term “antimicrobial stewardship” infers that the complexities associated with the development and dissemination of antimicrobial resistance (AMR) will require a multifaceted and multijurisdictional approach to mitigation (1). Dispensing policy, whether by prescription or OTC, is one among several tools available to policy makers to promote stewardship, but its success in mitigating AMR is dependent on the implementation of other strategies to manage the use of these important medicines (1). There are many terms used to characterize AMU: prudent, judicious, and justifiable. For the purposes of this document these terms will be used interchangeably, while recognizing their subtle differences in meaning.

This work was intended specifically to address a prescription use only policy as one piece of antimicrobial stewardship without its interaction with other measures of this concept; it did not endeavor to address prudent antimicrobial use and stewardship in general. The objective of this report was to evaluate the rationale for and definition of a policy of making all veterinary antimicrobials available only by prescription and its effects on antimicrobial use (AMU) in livestock and antimicrobial resistance (AMR) in food animals, related food products and humans using available data.

Description of the Current Prescription Use Only Policies

The federal *Food and Drug Regulation* defines what veterinary pharmaceuticals require a prescription in order to be sold, and which can be sold OTC, that is, sold without a veterinary prescription. In 2013 Health Canada amended the regulations under the *Food and Drugs Act* concerning prescription drugs, which repealed Schedule F and established a Prescription Drug List (PDL)[1]. This list includes those drugs that must be sold under veterinary prescription; however, there is now no provision to list the OTC drugs not requiring a prescription[2]. Health Canada categorizes antimicrobials based on their importance in human medicine, with I (Very High Importance) being the highest and IV (Low Importance) the lowest[3]. As illustrated in Appendix 1 (Table 12), veterinary prescription antimicrobials include drugs from Categories I, II and III compared to OTC drugs, which include drugs from Categories II, III and IV (the only Category I OTC antimicrobial is an intramammary polymyxin B product). In terms of Category I drugs, it is clear that the prescription drugs are of greater importance to human medicine. The same is true for some of the category II prescription drugs versus their OTC counterparts (e.g., extended spectrum and beta-lactamase resistant penicillins versus penicillin G). However, the relative importance of prescription versus OTC for other drug classes (e.g., lincosamides, macrolides, virginiamycin, tetracyclines) is less certain. Provincial and territorial legislation governing prescription requirements can be more stringent than the federal legislation and regulation, but cannot be less stringent.

The federal *Feeds Regulations'* Compendium of Medicating Ingredients Brochure (CMIB)[4] lists the medicating ingredients, including antimicrobials, which can be added to livestock feeds at specific doses without a veterinary prescription (2). Any deviation from the CMIB requires a veterinary prescription.

Québec and Newfoundland Labrador (NL) have more stringent veterinary prescription requirements compared to other provinces in Canada (Table 1). These policies are all considered to be prescription only, yet they vary in their definition of what drugs require a prescription. Specifically, all veterinary antimicrobials require a prescription in Québec, which enacted this policy in the 1985 primarily to control antimicrobials residues in food animal products. In comparison, Newfoundland & Labrador enacted a policy in 2012 to require a prescription for all veterinary antimicrobials with the exception of those listed in the CMIB. Health Canada and the Canadian Animal Health Institute are currently working with stakeholders on options to strengthen the veterinary oversight of AMU in food animals[5].

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[1] http://www.hc-sc.gc.ca/dhp-mps/prodpharma/pdl-ord/index-eng.php
[2] http://members.cvma-acmv.org:8080/AMSApps/Ams/ArticlesPublic/Details/20171#
[3] http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr_ram_hum-med_intro-eng.php
[4] http://www.inspection.gc.ca/animals/feeds/medicating-ingredients/eng/1300212600464/1320602461227
[5] http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr-notice-ram-avis-20140410-eng.php

Table 1. A comparison of antimicrobial dispensing policies among specified jurisdictions

Jurisdiction	**Dispensing policy**	**Antimicrobials available OTC[1] or by prescription**
Québec	Prescription only	Prescription: All antimicrobials[2]. OTC: None.
Newfoundland and Labrador	Combination of prescription and OTC-CMIB[2]	Prescription: All non-feed antimicrobials; OTC: Antimicrobials listed in the CMIB[3] (feed).
Other provinces in Canada	Combination of prescription and OTC	Prescription: F&D Reg.[4] Prescription Drug List and CMIB[2.]
European Union	Combination of prescription and OTC-Category IV	Prescription: All Category I-III antimicrobials; OTC: Category IV antimicrobials
USA	Combination of prescription and OTC	Prescription, OTC and Veterinary Feed Directive[5]

[1] Antimicrobials available over-the-counter that do not require a veterinary prescription.
[2] Regulation respecting the terms and conditions for the sale of medications: http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=3&file=/P_10/P10R12_A.HTM
[3] Compendium of Medicating Ingredient Brochures: http://www.inspection.gc.ca/animals/feeds/medicating-ingredients/eng/1300212600464/1320602461227.
[4] Food and Drug Act/Regulation, Government of Canada: http://laws-lois.justice.gc.ca/eng/acts/F-27/index.html
[5] Veterinary feed directive (VFD) is a written statement issued by a licensed veterinarian that orders the use of VFD drug in or on an animal feed. VFD is more restrictive than prescription since extra-label use is prohibited

British Columbia follows the federal regulation and allows the sale of prescription and OTC products. The BC Ministry of Agriculture collects annual data (kg of active ingredient) on purchases of veterinary antimicrobials by licensed OTC retailers, including feed mills[6]. Three different prescription AMU policies were applied to the BC OTC data from 2012 to illustrate how the distributed volumes of prescription compared to OTC drugs would be classified using the different policy definitions compared to the current Canadian regulation that is used by all provinces except Québec and NL. Antimicrobial purchases by veterinarians or pharmacists, whether prescription or OTC antimicrobials, are not included in the data. Figure 1 shows the application of the BC (Canada), Québec, EU and NL definitions of prescription use policies to BC's veterinary OTC AMU data. The data are further categorized by their importance to human medicine. Polymyxin B is the only category I antimicrobial available OTC, none of which was purchased by BC OTC retailers in 2012. The first bar shows the grouping of BC OTC data according to the current federal PDL. Using the Newfoundland & Labrador definition of prescription use only, the majority of use, including the majorities of category II and III usages and all of the category IV usage, remains OTC because approximately 95% of BC's OTC AMU

[6] http://www.agf.gov.bc.ca/lhmr/pubs/otcu_amu.pdf

is in feed. One option would be to include all medically important antimicrobials (i.e., category I, II and III drugs) to be under veterinary prescription. This accounts for more than half of BC's OTC usage, compared to all of the BC data falling under prescription using the Québec definition. Although all three policies are commonly considered prescription use only, two of the three allow OTC sales and therefore are actually combined OTC and prescription use policies of varying degrees. Similarly, Canadian human AMU is considered prescription use only, yet allows OTC sales of antimicrobials (e.g., Polysporin®). In the European Union (EU), category IV antimicrobials such as ionophores (monensin, lasalocid, maduramicin, narasin, salinomycin, and semduramicin) are classified as feed additives and are available OTC, even though the EU is commonly considered to be prescription use only for all veterinary antimicrobials[7].

In addition to the differences in what antimicrobials can be sold by prescription or OTC, the roles and responsibilities for AMU oversight vary with prescription and OTC drugs. The roles include diagnosing the condition, deciding on the appropriate antimicrobial treatment, dispensing and administering any antimicrobial treatment. Table 2 illustrates the differing roles and responsibilities for various animal AMU situations. For comparison purposes, human prescription use is included. Technically, veterinary oversight is considered to exist within a valid veterinarian-client-patient relationship (VCPR), and its application to agriculture is summarized in the footnote to Table 2. VCPRs are defined provincially by the veterinary regulatory bodies. A representative definition from Ontario is as follows (bolding added):

No member shall administer, dispense or prescribe a drug unless,

> *(a) the member has* ***assumed the responsibility*** *for making medical judgements regarding the health of the animal or group of animals and the need for medical treatment and the custodian of the animal or group of animals has indicated a willingness to* ***accept the advice*** *of the member;*
>
> *(b) the member has* ***sufficient knowledge of the animal or group*** *of animals by virtue of a history and inquiry and either physical examination of the animal or group of animals or medically appropriate and timely visits to the premises where the animal or group of animals is kept to reach at least a general or preliminary diagnosis;*
>
> *(c) the member believes that the* ***drug is*** *prophylactically or therapeutically* ***indicated*** *for the animal or group of animals; and*
>
> *(d) the member is* ***readily available*** *in case of adverse reactions to the drug or failure of the regimen of therapy.*

[7] http://ec.europa.eu/food/food/animalnutrition/feedadditives/docs/Report-Coccs-233-2008-EN.pdf

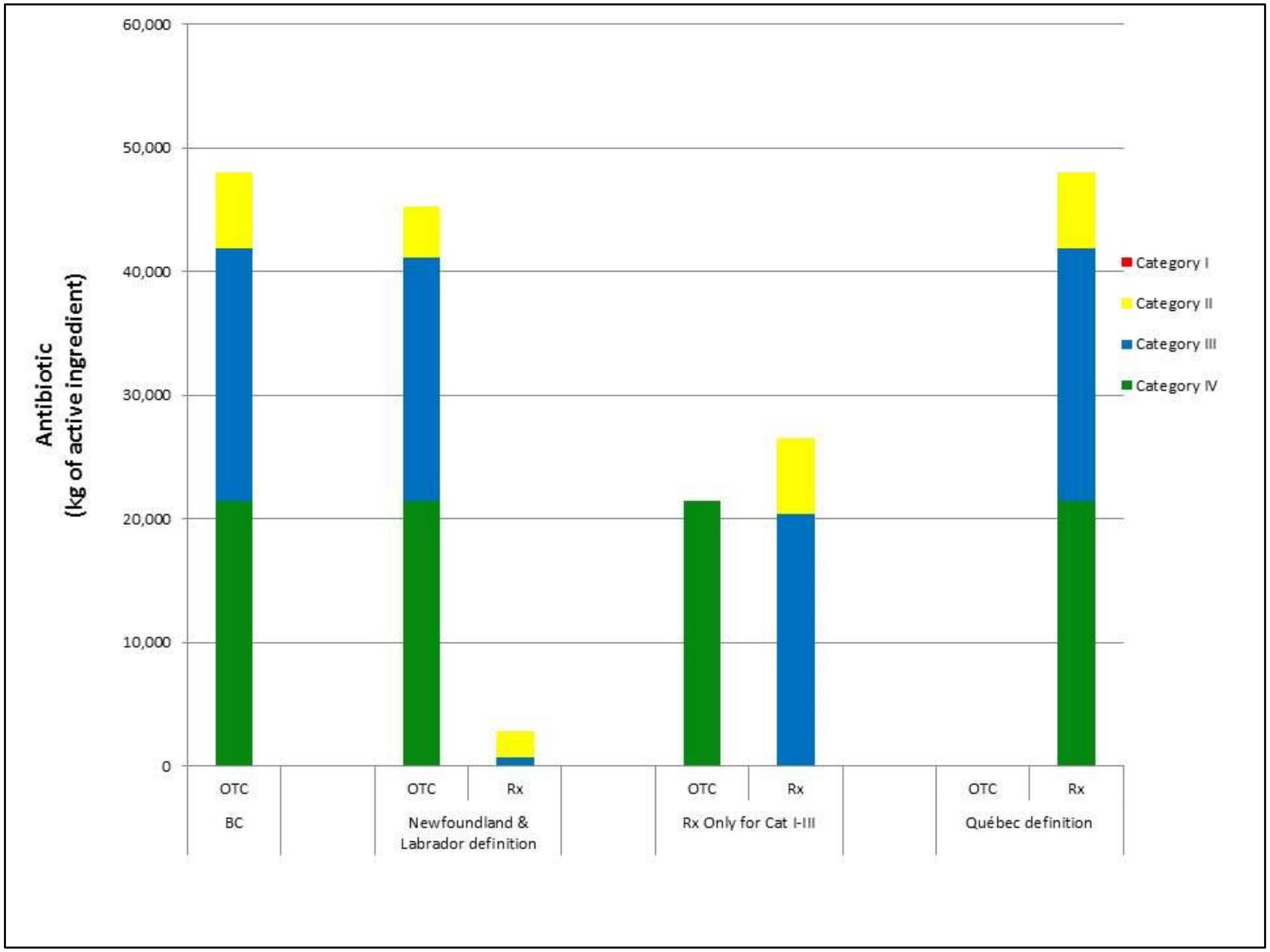

Figure 1. Impact of variation in three Canadian definitions of veterinary prescription use only policies when applied to British Columbia's 2012 OTC data, purchases by veterinarians or pharmacists not included. (OTC – over the counter; Rx – prescription)

Table 2. Roles and responsibilities in antimicrobial use for various situations, excluding hospital settings.[1]

Role	Human Rx	Animal		
		Small Animal Rx	**Livestock OTC**	**Livestock Prescription**
Diagnosis	Physician	Veterinarian	Primarily producer, with or without veterinary oversight[2]	Primarily producer with veterinary oversight[2]
Treatment Decision	Physician	Veterinarian	Primarily producer, with or without veterinary oversight[2]	Primarily producer with veterinary oversight[2]
Dispensing	Pharmacist	Veterinarian or Pharmacist	Feed mill, OTC retailer or veterinarian	Feed mill or veterinarian
Treatment Administration	Patient	Owner	Producer[2]	Producer[2]

[1] The assignments for primary responsibility for various aspects were given based on the majority of situations. Where this was not clear, the assignment was blended.
[2] The application of veterinary oversight in livestock production is variable, including between species, but in general a veterinarian will not issue individual animal prescriptions for food animals, nor necessarily be involved in animal diagnosis, treatment decisions or administration for each use of an antimicrobial. For example, veterinary oversight could be an annual visit to the premise with review of the producer's methods of diagnosing animals, determining appropriate treatments and administration of those treatments. Veterinary oversight includes support for unusual situations and that support could include remote consultation. The veterinary oversight could include the producer's access to appropriate antimicrobials, including prescription antimicrobials, for a period of time (for example, one year).

Veterinary oversight is required for use of prescription antimicrobials in livestock and companion animals, but not for OTC antimicrobials. The majority of small animal antimicrobials are issued under prescription. The application of the VCPR to small animal patients results in roles and responsibilities that are analogous with the human situation. A difference is the decreased role of the pharmacist in dispensing for small animals as veterinarians typically fill this role. Although prescription AMU in livestock requires veterinary oversight, this is typically less than what occurs with humans or small animals. Even though veterinarians may dispense OTC antimicrobials, in most provinces it is not necessary to have a valid VCPR to do so. This means that the veterinarian's duty of care and level of oversight when dispensing an OTC antimicrobial is less than that when prescribing a prescription antimicrobial. The effect on veterinarians' attitudes and behaviours to OTC antimicrobials of changing some, or all, of them to prescription status is unclear. Producers with a close relationship with their veterinarian might purchase OTC antimicrobials from a non-veterinary source for various reasons including convenience or price. It is not currently known how many producers in Canada operate without veterinary oversight.

Key Findings – Definition of policies:

- Veterinary prescription antimicrobials include drugs of very high, high and medium importance to human medicine (Categories I-III) compared to OTC drugs, for which almost all are Categories II-IV. The only Category I OTC drug is a single intrammary product. The Category I prescription antimicrobials are more important to human medicine than the single OTC product. The same relationship exists for some Category II antimicrobial classes, but for others, the relative importance is less certain.
- Rarely do prescription use only policies actually require a prescription for *all* antimicrobials.
- Although prescription use only is referred to as a single policy, the specific antimicrobials that require a prescription differ with the policy definition within a jurisdiction. The categories and volumes of antimicrobials that fall under veterinary oversight differ dramatically with the policy definition.
- Use of OTC antimicrobials for livestock may or may not involve veterinary oversight with the producer bearing primary responsibility for the diagnosis, treatment decision and treatment administration.
- Use of prescription antimicrobials in agriculture requires veterinary oversight and the producer often maintains primary responsibility for the diagnosis, treatment decision and treatment administration.
- Use of prescription antimicrobials in human medicine or small animal medicine includes the respective professional being responsible for the diagnosis and treatment decision, with the patient or owner respectively administering the treatment.

The Positions and Rationale of Various Organizations and Experts on Prescription Use Only

Policies pertaining to veterinary antimicrobial drug access and the application of prescription only requirements are diverse. Publicly available documents, written in English or French, were reviewed to determine the policy positions, context and explanations for the following organizations with respect to antimicrobial drug distribution relative to prescription only use.

Canada

Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health (2002)

A group of experts and stakeholders proposed 38 recommendations to Health Canada, or in some cases, to Health Canada's partners in provincial governments to address AMU and AMR issues in Canada (3). These included the following recommendation for prescription only use:

- '*Make all antimicrobials used for disease treatment and control available by prescription only*'

The report states: *'On purely scientific or human health grounds, there is little argument against a prescription-only system.'*

'*OTC availability of antimicrobials may contribute to the risks associated with AMR because there is no direct professional oversight of the use of the products. Without veterinary input, OTC use is largely incompatible with many of the principles of prudent use of antimicrobial drugs for disease treatment and control.'*

The committee was advised of concerns of potential increased cost of animal health care in a prescription only system. It did acknowledge that Québec successfully implemented a retail network for pharmaceuticals to the food-animal industry through veterinarians by means of price ceilings. The committee examined the advantages and disadvantages of a prescription only system, which are presented in Table 3.

Table 3. Advantages and disadvantages of prescription only system for veterinary antimicrobials [Source: (3)].

Advantages	Disadvantages
More prudent use (including use of culture and sensitivity)	Disruption of current system
Track quantities used (increases, reductions)*	Availability of drugs (pharmacy service in rural areas and possible veterinary monopoly)
Controls, oversight	Practicality of repeated prescriptions, especially for feed medications
Reduced resistance selection and co-selection	Veterinary oversight may not decrease use

*The committee identified the veterinary medical records and feed mill records of prescriptions as the sources of data to track the use of prescribed antimicrobials. To track non-prescription AMU, it identified records of OTC and medicated feed sales and possible on-farm treatments farm for antimicrobials imported for "own use" and purchased as active pharmaceutical ingredients.

The Committee suggested possible adaptations to a prescription only system

'(…) movement to a prescription-only system need not require a veterinarian to visit the farm each and every time an animal requires treatment. This would be both very expensive for the producer and impractical on many farms. Rather, prescriptions could be provided for specific conditions over a finite period of time, within the limits of valid VCPR, and with regular re-evaluations of the need for treatment by their veterinarian. Also, there are substantial implications arising from a system of prescription-only feed medications. Many veterinarians in Canada currently have had little to do with feed medication, and significant adaptations among veterinarians, feed manufacturers, and farmers would be needed to make the system work.'

Conference on antimicrobial stewardship in Canada agriculture and veterinary medicine (Toronto, October 30 – November 2, 2011)

A report from the Conference *Antimicrobial stewardship in Canadian agriculture and veterinary medicine. How is Canada doing and what still needs to be done?* was published in the Canadian Veterinary Journal (4). Some speakers made statements regarding prescription-only policy:

- Richard Reid-Smith (PHAC): *'The complexity of drug distribution in Canada (veterinary prescription, feed mills, over-the-counter, active pharmaceutical ingredient compounding, own use importation provisions) makes data collection difficult. In the more advanced veterinary antimicrobial use monitoring systems in Scandinavian countries (for example, Denmark, Norway, Sweden), data collection is facilitated by requiring prescriptions for all antimicrobial drug use.'*

- Scott McEwen (University of Guelph): '*Veterinary prescription of all antimicrobials in animals is a hallmark of prudent use but that veterinarians should not be allowed to profit from such a monopoly.'*

Canadian Veterinary Medical Association (CVMA)

CVMA has a position statement on AMU in animals, but it does not specifically address making antimicrobials available by prescription only:

'The CVMA recognizes the public health implications of antimicrobial use in veterinary medicine and takes the responsibility of protecting both animal and human health and welfare very seriously.

The CVMA supports and encourages all veterinarians to use antimicrobials prudently.

The veterinarian is in the best position to assess the benefit /risk ratio of antimicrobial use in animals. Veterinarians must explain to their clients the importance of prudent use of antimicrobials. Veterinarians must achieve a balance between maximizing animal health and welfare, minimizing bacterial resistance, and conserving antimicrobial efficacy' (5)

The CVMA Council declared that the Prudent Use of Antimicrobials would be its strategic priority for 2014. The CVMA held its annual Summit of Veterinary Leaders at its annual convention in July 2014, where the topic of discussion was "Prudent Use of Antimicrobials". Experts from Canada, the US and Europe discussed the topic of prudent use. The work for this report was completed prior to the Summit. Further Summit details are expected, but are not included in this report.

Canadian Medical Association (CMA)

At its 144th annual general meeting in 2011, CMA adopted a resolution urging the implementation of mandatory veterinary prescriptions for all antimicrobials used in animals (6). One provided reason cited the volume of antimicrobials used in agriculture compared to human medicine: '*"Because agriculture accounts for the highest volume of antibiotic use, the farm environment serves as a reservoir of resistant genes," British Columbia delegate Dr. Bill Mackie told council.'*

The effectiveness of veterinary oversight was questioned: *'Some delegates countered that mandatory prescriptions would indiscriminately raise barriers for Canadian hobby farmers, who are already strictly regulated and make only marginal contributions to the spread of antibiotic resistance.'*

International organizations

World Health Organization (WHO)

For 2011 World Health Day "*Antimicrobial resistance: no action today no cure tomorrow"*, WHO developed a five-point policy package to combat the spread of AMR (7). Reducing AMU in food-producing animals is one of these five points; the remaining four are directed primarily at human AMU. For reduction of use in animals, stakeholders in food-producing animal sectors are encouraged to provide national leadership and promote inter-sectoral collaboration, create and enforce an enabling regulatory framework, strengthen surveillance and monitoring, promote education and training on antimicrobial use in food-producing animals, and reduce the need for antimicrobials through better animal husbandry. A requirement for obligatory prescriptions for all AMU is one of five recommended actions under "create and enforce an enabling regulatory framework". This is based on the "significant direct and indirect effects of AMU in animals on AMR in human pathogens" from several lines of evidence, even though WHO acknowledged that the relationship cannot be fully evaluated based on current information (8). WHO also acknowledged that a lack of data on the occurrence of resistance and on AMU in animals and a lack of standardized data collection are challenges that need to be overcome (9).

World Organisation for Animal Health (OIE)

Canada is one of the 178 OIE member countries. Chapter 6.9 of the Terrestrial Animal Health Code 2013 defines the responsibilities of all stakeholders to ensure judicious use of antimicrobials (10). Chapter 6.9 assigns the responsibilities for this matter to the Competent Authority of member countries (11 responsibilities), the veterinary pharmaceutical industry (5), wholesale and retail distributors (3), veterinarians (6), food-animal producers (3) and animal feed manufacturers (5), including responsibilities concerning the prescription of veterinary medicinal products. The OIE's recommendation is that all antimicrobials should be available only under veterinary prescription. This recommendation was developed during the OIE global conference on the responsible and prudent use of antimicrobial agents for animals (Paris, France, March 2013), where prescription use only was one among 16 recommendations (11).

Other countries

The rationale that led these jurisdictions to mandate prescription requirements for the distribution of antimicrobials was not easily available. Several reasons could explain the challenge of accessing the information. In some cases, documents might be available only in the national language of the jurisdiction. In some cases, jurisdictions adopted mandatory prescriptions more than fifteen years ago (Sweden in 1986 and Denmark in 1998) and either the documents were never available online or they were archived. As a result, rationale for these jurisdictions could not be described in this report. The US Government Accountability Office (GAO) reported on US Congressional hearings where Danish government officials were interviewed (12): "*Government and industry officials we spoke with in Denmark emphasized that their bans on growth promotion antibiotics began as voluntary industry efforts that were later implemented as regulations by the government. EU officials and both industry and government officials from Denmark said the most important factor in the development of their policies was sustained consumer interest in the issue of antibiotic use in food animals and concerns that such use could cause resistance affecting humans. In the face of these concerns, officials explained that EU policies were developed based in part on the precautionary principle, which states that where there are threats of serious or irreversible damage, lack of scientific certainty should not postpone cost-effective measures to reduce risks to humans*." These comments were specific to policy decisions by Denmark and EU to ban antimicrobial growth promotion. The broader rationale of the precautionary principle also applied to other EU policies, such as the decision to make all veterinary drugs available by prescription only in 2007 (13).

Several jurisdictions are recognized for their requirement for a veterinary prescription for antimicrobial dispensing (Figure 2), in addition to other measures, such as banning the use of specific antimicrobials and growth promoters (including ionophores), and changes in farming practices and AMU monitoring aimed at reducing use (14; 15). The jurisdictions are ordered according to the stringency of their requirement for veterinary prescription to dispense antimicrobials. Stringency increases from the left to the right of the figure. The definition of prescription only policy varies among jurisdictions, especially regarding the classification of molecules least important to human medicine such as ionophores. In Canada, ionophores are classified as antimicrobials of low importance in human medicine (Category IV) because they are not used in humans and there are no known links between resistance to these drugs and drugs used in human medicine; the EU has classified ionophores as food additives, not veterinary drugs, and thus they do not fall under the purview of prescription only antimicrobial use policies. Given that Category IV antimicrobials may be exempt under Health Canada's consideration to harmonize with the US, and that they are considered veterinary drugs in Canada, it is not depicted in the Figure 2 as meeting the strict definition of a prescription only AMU. In contrast, even though ionophores are sold OTC in the EU, they are not classified as a veterinary drug but as a feed additive. As a result, EU members have been placed to the right side of the policy gradient in Figure 2, along with other jurisdictions that require veterinary prescriptions for all AMU in animals.

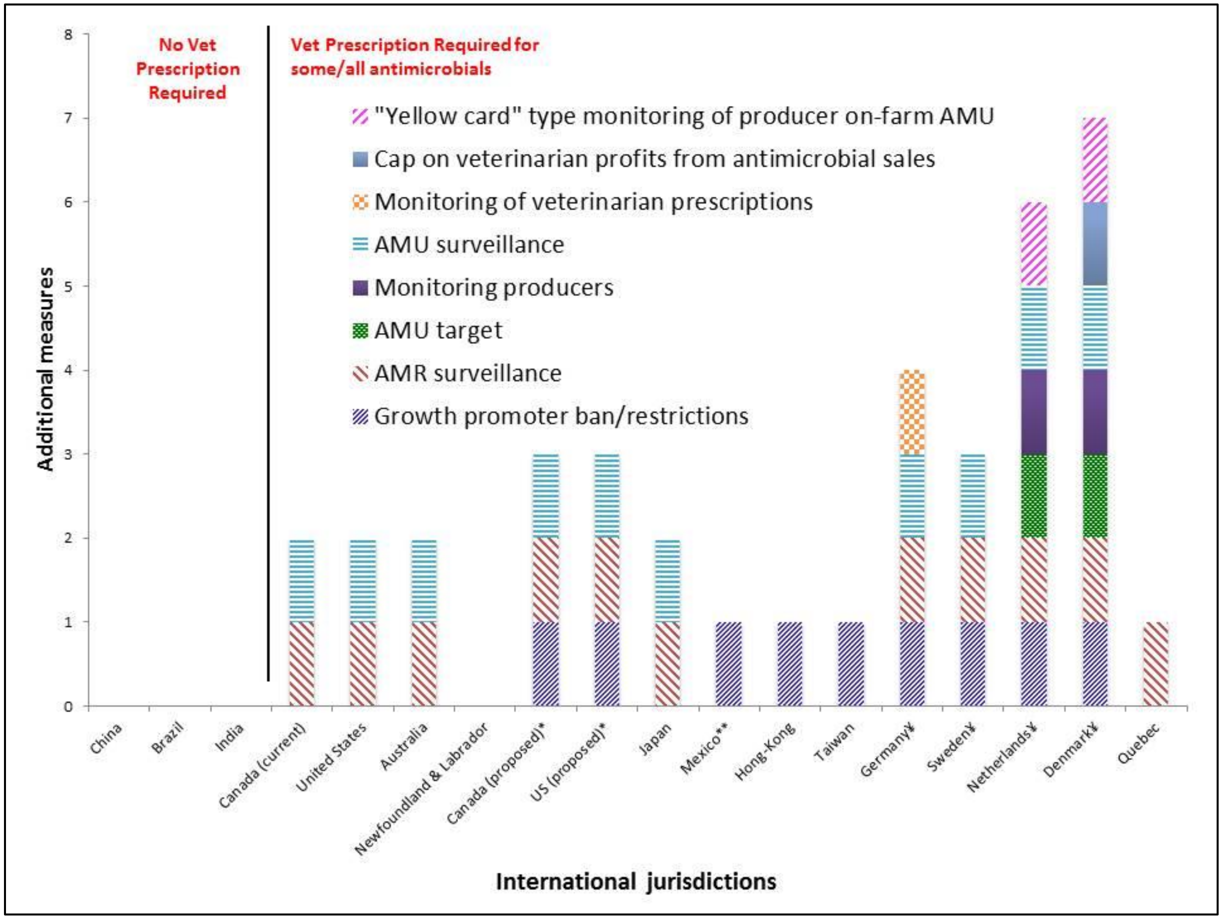

Figure 2. Continuum of prescription use only policies in Canada and around the world.

* Proposed refers to Health Canada VDD's consideration for regulatory harmonization with the voluntary USFDA Guidance for Industry 209/213.

** Mexico has a partial growth promoter ban and 15 antimicrobials are allowed.

¥ Countries are part of the European Union and have implemented antimicrobial use measures beyond those required by the European Union.

United States Food and Drug Administration (USFDA)

There are three categories of drugs in the US: prescription, OTC and VFD (veterinary feed directive). A VFD is a written statement issued by a licensed veterinarian that orders the use of a VFD drug in or on an animal feed (16). Their VFD is more restrictive than prescription as extra-label use is prohibited.

The USFDA believes that all medically important antimicrobials should be prescription only, regardless the route of administration. As a first step towards this goal, the USFDA recently developed a strategy in Guidance For Industry (GFI) #213 (17), in collaboration with many stakeholder groups as well as the US Department of Agriculture (USDA), to strengthen judicious use of antimicrobials by asking pharmaceutical companies ('drug sponsors') to voluntarily phase out label claims for production uses (e.g., growth promotion) for antimicrobials that are medically important in human medicine. In addition, the document recommends that "*drug sponsors [**voluntarily**] revise the conditions of use of their medically important antimicrobial new animal drugs and combination new animal drug products to reflect the need for the professional oversight of a licensed veterinarian*" for the remaining therapeutic uses of these antimicrobials, with their highest concern being for antimicrobials administered in feed and water.

FDA reasoning for involving the oversight of a veterinarian :*"(…) FDA believes that the judicious use of medically important antimicrobial drugs intended for use in food-producing animals should involve the oversight of a licensed veterinarian, given the benefit of that individual's scientific and clinical training. This is because judicious use involves accurately identifying bacterial disease that is present or likely to be present, and selecting the suitable antimicrobial drug. The veterinarian's decision to use a specific approved drug or combination drug is based on factors such as the way the drug acts against the particular bacteria in question, whether it can effectively get to the place of infection, and how long the drug maintains effective levels at the site of infection."* (18)

Further, the USFDA GFI #209 recommended two voluntary principles, one of which included (19):

1. *The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation*."

Document 209 reviewed international reports to provide context to FDA current thinking on the judicious use of medically important antimicrobials in food-producing animals. Though not directly stated, the document implies that the use of non-medically important antimicrobials, including for growth promotion, would remain OTC where labels permit.

"(…), the public health concerns associated with the use of medically important antimicrobial drugs in food-producing animals have been the subject of scientific interest for the past 40 years.

FDA has considered all available information and believes that the weight of scientific evidence supports the recommendations outlined in this guidance document.

To effectively respond to the public health concerns associated with antimicrobial resistance, FDA believes it is important to broadly consider how antimicrobial drugs are being used. The scientific community generally agrees that antimicrobial drug use is a key driver for the emergence of antimicrobial-resistant bacteria. It is imperative that strategies for controlling antimicrobial resistance include a consideration of how antimicrobial drugs are being used and measures to address those uses that are injudicious in nature."

"(…), it is in the interest of both human and animal health that we take a more proactive approach to considering how antimicrobial drugs are being used, and take steps to assure that such uses are appropriate and necessary for maintaining the health of humans and animals."

"*Veterinarians can play a critical role in the diagnosis of disease and in the decision-making process related to instituting measures to treat, control, or prevent disease*" as they are the best trained and positioned professionals to make such decisions.

US National Strategy for Combating Antibiotic-Resistant Bacteria

In September 2014, The White House published their National Strategy for Combating Antibiotic-Resistant bacteria[8]. This plan brings the objective to "*Eliminate the use of medically important antibiotics for growth promotion in animals and bring other in-feed uses of antibiotics, for treatment and disease control and prevention of disease, under veterinary oversight*" to achieve the Strategy's goal 1: "*Slow the Development of Resistant Bacteria and Prevent the Spread of Resistant Infections*". The Strategy was released simultaneously with the Report to the President on Combating Antibiotic Resistance by the President's Council of Advisors on Science and Technology (PCAST)[9]. The PCAST strongly supported the FDA's GFI #209 and #213 with a view to promote judicious use of antimicrobials. It recognized the gaps in the understanding of the complexity of AMR across multiple species and environments and the unclear relative contribution of AMU in agriculture to AMR in humans compared to inappropriate or overuse in health care settings. However, the PCAST reiterated that there is evidence that AMU in agriculture promotes the development of AMR in animals and that retail meat can be a source of these bacteria. As at least some drug-resistant pathogens evolve under selective pressure from AMU in agriculture and may contribute to resistance in human clinical settings, the PCAST recommended that the national strategy must include substantial changes to

[8] http://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf
[9] http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf

AMU in agriculture. The PCAST recognized that another reason to take action is that AMR also limits the therapeutic effectiveness of antimicrobials in animals.

American Veterinary Medical Association (AVMA)

In 2010, the American Veterinary Medical Association (AVMA) published the Antimicrobials Use Task Force Report (20). One side stressed that:

1. OTC does not necessarily equate to a complete lack of veterinary oversight.
2. OTC is essential to ensure animal health, especially for therapeutic uses, because of the shortage of food animal veterinarians.

The opposing side expressed concerns that:

1. There is potential for arbitrary and therefore injudicious use of OTC products for production purposes.
2. Some of these OTC products are or belong to drug classes that have importance to human medicine.
3. Increased scrutiny of the use of OTC antimicrobials and use for production purposes could lead to negative impacts on livestock production (e.g., decline of drug availability).
4. Failing to acknowledge and address these concerns could result in loss of consumer confidence (aka "social license").

There was no consensus by the AVMA regarding prescription only access to antimicrobials. However, members universally agreed: "*Veterinarians should be involved in the decision-making process for the use of antimicrobials regardless of the distribution channel through which the antimicrobial was obtained.*" Members were able to reach consensus regarding production uses of antimicrobials. Although there was no consensus regarding increased oversight, a list of processes to enhance veterinary oversight emerged from the discussion, including the availability of antimicrobials only by veterinary prescription, certification requirements for access to antimicrobials, a tiered approach, and electronic/telemedicine approaches.

The AVMA Task Force Report highlighted the major potential barriers to implementing greater veterinary oversight in the US: available veterinary workforce to ensure all livestock producers have veterinary access, VFD, and the definition of a VCPR. These factors may or may not share relevance in the Canadian context.

The Report also highlighted the potential unintended consequences of implementing greater veterinary oversight in the US are: diminished veterinary workforce, reduced economic viability of food animal stakeholders, decreased animal health and welfare, negative public perceptions of veterinarians due to a potential conflict of interest of veterinarians as prescribers and dispensers, and the circumvention of the VCPR.

Lastly, the Report identified the potential benefits of increased veterinary oversight in the US: enhanced consumer confidence, improvement in animal and human health, increased funding for veterinary workforce needs, increased clarification of the VCPR, and facilitation of antimicrobial use monitoring (e.g., tracking of veterinary prescriptions).

Denmark

An amendment of 2001/82/EC from the European Parliament and Council of the European Union restricted AMU in food animals so that as of January 1, 2007, a veterinary prescription shall be required for all veterinary medicinal products for use in food animals (15) (amendment 41)a)ii). (13). However, starting in the mid-1990s Denmark began implementing a number of other antimicrobial stewardship policies to combat AMR in livestock species that conferred resistance to human pathogens. Specific measures were taken, such as the banning of avoparcin as a growth promoter in swine and poultry, to limit the development of vancomycin-resistant *Enterococci* (VRE), an opportunistic pathogen in humans (21). Ultimately, Denmark banned all growth promoters in livestock in 2000, while having established national AMU and AMR surveillance via DANMAP in 1995 and invoking legislation to remove veterinarians' ability to profit from antimicrobial sales. All veterinary prescription drug sales must be reported to the VETSTAT register that is then transferred to DANMAP (22). Their surveillance showed that although the growth promoter ban was associated with an increase in therapeutic use, the total volume of antimicrobial use declined. Due to concerns over inappropriate prescriptions for hog farms, the Danish agriculture ministry began issuing warning letters or 'yellow cards' to hog producers with the highest AMU in 2010. In two years the yellow card system has resulted in a 25% reduction of AMU among hog farms. The EU moved to prescription use only in 2007. From the mid-1990s to 2012 Denmark's AMU policies, including prescription use only, are collectively associated with a 60% reduction in AMU per kg of produced livestock (21).

The US Government Accountability Office (GAO) reported on US Congressional hearings where Danish government officials were interviewed (12): "*According to Danish government officials, Denmark's antibiotic use data are detailed enough to allow the country to track trends in use and monitor the effects of their policies. ... According to Danish officials, Danish data on antibiotic resistance in food animals and retail meat show reductions in resistance after policy changes in most instances. ... Danish officials told us that Denmark's resistance data have not shown a decrease in antibiotic resistance in humans after implementation of the various Danish policies, except for a few limited examples.*" This would suggest that while Denmark's efforts to reduce antimicrobial use in livestock may have met with some success in reducing AMU and AMR in live animals and retail meat, this has not translated into a corresponding reduction in AMR in humans.

Netherlands

The Netherlands complied with the EU requirement for veterinary prescription in 2007, after enacting the EU bans on antimicrobial growth promoters in 1999 and 2006. The result was no net effect on AMU in livestock as therapeutic use doubled and replaced that of growth promoters (23). This resulted in government legislation introducing targets for reducing AMU in livestock by 20% in 2012 and 50% in 2013 (compared to 2009), as well as mandating the registration of all veterinary prescriptions for food animals and establishing the Netherlands Veterinary Medicines Authority (24). The Netherlands reported a 50% reduction in livestock AMU by 2012 ahead of its target of 2013. However, it is unclear and remains too early to tell what effect this approach has had on AMR in livestock or humans.

Key Findings – Positions and rationale support for prescription use only policy:

- Various groups of experts and stakeholders support a prescription use only policy.
- A prescription use only policy, requiring veterinary oversight for antimicrobial use, is recommended by several international organizations as one of a number of components of antimicrobial stewardship, suggesting that such a policy would require other policies/interventions to significantly decrease antimicrobial use and resistance.
- A common motivator for adopting a prescription only policy is a non-specific and non-measured concern that antimicrobial use in livestock results in resistance in human pathogens and infections.
- Some groups noted that a prescription use only policy may not reduce AMU or AMR in agriculture and/or AMR in humans.
- Prescription use only policies have been in place in a number of countries for over a decade. The USFDA is moving towards voluntary implementation of veterinary oversight through prescription through GFI documents 209/213. Health Canada VDD proposes to harmonize with the US.
- Many countries with prescription use only policies have also implemented other measures to promote antimicrobial stewardship and reduce AMU in agriculture (e.g., Denmark, the Netherlands).
- No study evaluating the sole effect of prescription use only policies was found.

Review of the British Columbia OTC Antimicrobial Sales Data

The province of BC collects annual purchase data for veterinary antimicrobials from its licensed OTC retailers[10]. These data offered the ability to understand how OTC antimicrobials are used in livestock in one province with respect to their importance to human medicine and particulars of administration. British Columbia OTC AMU in livestock (mg of active antimicrobial ingredient/tonne of steady state livestock biomass) was estimated using the OTC sales data as a proxy for direct use in livestock as there were no data to relate purchase to use in food animals. These data were further categorized according to Health Canada's classification based on their importance to human medicine (I – very high importance, to IV – not important) to understand the differences in OTC antimicrobial category distribution. The BC data were the only provincial OTC antimicrobial distribution data available for analysis. Purchases by pharmacists and veterinarians were not included in the data. Purchases were linked with label information including active antimicrobial ingredient, concentration, animal species, administration method and usage category (therapeutic, disease prevention, or growth promotion) and antimicrobials were grouped according to Health Canada's categorization.

Annual purchase data for antimicrobials from BC OTC retailers (2002-2012) were standardized by steady state biomass for livestock. The annual steady state biomass of the following agricultural livestock commodities was calculated for beef cattle, dairy cattle, poultry (broilers, layers, broiler breeders, and turkeys), hogs, sheep, goats, and horses. The resulting steady state biomass estimates represented the total weight of BC livestock averaged over a year (kg livestock biomass for an average day in the year). The biomass was calculated using a variety of data sources including Statistics Canada Census of Agriculture data, livestock commodity groups and Agriculture and Agri-Food Canada slaughter data. The calculation for a given commodity included the estimated number, weights and lifetimes of the various production classes. Both breeding livestock and slaughter animals were included for a given commodity.

Figure 3 shows the total BC OTC antimicrobial sales over the 11 years, standardized by biomass and broken down into categories of importance in human medicine (categorization of each drug at the time of the analysis). Sales by category fluctuated; however, the average annual sale of categories I, II, III, and IV are 0%, 9%, 42%, 49%, respectively. The sale of category IV antimicrobials remained highest relative to other categories, with the exception of 2008-2009, where category III was highest. Category II sales remained well below Categories III-IV. In 2010 there was a down-trend in Category III sales while Category II sales increased for the same time, but this trend reversed in 2011-2012.

[10] http://www.agf.gov.bc.ca/lhmr/pubs/otcu_amu.pdf

With the exception of 2004-2006 there were no category I antimicrobials sold OTC in BC. From 2004-2006, the category I antimicrobial polymyxin B was sold on the order of 0.000004 gm/biomass tonne (4.5grams raw mass, less than 0.00001% of the total annual sales). The polymyxin B was in an intramammary preparation for the treatment of mastitis in dairy cows.

The category II antimicrobials virginiamycin (streptogramin) and penicillin G (penicillin) accounted for approximately 60 to 85% of annual category II sales. In 2011 and 2012, penicillin G accounted for over half of the category II sales alone. Tylosin (macrolide) was typically the third most sold antimicrobial in this category, but in 2011 and 2012 streptomycin (aminoglycoside) was third. Other category II antimicrobials included neomycin and dihydrostreptomycin (aminoglycosides), lincomycin (lincosamide) and erythromycin (macrolide).

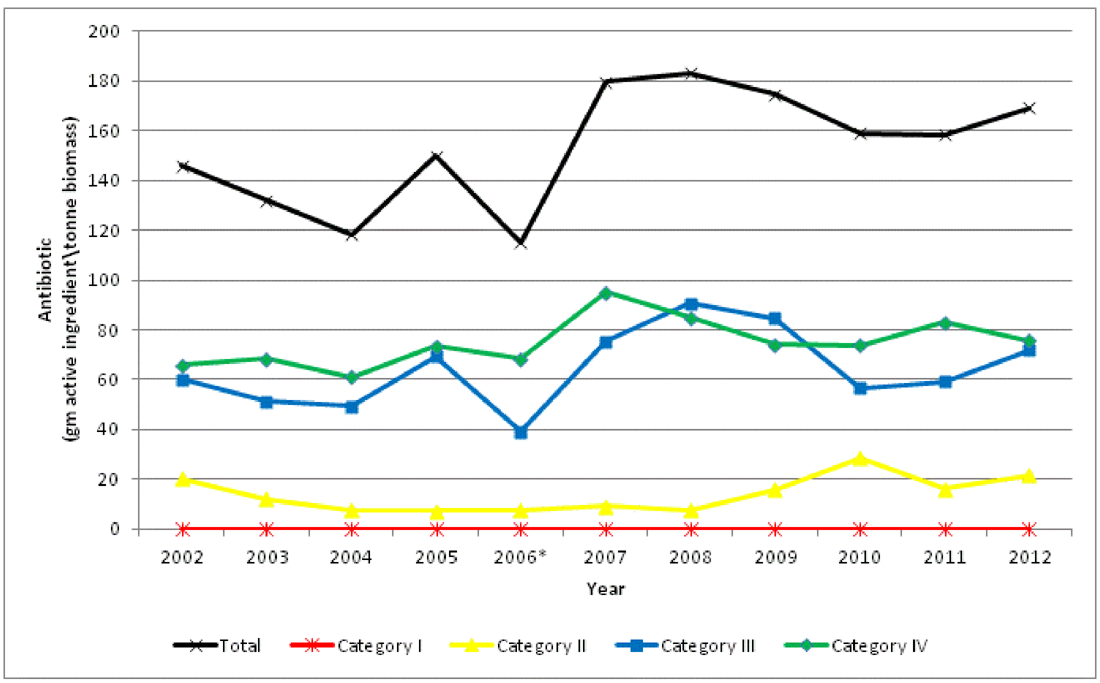

Figure 3. Annual OTC antimicrobial purchases by retailers in BC categorized by importance in human medicine, 2002 – 2012, purchases by veterinarians or pharmacists not included.
* Missing data.

The combination of bacitracin and tetracyclines (oxytetracycline, chlortetracycline, and tetracycline) accounted for over 90% of the annual category III sales. The third highest was non-potentiated sulphonamides, averaging approximately 5% from 2002 to 2012. The other category III classes sold were aminocyclitols (spectinomycin), pleuromutilin (tiamulin), coumarins (novobiocin), nitrofurans (nitrofurantoin, nitrofurazone), and topical aminoglycosides (neomycin). Monensin accounted for approximately half of the category IV sales followed by narasin, salinomycin, lasalocid, all ionophores. The other category IV product was bambermycin, a flavophospholipol.

Over the 11 year span, total BC OTC antimicrobial sales increased by an estimated 11% (approximately 1% annually), though the annual total fluctuated up and down by year, with a peak in 2008. Penicillin G accounted for a large portion of the category II sales over the period. Its Health Canada categorization as having high importance in human medicine was examined in the BC report. Despite its narrow spectrum of activity and limited use in human medicine, penicillin G is categorized same as the extended spectrum penicillins, beta-lactamase resistant penicillins, first and the second generation cephalosporins, all of which require a prescription.

Of all the OTC antimicrobials sold in BC, according to their labels, approximately 95% are approved for administration in feed, 5% in water, with all other methods accounting for less than 1%. Approximately one-third of the antimicrobials have a single label usage category (therapeutic, prophylaxis, or growth promotion) while the majority were labelled for two or more of these usages. The majority of antimicrobials are approved for use in more than one species. Those labelled for poultry, cattle & swine or poultry & swine accounted for 83% of total sales.

Key Findings – Review of OTC Policy:

- Category I antimicrobials are generally not distributed OTC in British Columbia.
- Category II antimicrobials account for only 9% of OTC sales in BC.
- Category IV antimicrobials account for approximately half of all OTC sales in BC.
- These data illustrate the variation of BC OTC antimicrobial sales over time and that more detailed information is required to better understand the relationship between use and resistance.

Analysis of Antimicrobial Use and Resistance Data from Canada to Determine the Potential Impacts of a Prescription Use Only Policy

Hypotheses and Rationale

Based on a consolidation of potential reasons for enacting a prescription use only policy, the following hypotheses were developed:

- Producers have access to OTC antimicrobials potentially without veterinary supervision that could result in injudicious use, resulting in increased use and increased AMR.
- Requiring a prescription results in more judicious use and decreased AMR because veterinary supervision is required to access antimicrobials.
- Producers under veterinary oversight will make more judicious choices for antimicrobial therapy than producers without veterinary oversight.
- Antimicrobial resistant bacteria and/or their genetic determinants may be disseminated through the environment, the food chain and by direct contact between animals and humans.
- Less AMR in animal bacteria reduces AMR from human bacteria.

Other considerations in the development of the hypotheses:

- A prescription use only policy could increase the use of prescription antimicrobials as producers who previously operated without veterinary supervision (and without prescription antimicrobials) will have access to prescription antimicrobials by means of veterinary supervision.
- Though prescription drug use could increase, it is not clear how much and whether or not this represents judicious or injudicious use under a stewardship lens, and its impact on AMR is uncertain.

Based on the above rationale, the following testable hypotheses were developed on the potential impacts of OTC and prescription use only policies:

<u>OTC Antimicrobials (based on the federal PDL)</u>

Null hypothesis (H_0): Regions that allow OTC dispensing of antimicrobials do not have greater OTC AMR and AMR compared to those that only allow AMU through veterinary prescription.

Alternative hypothesis (H_a): Regions that allow OTC dispensing of antimicrobials have greater OTC AMU and AMU compared to those that only allow AMU through veterinary prescription.

Prescription Antimicrobials (based on the federal PDL)

Null hypothesis (H_0): Regions that only allow AMU through veterinary prescription do not have greater prescription AMU and AMR compared to those that allow OTC dispensing of antimicrobials.

Alternative hypothesis (H_a): Regions that only allow AMU through veterinary prescription have greater prescription AMU and AMR compared to those that allow OTC dispensing of antimicrobials.

The presence of prescription use only policies and combined OTC-prescription AMU policies among Canadian provinces presents an opportunity to test the hypotheses using available regional Canadian surveillance data. The majority of the data analyzed was kindly provided by the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS). Provincial dairy AMU and AMR data were also analyzed. There were no other known data from provinces for AMU or AMR that could be incorporated into the analysis.

CIPARS Farm, Abattoir, Retail and Human AMR, and Dairy AMR/AMU Analyses

Methods

CIPARS shared provincial or regional data on AMR from various bacteria (for example, *Salmonella* spp, *E. coli*, *Enterococcus* spp, *Campylobacter* spp) associated with various host species (for example, cattle, chickens and hogs). The animal isolates are from various sectors including farm, abattoir and retail; human isolates are from clinical cases. Human data was taken from publicly available CIPARS reports. The CIPARS AMR data from swine farms, abattoirs, retail meat and humans spanned from 2006, 2002, 2003, and 2003, respectively, to 2011. CIPARS Farm-Swine antimicrobial resistance data are for bacteria isolated from composite pen fecal samples collected on grower-finisher operations. Provincial AMU and AMR data associated with dairy cattle were available from Journal of Dairy Science (JDS) articles (25; 26; 27). The dairy AMR data were the results of susceptibility tests conducted on bacteria isolated from milk samples collected directly from cows on farm.

The antimicrobial active ingredients in the AMR and AMU data sources were classified as OTC, prescription or neither, based on the definitions of the Canadian *Food and Drug Regulation* PDL. Those without a classification were excluded from the analysis. Exclusion was primarily due to an absence of veterinary products with the respective active ingredient and no recognized extra-label use of human products. Testing the hypotheses involved comparing AMR or AMU between regions or provinces that varied in their antimicrobial dispensing policy, OTC vs. prescription use only. The AMR and AMU data were not normally distributed. Non-parametric methods were used to analyze all the CIPARS AMR data, the JDS data, and the

CIPARS Farm-Swine AMU data. Parametric methods were used to analyze the abattoir, retail and human CIPARS AMR data and compare results to the non-parametric results. All statistical tests were conducted using a P-value ≤ 0.05. The prescription use only region was Québec. The other regions had blended OTC-prescription policies for the time period and were compared as individual provinces or combined in varying ways depending on the data: Atlantic (PEI, New Brunswick, Nova Scotia and Newfoundland Labrador), Maritimes (PEI, NB, NS), Prairie (Manitoba, Saskatchewan and Alberta), or West (MB, SK, AB and BC). The parametric and non-parametric statistical comparisons between regions were conservative in that two-tailed tests were used to assess statistical significance, whereas the hypotheses presented are one-sided. Highlighting of the prescription use only province in the results and hypotheses in Tables 4-7 and 13-14 is included as an aid in interpreting the analytical results.

Non-parametric Analyses:

The CIPARS AMR data were quantified as the regional annual proportions of bacterial isolates of a given bacterial genus resistant to a given antimicrobial. Preliminary analysis to adjust for clustering of the swine farm AMR proportions had no effect on the results and was not used further (data not shown). The JDS AMR data (26; 27) included regional odds ratios of resistant *E. coli* or *Staphylococcus aureus* to a given antimicrobial. The odds ratios were from logistic regression models using data from approximately 75 farms and 394 *E. coli* isolates or 562 *Staphylococcus aureus* isolates. An AMU observation for the JDS data (25) was the average antimicrobial drug use rate (Animal Defined Daily doses per cow-days) for each antimicrobial for each region based on a total of 89 dairy farms.

The Friedman test was used to determine if the variation in AMR or AMU across regions was statistically significant. If the variation was significant, the Wilcoxon signed rank test was used for pairwise comparisons between the prescription use only region and the other regions. The statistical significance of the non-parametric analyses did not account for the observations being means, and thus are conservative. A separate analysis was conducted for each sector sampled (i.e., dairy farm, swine farm, abattoir, retail meat and human) on the expectation that the pattern of AMR could change along the supply chain; for example, the impact of animal AMU on AMR could diminish along the supply chain. Further, separate models were run for individual bacteria. A large number of models were run. Results are presented for separate bacterial genera and by consolidating bacteria within sector to help the reader see the regional trends in overall resistance. The rationale for the prescription use only policy consideration was not specific to individual bacterial genera or resistance to specific antimicrobials. As a result, this consolidation best addressed the question at hand (AMR and AMU in regions with and without strict prescription only use).

Parametric Analyses:

The parametric analysis of the CIPARS AMR data used a negative binomial or zero inflated negative binomial regression models as determined by the data. The dependent variable was the number of bacterial genus isolates resistant to a given antimicrobial. Region and year were included as independent, categorical variables, with the prescription use only region and 2002 being the respective referent groups. A large number of models were run and not all converged. Year was excluded from analysis of the human data to allow for model convergence. Models were run by bacterial genus and sector: retail and abattoir data were combined and human models were run separately.

Methods – Limitations:

The findings of this analysis need to be considered in light of the fact that they are detecting associations between AMR within different regions with or without a prescription use only policy. They do not necessarily represent a direct causal relationship (i.e., one cannot say with certainty that the prescription policy in one region is necessarily the direct cause for its level of AMR being more or less than another region). Detected associations can still provide useful information when considering a prescription use only policy, but one must remember the limitations of the analysis and the evidence.

This analysis was not able to control for confounding variables that could impact levels of AMR within different regions outside of the prescription status of antimicrobials. This analysis was based on, at times, limited data gathered from different sources (several CIPARS combinations of sectors, species and bacteria, human isolates in clinical cases, and a study in the Journal of Dairy Science). Variables such as management practices, disease risks and rates, environmental factors and cultures of veterinary practice can easily vary between regions. Further, it is possible that levels of resistance within certain bacterial genera and species to certain drugs may cluster within livestock species, region or at other levels. Unfortunately, the surveillance data available did not capture information to allow for the control of confounding variables. Preliminary attempts were made to assess clustering by herd (see non-parametric below) but it did not seem to have a large effect on results. As a result, detailed cluster analyses were not performed. Most importantly, samples sizes were small and it is likely that control of confounding variables, if information had been available, would have been hindered by a lack of power.

Results

Tables 4 and 6 present the consolidated sectoral results from the non-parametric analysis for OTC antimicrobials and prescription antimicrobials, respectively. The Ranking column presents the order of the regions' AMR or AMU from highest to lowest based on the Friedman test. The asterisks in the Ranking column denote the regions that are statistically different than the prescription use only region using the Wilcoxon signed rank test. Detailed non-parametric results by bacteria are presented in Appendix 1 (Tables 13 and 14). Tables 5 and 7 present the results of the parametric analysis of the AMR data for OTC antimicrobials and prescription antimicrobials, respectively. Parametric results are presented for models where the indicators for region were significant to the model as a group ($P \leq 0.05$). Individual regions that are not shown to be significantly different than the referent cannot be considered to have different levels of AMR. The hypotheses are laid out in each table. For the OTC analysis (Tables 4 and 5), null hypothesis was that the prescription use only region (Rx) had average levels of resistance compared to the OTC regions, while the alternative was that it had the lowest resistance to OTC antimicrobials. The alternative hypothesis for the prescription analysis (Tables 6 and 7) was the opposite, that the prescription use only region had the highest resistance.

The results for the relationship between regions with a prescription use only policy and resistance to OTC antimicrobials were generally consistent between the non-parametric (Tables 4 and 13) and parametric (Table 5) analyses, despite the different analytical approaches and differences in how the data were used for the analyses. The region with prescription use only dispensing had consistently among the highest rankings for resistance to OTC antimicrobials compared to the regions with combined OTC-prescription use. This effect appeared strongest for bacterial isolates originating from animals or retail meat and weakened with human isolates (Tables 4 and 5). Generally, AMR in the prescription use only region was statistically greater than the other regions in the non-parametric analysis. This finding was echoed in the parametric analysis, but was not as consistent. Dairy herds in the prescription only province ranked the lowest in terms of OTC antimicrobial use relative to the other regions in the study. When models results were split out by bacterial species (Table 13), the general trends remained the same as noted above. Exceptions included higher resistance in *Salmonella* from farm swine and retail chicken in ON versus QC.

The results for the effect of a prescription use only policy on resistance to prescription antimicrobials were less consistent between the non-parametric (Tables 6 and 14) and parametric (Table 7) analyses. The non-parametric results showed that the prescription use only region consistently ranked in the top-half for resistance to prescription antimicrobials and was generally statistically higher than the bottom ranked regions; however, exceptions are evident in the results in Table 14. The parametric results showed bacterial genera and sector variation in levels of resistance to prescription antimicrobials in the prescription only compared to other regions. The parametric resistance results for human isolates were consistent but that from the retail and abattoir isolates varied. The prescription only region ranked in the bottom half for prescription AMR among abattoir and retail associated *Salmonella* isolates, average or above for *E. coli* isolates from the same sectors and above average for the *Enterococcus* and *Campylobacter* isolates from the same sectors. The non-parametric analysis of resistance to prescription antimicrobials among milk isolates from dairy cows ranked the province with prescription only dispensing at a tie for second among the four regions. Dairy herds in the prescription only province ranked third in terms of prescription antimicrobial use relative to the other three regions. The prescription use only region ranked above average for resistance to prescription antimicrobials among human *Salmonella* isolates in the non-parametric and parametric analysis, which was not consistent with the low ranking among the abattoir and retail associated *Salmonella* isolates from the parametric analysis.

These results suggest that when considering consolidated resistance to OTC antimicrobials from multiple bacteria and sectors, the levels of resistance in regions allowing OTC sales was not more than the region with prescription only use. In fact, the opposite relationship was often found. Similar results were noted for consolidated resistance to prescription antimicrobials; however, the results were not as consistent as those for resistance to OTC antimicrobials. The prescription only region has higher levels of resistance to prescription antimicrobials for some bacterial-sector combinations, but not for others, and these results varied between the non-parametric and parametric analyses.

Key Findings - CIPARS antimicrobial resistance data analyses:

- Resistance to OTC antimicrobials: the prescription only province was among the highest rankings compared to regions that allow OTC dispensing.
- In assessing resistance to prescription antimicrobials, the results of the non-parametric and parametric analyses were less consistent and varied by bacterial species and data source (sector).
- Generally, the prescription use only province had increased resistance to prescription antimicrobials compared to other regions.
- These results need to be interpreted in considerations of the limitations discussed on page 26. For example, the results provide measures of association, but not direct causal evidence for a link between the prescription use only policy in one region and the level of AMR being more or less than other regions.

Key Findings - Dairy antimicrobial use and resistance analyses:

- The prescription only province was among the highest rankings for resistance to OTC antimicrobials.
- The prescription only province was among the highest rankings for resistance to prescription antimicrobials.
- The prescription only province was among the lowest rankings for the use of OTC and prescription antimicrobials in dairy herds.

CIPARS Farm-Swine Antimicrobial Use Data Analyses

Data collected through the CIPARS Farm-Swine surveillance program, 2009-2012, were used to assess regional differences in antimicrobial use. Two analyses were conducted: a parametric analysis of the frequency of AMU and a non-parametric analysis of quantitative antimicrobial exposure data. It is important to note that the CIPARS Farm-Swine AMU data come from 90-100 grower-finisher sentinel swine herds (number varies with the year) in the five major pork producing provinces (Ontario, Québec, Alberta, Saskatchewan and Manitoba). Data from the three Prairie Provinces were pooled for the analysis; management and demographic factors are similar for these provinces. The results provide data for a sample of grower-finisher farms from provinces that represent 85% of Canadian pork production.

Analysis 1: Methods

The data analyzed for the first analysis were herd level data in the form of farm counts for reported antimicrobial uses by active antimicrobial ingredients/classes. Two multivariable logistic regression models were used to compare the frequency of AMU in grower-finisher pigs. For the first set of models, the dependent (outcome) variable was the use of an antimicrobial class on a farm by any route of administration (feed, water, injection) = Yes. In the second set of models, the dependent variable was the use of an antimicrobial belonging to a specified category of importance to human medicine (I-IV) for each route of administration (feed, water, injection). The models included two explanatory variables: Region - locations of farms in the Prairie region (Alberta, Saskatchewan and Manitoba), Ontario or Québec, the latter being the referent region; Year - 2009, 2010, 2011 and 2012 (referent). Model estimates were converted to odds ratios - the odds of a herd-level use of a specified antimicrobial class in a particular region and year relative to the referent region and year.

Analysis 1: Results

Tables 8 and 9 provide summaries of the CIPARS Farm-Swine AMU herd count data and logistic regression analysis results, respectively. The most commonly used antimicrobials in all grower-finisher swine herds combined across all years, by any route of administration, were ceftiofur (Cat. I), chlortetracycline (Cat. III); penicillin G, tylosin and lincomycin (Cat. II) and salinomycin (Cat. IV) (Table 8). The only category I AMU reported was ceftiofur, an extended spectrum cephalosporin, administered by injection. Ceftiofur was the only Category I antimicrobial listed in the CIPARS-Farm-Swine questionnaire as enrofloxacin was not registered for use in swine prior to 2012; no other category I antimicrobials were reported under “Other”.

In general, the results of logistic regression analyses indicated that the odds of a farm reporting an antimicrobial being administered to grower-finisher pigs, by any route of administration, was lower in herds located in the Prairie or Ontario regions compared to herds in the Québec region. Compared to Québec the odds of using extended spectrum cephalosporins, potentiated sulfonamides, macrolides, streptogramins and tetracyclines were statistically significantly lower for herds in the Ontario and Prairie regions. The herds in the Prairie region had significantly lower odds of using penicillins but significantly higher odds of using lincosamides (3x) than Québec. Use of ionophores was significantly lower in Ontario than Québec herds. The only significant temporal difference was for 2010 and 2011 where herds had greater odds of reporting the use of potentiated sulfonamides in those years compared to 2012 for all regions. Although not explicitly asked in the questionnaire, the odds of not using any antimicrobials during the grower-finisher period where 8 and 22 times greater in Ontario and the Prairie region, respectively, compared to that in Québec. Year was not significantly associated with producers reporting no AMU. Models were run including and excluding herds that reported no AMU by any route of administration – there were minor differences in the estimates for each of the specified antimicrobials but there were no substantive differences in the significant associations among AMU frequency, region and year whether "no AMU" herds were included or not.

Table 10 shows result for models assessing AMU frequency by category of importance to human medicine. These revealed that, with the exception of category III antimicrobials administered in water or by injection, there were significant regional differences across all categories. The number of farms in Ontario or the Prairie regions, or both, reporting AMU were lower for Category I injections, Category II administered by feed, water and injection, and Category III/IV use in feed compared to Québec.

Key Findings – Grower-Finisher Swine Herd-level antimicrobial use analysis:

- The most commonly used antimicrobials in all grower-finisher swine herds across all years: ceftiofur (Cat. I), chlortetracycline (Cat. III); penicillin G, tylosin and lincomycin (Cat. II); and salinomycin (Cat. IV).
- The only Category I antimicrobial used was ceftiofur, a third generation cephalosporin, administered by injection.
- With the exception of lincosamides, the odds of AMU for the majority of antimicrobials, was significantly lower in herds located in the Prairies (Alberta, Saskatchewan and Manitoba) and Ontario regions relative to those in the Québec region.
- The odds of Québec herds reporting use of antimicrobials across categories of importance to human medicine was higher by any route of administration, except for Category III antimicrobials administered in water or by injection.
- These results need to be interpreted in consideration of the limitations that are discussed on Page 29.

Analysis 2: Methods

The second analysis compared differences in quantitative antimicrobial exposures through medicated feed using herd level data that quantified AMU as grams of active ingredient per thousand pig-days at risk (gAI/1000PD). Estimates of gAI/1000PD were derived from the reported inclusion rate (grams of active ingredient per tonne of feed) of an antimicrobial in a medicated ration, the number of pigs in the grower-finisher group, the pig weights at the start/end of the ration feeding period, and feed consumption estimates from *Nutrient Requirement of Swine 2012* (28). Medicated feed represents the only route of administration for which quantitative data were collected. An assessment of the gAI/1000PD data for most of the antimicrobials were skewed and did not satisfy the distributional assumptions for parametric analyses. Non-parametric alternatives were used to assess significant regional and temporal associations with quantitative feed AMU, $P \leq 0.05$: Kruskal-Wallis and Wilcoxon Rank Sums Tests were applied to identify significant regional differences; pairwise two-sided multiple comparison analysis for comparing region pairs were conducted using the Dwass, Steel, Critchlow-Fligner Method (SAS 9.3, SAS Institute Inc., Cary, NC, USA). Friedman Chi Square Tests were used to test for associations between Region and AMU while controlling for Year. Measures of central tendency for grams of active antimicrobial per 1000 pig-days were reported as the median values for each specified antimicrobial use by herds in a region for a given year, but medians were not compared statistically. Only herds who reported using a specified antimicrobial where included in the analysis for that AMU.

Analysis 2: Results

Results of the non-parametric analyses to assess significant regional and temporal differences in quantitative antimicrobial exposure through feed are summarized in Table 11. The antimicrobials most commonly used in medicated swine rations were chlortetracycline (Cat. III), tylosin and lincomycin (Cat. II) and salinomycin (Cat. IV). Regional median values reflect the variation in inclusion rates (grams of active antimicrobial ingredient per tonne of feed) between regions. The only significant regional difference in the quantity of antimicrobial used in feed was for chlortetracycline and tylosin. The median quantity of chlortetracycline used in medicated feeds was greater on a herd basis in Québec compared to Ontario, while the quantity used in Ontario herds did not differ significantly from those in the Prairie region. Relative to Québec herds, those in the Prairies used higher levels of tylosin in feed but there was no significant difference in the quantity used in Prairie Provinces compared to Ontario. The quantity of chlortetracycline and tylosin used in feed were both significantly associated with year. For certain antimicrobials, there were only a few herds in a region using the specified antimicrobial, which could result in a lack of power to detect significant differences. Tables 9 and 11 show the challenges of comparing regional use at the class versus ingredient level when considering the regional differences in tetracycline ingredients. For several antimicrobials, there were an insufficient number of herds using the antimicrobial or only a single province represented in the data, making comparisons invalid or impossible.

Key Findings – Grower-Finisher swine feed antimicrobial use, quantitative analysis:

- The antimicrobials most commonly used in grower-finisher swine rations: chlortetracycline (Cat. III); tylosin, and lincomycin (Cat. II); and salinomycin (Cat. IV).
- There were no Category I antimicrobials used in medicated feeds (there are no Category I drugs approved for in feed use).
- There were significant regional differences in the quantity of chlortetracycline and tylosin administered through grower-finisher rations.
- The median quantity of chlortetracycline administered through feed in Québec herds was significantly higher than that in herds in the Prairie and Ontario regions.
- The median quantity of tylosin administered through feed in herds located in the Prairie region was significantly higher than that in Québec herds.
- For several antimicrobials, there were an insufficient number of herds using the antimicrobial or only a single province represented in the data, which precluded the analysis of those antimicrobials. Further limitations are discussed on page 29.

Discussion

There is little doubt that the issue of AMU and AMR is a growing global public health concern. A recent report released by WHO calls it "a problem so serious that it threatens the achievements of modern medicine" and states that we are entering "A post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century" (29).

Preserving antimicrobial effectiveness and protecting public health is also of concern to Canada's veterinary and agricultural sectors. When the CCVO formed the Antimicrobial Use in Animal Agriculture Committee in 2012, its overarching goal was to share information and provide policy recommendations on this matter to the CCVO. This information would assist the CCVO in forming policy advice to preserve the efficacy of antimicrobials for human and animal health by promoting antimicrobial stewardship in agriculture and veterinary medicine. A number of different policy recommendations were suggested, including a prescription use only policy for antimicrobials given to animals. This suggestion did not receive unanimous support from Committee members; consequently, a working group was struck to study the evidence supporting a prescription use only policy. It must be made absolutely clear to the reader – the efforts of the working group and the generation of this report specifically address a prescription use only policy as one piece of antimicrobial stewardship without its interaction with other measures of this concept; it does not endeavor to address prudent AMU and stewardship in general.

Agriculture and veterinary medicine face increasing criticism about the seemingly disproportionate use of antimicrobials in livestock as opposed to human medicine when comparing total kg of active ingredient sold, with disparities of 80% vs 20% respectively (30; 31). Though not in dispute, this statistic is misleading in that it does not consider:

- Reason for treatment (therapeutic, prophylactic or growth promotion);
- Categorization of the human versus animal use with respect to importance in human medicine, for example, the 80% includes Category IV antimicrobials (e.g., ionophores) that are not used in human medicine and, in some countries, are not classified as veterinary drugs;
- The size of the underlying populations at risk of treatment. Taken collectively, it is possible that the total weight of livestock treated far exceeds that of weight of humans treated. As a result, it is possible that when this biomass is considered (i.e,. mg of drug used per kg of body weight), this disparity may no longer exist and may actually favour higher use in humans versus livestock in a biomass context, but this work remains to be completed.
- Mass of active ingredient is a coarse measure of use. For example, the antimicrobials most important to human medicine tend to require lower doses.

Regardless of the statistics, the important question remains: what is the impact of AMU in livestock on AMR and its negative health effects in humans? This work did not endeavour to answer this question, but its consideration is important to understand the current context for AMU in livestock production as a risk for human health. Antimicrobial use ultimately selects for AMR and there is evidence that AMU in livestock selects for resistant bacteria and that these can transfer to humans, primarily via the food chain (32; 33; 34; 35; 36; 37; 38; 39; 40). However, the quantitative risk of agricultural AMU for the negative health effects of AMR in humans remains unclear due to the complex epidemiology of resistance development and transfer at the bacteria-drug-host interface and a larger ecological context (41). An extensive review of the literature by Phillips et al. (2004) concluded that, with respect to AMR in humans due to AMU in livestock, "little additional harm results from resistance, even when infection supervenes" (42). While lack of data and information gaps make it difficult to accurately assess the risk, simulation modelling has been applied by some researchers to attempt to quantify risk. Results of some risk assessments indicate that AMU in food producing animals has a relatively small impact on human health and that banning antimicrobial use in livestock would more likely negatively impact human health since it would result in increased disease in the animals which translates into increased foodborne disease risk (43; 44; 45; 46; 47; 48; 49). Recent genetic modeling suggests that epidemics of highly resistant *Salmonella* Typhimurium DT104 may be highly contained within animal and human populations, respectively (50). However, there are other risk models that demonstrate the etiologic fraction of human infections with resistant *Salmonella* infections as a direct result of subtherapeutic use of antimicrobials in livestock but the magnitude of this result is uncertain (50). Other models have sought to provide quantitative estimates of fluoroquinolone-resistant *Campylobacter* cases in humans that are attributable to eating chicken meat or human cases of ceftiofur-resistant *Salmonella* Heidelberg that are attributable to eating chicken meat or to human prior antimicrobial consumption (51; 52). To highlight the paucity of broader information for quantitative risk, these latter three studies focus on specific bacterial-drug combinations and do not speak to the global question of risk from AMU in agriculture.

This work sought to elucidate the positions and rationale of various organizations and experts on prescription use only policies to better understand the move towards prescription use only policies by multiple jurisdictions and agencies. The working group accessed documents publicly available on the internet but learned that not all jurisdictions or agencies posted this information and not all were available in English or French. In some cases, policies were implemented 10-15 years in the past and the documents were never available online or were archived.

The lack of specific and measurable policy objectives hindered the ability to determine the outcomes of prescription use only policies. It is possible that the objective of reducing the use of OTC antimicrobials by bringing them under veterinary prescription may have impacts on the volume of use of higher category drugs (e.g., use of category I drugs could increase). However, it is very difficult to determine whether this is judicious or non-judicious use. It is important to note that even with a prescription only system the producer maintains a significant role in the diagnosis and treatment decisions for their animals. Invariably, no reviewed group or agency presented evidence about the impacts of a prescription only policy. For example, the WHO's recommendations for reducing antimicrobial use in food-producing animals were "based on the 'significant direct and indirect effects of AMU in animals on AMR in human pathogens…from several lines of evidence" (53), while at the same time acknowledging that the relationship could not be fully evaluated based on current information. The WHO also acknowledged that a lack of data on the occurrence of resistance and on AMU in animals and a lack of standardized data collection are challenges that need to be overcome.

In general, non-specific and non-measured concerns that AMU in livestock results in harm to human health are a common motivator for the support for a prescription use only policy. Some organisations (e.g, WHO) cite evidence for the transfer of AMR to humans or to human pathogens. There are increasing publications of specific estimates of the risk of human health impacts, treatment failures or case numbers (e.g., the probability of and the likelihood of effect of AMR exposure). However, due to the complex epidemiology of AMR, it is extremely difficult to quantify the global estimate of risk to human health from livestock AMU. In other cases, policy decisions are based on broader generalizations, e.g. *"Because agriculture accounts for the highest volume of antibiotic use, the farm environment serves as a reservoir of resistant genes" (Dr. Bill Mackie, British Columbia delegate to the CMA* (54)*)*. However, it is important to note that moving towards prescription only use is seen as a means to maintain agriculture's social license to retain access to antimicrobials for food animal production. Veterinarians are the most appropriate professionals to make decisions about diagnosis, treatment and antimicrobial administration based on their training and experience (6). This social license may be improved in the eyes of the public and consumers if all antimicrobials were strictly overseen by veterinarians who meet societal standards and regulations that are upheld by provincial legislation. Using the legal tools of self-regulation, these professionals are held in account and presided over by their peers and the public within regulatory bodies in each province. However, care must be taken in using social license as a reason for prescription only policy. There is potential for negative societal reaction given that veterinary oversight of agricultural AMU does not equate to the level of oversight by physicians in the human medical system. The Health Canada (2002) report raised the potential for conflict of interest when veterinarians act as prescribers and dispensers with the ability to derive profit from the sale of antimicrobials (3). Further, a prescription only policy alone is unlikely to reduce agricultural AMU. There is also concern that a more strict policy to restrict AMU in agriculture could compromise animal health and welfare in certain situations. As mentioned in the recently released US Report to the President on Combating Antibiotic

Resistance[11], it is generally recognized that all uses of antimicrobials in human and animals promotes the emergence and spread of AMR. Therefore, it is important for the agriculture industry in Canada to achieve antimicrobial stewardship as part of this social license.

In almost no case was a prescription use only policy recommended as a stand-alone solution to reducing AMU, or promoting judicious use in food producing animals or broader antimicrobial stewardship. The only group to make such a recommendation was the Canadian Medical Association in 2011. Instead, prescription use only was typically endorsed or used as one of many tools recommended to promote judicious AMU in livestock. The WHO recommended reducing AMU in food producing animals as just one of six points in their policy package for combating spread of AMR (55), and under this point prescription use only policy is just one of 17 recommended actions (7).

The BC data show that the majority of OTC antimicrobial drug distribution included Category III and IV drugs. This suggests that OTC AMU in BC livestock did not impart a large direct selection pressure for resistance in antimicrobials of high importance to human medicine (Categories I-II). A stewardship principle promoted in the CVMA Prudent Use Guidelines and other sources is that livestock usage of antimicrobials of less importance to human medicine is preferable to those that are more important to human medicine (9; 1; 56). Generally, usage of lower category antimicrobials imparts little to no direct selection pressure for resistance to drugs of higher human importance. However, it is possible that selection of resistance to Category III drugs could have an indirect effect on resistance of more important drugs through cross-selection to drugs in the same class. Further, usage of lower category drugs could co-select for resistance to higher category antimicrobials through genetic linkage of resistance elements for completely unrelated antimicrobials on mobile genetic elements, with potential clonal expansion of the higher category resistance. There is evidence for this specifically with tetracycline use and selection for ceftiofur resistance and clonal expansion of the resistance determinant in feedlots (57). This group had debate about whether or not use of lower category drugs of less importance to human medicine (III-IV) represents more judicious use than that of higher categories (I-II). We recognized that evaluating the judiciousness of AMU based on metrics of overall drug use based on categories of human importance is challenging and may not be the best metric for policy decisions. Cross and co-selection for AMR should be considered in policy development. However, there are gaps in the knowledge about cross and co-selection and its impact on the ecology of AMR. It is important to note that there are no known linkages between resistance elements for Category IV drugs and drugs of higher importance. It is also possible that for some animal diseases, usage of a more important drug may be more prudent to treat the bacterial infection in an expedient manner compared to a lower-category drug (*Dr. Paul Morley, CanWest*

[11] http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf

Veterinary Conference, 2012). Antimicrobial volume use metrics are an important measure of AMU, but there is no agreement on this measure to assess prudent use. Agreement on AMU metrics and measures and objectives for their use are critical for implementing and evaluating AMU policy.

It has been suggested a prescription use only system will facilitate the generation of AMU data for surveillance. Yet no Canadian province or territory has generated veterinary AMU data despite long standing veterinary prescription systems. Similarly, human prescribers (e.g, physicians and dentists) do not generate AMU surveillance data. With the exception of the CIPARS swine and broiler farm surveys, all existing Canadian AMU data are generated by dispensers or manufacturers regardless of whether the antimicrobials are OTC or prescription. Human pharmacists or government databases are the source of Canadian human AMU data. Similarly, BC's aquaculture prescription AMU data are sourced from the feed mills supplying the feed, not from the prescribers. The BC OTC AMU data are generated by the OTC retailers. The Canadian Animal Health Institute supplies AMU information on the distribution of antimicrobials to the provinces and territories. A few countries report to use or include prescriptions as a source of data (France, Denmark and the Netherlands). However, their monitoring systems are not based only on prescriptions. Another working group of the CCVO's Antimicrobial Use in Animal Agriculture Committee is working on assessing AMU surveillance systems in Canada and other jurisdictions to make Canadian recommendations for future surveillance.

In Canada a unique situation exists where one province has had a prescription use only policy in place for many years, which was instituted mainly for reasons of residue avoidance and trade. Though this policy was not initially enacted to reduce AMR, it presented an opportunity for the working group to investigate whether it had any impacts on AMR or AMU compared to other regions in Canada. Furthermore, AMR data has been collected across Canada by CIPARS since 2003, along with AMU data from monitored swine herds from 2009 to 2012. Regional differences in prescription policies and the availability of AMR/AMU data provided the working group with the opportunity to investigate the impact of prescription use only policy on the prevalence of AMR and swine AMU. The working hypotheses were that regions allowing OTC sale of antimicrobials would have higher OTC AMU and AMR than regions with strict prescription use only and that the opposite would be true for prescription AMU and AMR in the prescription only region compared to OTC regions.

The results indicated that isolates from food producing animals in the province with a prescription only policy consistently ranked significantly higher for AMR to OTC and prescription antimicrobials compared to regions allowing OTC dispensing, with a few exceptions depending on specific pathogen-antimicrobial combination or species treated. There were similar trends for regional rankings across sectors (farm, abattoir, retail and human) using two different statistical methods. With respect to isolates from humans, the prescription use only province ranked significantly higher for prevalence of AMR than the majority of other provinces. One might speculate that potentially higher AMU when considering the frequency of use in swine herds in the prescription only province could be the cause of higher AMR. Although there were a few exceptions, generally the herd level frequency of antimicrobial use was greater in Québec relative to that in Ontario or Prairie herds, which mirrors the rankings reported for the AMR analysis. However, this only represents the frequency with which herds reported using these antimicrobials. As a result, the quantitative analysis for in feed antimicrobials (mg active drug per 1000 pig days) was conducted to look at actual animal exposure. This analysis only found significant regional differences for two specific drugs (chlortetracycline and tylosin). The former was significantly lower in Ontario than Québec, while the latter was significantly higher in the Prairies than Québec. The limitations of the AMU data (grower finisher swine, herd-level frequency data and the quantitative data only for in feed antimicrobials) make it difficult to draw causal conclusions between the AMU and AMR results.

These results must be interpreted with caution owing to limitations in the data and the analysis. The human AMR data, for example, do not take into account all the other potential sources of resistance risk factors/exposures which could be the source of the human AMR infections/findings. There are substantial provincial differences in human AMU, driven by differences in infectious disease rates, demographics, and formularies. For example, Québec typically has one of the lowest human AMU rates among the regions, based on CIPARS data (31). Also, the human data do not differentiate between cases that were acquired in Canada or those acquired abroad and may not be an entirely accurate reflection of the AMR situation within Canada. We do not know about the evenness of distribution of these cases across Canada and therefore cannot speculate on the impact to these results. Similar regional differences in animal AMU, demographics and disease rates were also not taken into account. Though the volume of distribution AMU data do not include drugs that were imported into Canada under the own use or active pharmaceutical ingredient provisions, these data were not used in the AMU parametric or non-parametric analysis. Conversely, the swine on-farm AMU data from CIPARS and the published dairy cattle use data include imported drugs with domestic distribution. This AMU analysis was conducted on grower-finisher swine and dairy cattle as these were the only commodities for which AMU data existed that represented multiple provinces including Québec. The lack of information and small amount of data did not allow for inclusion of potential confounding variables in the statistical models for any part of the analysis. As a result, statistical associations between region and resistance or use could be the result of the policy differences, but they could also be the result of other confounding factors, such as animal density, disease outbreaks, management factors, etc.

It is well recognized that AMR and its genetic determinants have a complex epidemiology that involves all aspects of the ecosystem where antimicrobials are used and their residues distributed. This report does acknowledge that the approach of combining results from different bacterial genera and antimicrobial classes may miss specific significant differences between regions that do not agree with the overall conclusions of this work. One can argue that such a consolidation is not valid to answer the question of these regional differences at specific levels. However, given the high level of the question at hand (does prescription use only result in less AMR), this consolidation made sense. It allowed a consideration of resistance at a more global level (multiple bacteria and sectors). It represents only one method of assessment of such a policy. The results presented in Appendix Tables 13 and 14 show that results by individual bacterial genus are generally consistent with the consolidated results, with a few noted exceptions. The number of models required for separate analysis of each antimicrobial or class on its own was huge. A number of models failed to converge, reducing the already sparse data that was used to inform the analysis and conclusions. Conducting these analyses and presenting the large number of results would preclude the ability to make global conclusions about overall AMR in a prescription use only versus combined prescription-OTC regions. As a result, consolidated models and results were presented. Further, drug-specific comparisons were not completed. Focused bacteria-drug comparisons are a topic for future specific research questions.

The hypotheses used in this work were simplistic in that they ignore the effect of cross and co-selection for resistance by AMU when making separate comparisons of AMR and AMU for prescription versus OTC drugs. Many more possibilities for analysis exist and they should be considered, but given the scope and resources of the working group, these analyses and results are presented in a consolidated fashion. The strength of this work is that it utilized the integrated AMU-AMR data from CIPARS and related sources. It is the first such consideration of these data. The results undoubtedly create further questions that should be addressed in future work. The CIPARS data in itself is not perfect, but it represents the best national data available in Canada.

It became evident in the review that not all prescription only policies are created equal. A review of existing prescription use only policies found important differences in how they were defined or applied. They ranged in their stringency of application to some or all antimicrobials and this application depended on how antimicrobials were defined as veterinary drugs versus feed additives in each jurisdiction. For example, though both provinces are considered to have prescription use only policies, all veterinary antimicrobials require a prescription in Québec regardless of method of use, while Newfoundland and Labrador requires a prescription for all veterinary antimicrobials other than those permitted in feed according to the CMIB. The European Union is well-known for their prescription use only policy; however, their definition of "antimicrobial" differs from Canada, in that ionophores are not classified as antimicrobials and are available for use as feed additives without a prescription or veterinary oversight.

Other than Québec and Newfoundland and Labrador, other Canadian provinces and territories follow the federal regulation where antimicrobials are sold by prescription and OTC. To illustrate the impacts of differing prescription use only policies on the volume of OTC sales of antimicrobials, Québec's, Newfoundland and Labrador's and an alternative classification scheme with all Category I-III drugs as prescription only were applied to British Columbia's 2012 OTC sales data[12]. Since almost 95% of British Columbia's OTC AMU is in feed as permitted by the CMIB, application of Newfoundland and Labrador's prescription policy would have little impact on overall OTC sales in BC. In contrast, a proposed reclassification scheme that would make all Class I-III (not Class IV) antimicrobials available by prescription only would reduce the total volume of OTC sales by approximately 55%. Application of Québec's policy would eliminate OTC sales entirely.

Regardless of variations in definition, the overarching premise of antimicrobial prescription use only policies is to ensure veterinary oversight of AMU in food producing animals under the belief that veterinary oversight will promote/ensure judicious AMU and enhanced antimicrobial stewardship. However, it remains to be seen what the effect of veterinary oversight will truly have on agricultural AMU and speaks to the need for oversight as part of a larger policy umbrella to address antimicrobial stewardship. One must consider that the application of veterinary oversight in livestock production is variable between species and by route of administration and type of antimicrobial (prescription versus OTC). In general, a veterinarian will not issue individual-animal prescriptions for food animals, nor necessarily be involved in animal diagnosis, treatment decisions or administration for each use of antimicrobials. For example, veterinary oversight could be an annual visit to the premise with review of the producer's methods of diagnosing animals, determining appropriate treatments and administration of those treatments. The veterinary oversight could include the producer's access to appropriate antimicrobials, including prescription antimicrobials, for a period of time (for example, one year). Denmark's prescription use only policy includes more strict requirements for veterinary supervision of food animal AMU, not unlike physicians' supervision of their patients. CDC Atlanta states up to 50% of all the antimicrobials prescribed for people are not needed or are not optimally effective as prescribed (58). Denmark has continued to institute further controls on AMU in livestock, suggesting prescription use only was not sufficient to ensure judicious or reduce use. However, without a policy of prescription use only, Denmark may not have been able to implement those stricter controls.

Stakeholders outside the veterinary and agricultural communities may not know that veterinary oversight does not always mean direct supervision of AMU in livestock. While supervision under a prescription use only policy may sometimes be indirect, it is recognized that veterinarians are "in the best position to assess the benefit/risk ratio of antimicrobial use in animals" (5). The rationale is that increased veterinary oversight will lead to increased judicious use of antimicrobials in food producing animals through appropriate drug selection and dosing. However, the results of this work and evidence from human AMU, where physician oversight is

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[12] http://www.agf.gov.bc.ca/lhmr/pubs/otcu_amu.pdf

much stronger, suggest that increased veterinary oversight on its own may not have the desired effect on reducing AMR and changing agricultural AMU without the appropriate policy measures to support a more global approach to antimicrobial stewardship.

There are potential negative impacts of implementing a prescription use only policy without other stewardship policies. Requiring a veterinary prescription for all Category I-III antimicrobials will increase producer access to antimicrobials of higher importance to human medicine as they will have increased interaction with veterinarians who can prescribe these drugs. Though this could result in their increased use, imparting more direct selection pressure for resistance to these drugs, this use may actually be more judicious in terms of using the correct drug for the bacteria. A prescription use only policy assumes that all producers have adequate access to veterinary services, which may not be true in all cases across the country. There is concern that remote or rural areas in Canada may not have adequate access to veterinary services, or services are limited and not in close proximity to the farm. Moving towards a prescription use only policy for Category I-III antimicrobials would require collaboration between the federal and provincial governments, veterinary regulatory bodies and agricultural industry groups to develop a service structure to insure the availability of services for all livestock producers. While farms could benefit from increased veterinary involvement, this increased oversight comes at a financial cost. Concerns have also been expressed about the potential conflict of interest of veterinarians acting as the prescribers and dispensers of antimicrobials. There is the potential for the cost of antimicrobials to rise under a prescription use only system. Increased costs of animal production could translate into increased cost for meat and other animal products. However, others suggest that increased veterinary involvement in management decisions could result in cost savings to producers through disease management and prevention outside of AMU. These relative costs and savings are not possible to predict and warrant future research.

Conclusion

Based on the work of this group, the reviewed policies and the results of analysis of available data, there is no indication that application of a prescription use only policy in isolation will reduce AMR or AMU in food producing animals in Canada.

Evaluation of current prescription use only policies revealed that they rarely require a prescription for all antimicrobials. The categories and volumes of AMU that fall under veterinary oversight differ dramatically between jurisdictions with different policy definitions. Regardless of the definition, prescription use only requires veterinary oversight, but the producer still maintains a significant role in the diagnosis and treatment decisions for their animals.

A common motivator for adopting a prescription use only policy is often a non-specific and non-measured concern that agricultural AMU results in AMR in human pathogens and infections. Other countries included a prescription use only policy within a larger policy umbrella to promote antimicrobial stewardship to ultimately affect change and reduce agriculture AMU. As a result, the global effects of a prescription use only on AMR in humans are not certain. None of these countries evaluated the impact of a prescription use only as a stand-alone piece. Given that it was often included with other policies, it is not clear if this piece was required to affect changes in livestock AMU.

The BC OTC AMU revealed that on a biomass basis, the majority of OTC antimicrobials distributed for livestock were Category III and IV antimicrobials. Generally, Category I antimicrobials are not available by OTC in Canada. It is not known how a change to prescription use only would affect the quantity of use of antimicrobials in higher categories, but there is a risk that it could increase. Though the BC OTC data represents less direct selection pressure for resistance of antimicrobials in higher categories, the role of indirect selection is not clear and should be considered. Antimicrobial volume use metrics are an important measure of AMU, but there is no agreement on this measure to assess prudent use. Agreement on AMU metrics and objectives for their use are critical for implementing and evaluating AMU policy.

Analysis of Canadian surveillance data found that a region with prescription use only typically ranked significantly higher for AMR to OTC and prescription antimicrobials compared to regions that allowed OTC dispensing. More swine herds in the prescription use only region used antimicrobials on a frequency basis, but among herds that use antimicrobials, there were no consistent regional trends of quantitative AMU (gAI/1000PD), with the specific exceptions of tylosin and chlortetracycline. The limitations of the AMU data (grower finisher swine only, herd-level reporting frequency data and only having the quantitative data for in feed antimicrobials) make it difficult to draw causal conclusions between the AMU and AMR results.

It is important to recognize that AMR mitigation was not among the main reasons for the implementation of a prescription only policy in Québec in 1985. As a result, there were no supporting policies or strategies that promoted justifiable AMU in agriculture. Other measures of antimicrobial stewardship were implemented only very recently, almost 30 years after the implementation of the prescription only policy.

The limitations of Canadian surveillance data used in this analysis make it difficult to comment with certainty on the direct effect of a prescription use only policy on AMR in humans in Canada. The fact that other countries have incorporated this with a variety of other policy changes to reduce AMU in livestock suggests that it may not be effective on its own. However, these countries did not assess the direct effect of this policy on AMU. Other elements of antimicrobial stewardship, which could be in the form of policy or other methods, include:

1. Enhancing integrated Canadian surveillance of AMR and AMU to provide comprehensive information against which future policies can be measured and to allow timely response to identified concerns.
2. Addressing the federal legislation in Canada that currently allows the importation of antimicrobials for own use or as active pharmaceutical ingredients.
3. Improved veterinary education regarding AMU, AMR, judicious use and stewardship.
4. Improved access to rapid and affordable diagnostics to allow for appropriate antimicrobial treatment decisions.
5. Promoting the adoption of management and biosecurity practices to reduce the need for antimicrobials in livestock (e.g., practices aimed at increasing herd/flock environment hygiene, enhancing herd/flock immune status, and decreasing the pathogen load on farms).
6. Reviewing/phasing out AMU for growth promotion/production purposes in livestock.
7. Promoting the development of new antimicrobial drugs.
8. Promoting the development of vaccines and other products to control/prevent infectious diseases in livestock.
9. Consideration of the potential conflict of veterinarians as antimicrobial drug dispensers.
10. Herd level monitoring of AMU.
11. Banning the use of certain products in livestock.
12. Banning certain types of use (e.g., ELDU of certain products).
13. Oversight controls on the use of certain products.
14. Oversight of veterinarians.

A prescription use only policy is one of many possible tools available to encourage judicious AMU and promote antimicrobial stewardship in agriculture. Though this work found no evidence that this policy in isolation will improve antimicrobial stewardship and reduce AMR, it may be important to maintain agriculture’s social license to retain access to antimicrobials for food animal production. This social license is vital to avoid further restrictive agricultural AMU policies that compromise animal health and welfare.

Analysis Results - Tables

Table 4. OTC Antimicrobials: Summary of the non-parametric analyses of the effect of a prescription use only policy versus a combined OTC-prescription use policy on AMU and AMR. Atlantic (AT): PEI, NS, NB, NL. Maritimes (MA): PEI, NS, NB. West: BC, AB, SK, MB. Prairie (PR): AB, SK, MB.

AMR or AMU	Data Source	Sector	Species Sampled	Bacteria	n	Ranking (Highest to Lowest)
AMR	JDS	Farm	Dairy (milk)	*E. coli*, *Staphylococcus*	6	MA-QC (tied), AB, ON
AMR	CIPARS	Farm	Swine	*E. coli*, *Enterococcus*, *Salmonella*	79	QC, ON, West*
AMR	CIPARS	Abattoir	Chicken, swine[1]	*Campylobacter*, *E. coli*, *Salmonella*	91	QC, BC*, ON*, Pr*, AT*
AMR	CIPARS	Retail meat	Chicken[2]	*Campylobacter*, *E. coli*, *Enterococcus*, *Salmonella*	35	QC, ON*, AT*, Pr*, BC*
AMR	CIPARS	Human	Human (clinical)	*Salmonella*	81	BC*, AB*, QC, MB, ON*, NS*, SK*, NB*, NL*
AMU	JDS	Farm	Dairy		4	AB, ON-MA(tied), QC
	H_0	OTC AMR in OTC regions = OTC AMR in Rx region (see page 23)				OTC, OTC, Rx, OTC, OTC
	H_a	OTC AMR in OTC regions > OTC AMR in Rx region (see page 23)				OTC*, OTC*, OTC*, OTC*, Rx

[1] Samples collect at abattoir are attributed to the region an animal was shipped from. This attribution for AMR samples from beef cattle is questionable given the inter-regional shipment of cattle for backgrounding or feeding. Therefore, the beef cattle abattoir data were excluded from the analysis. Exclusion of the beef abattoir data had no effect on the AMR results for OTC antimicrobials.

[2] Due to concerns with the ability to attribute retail pork or retail beef to production in that region, only results from retail chicken is presented. Exclusion of the beef and pork data had no effect on the AMR results for OTC antimicrobials.

*Statistically different from Québec, $P \leq 0.05$ using a 2 tailed test.

Table 5. OTC Antimicrobials: Summary of the parametric analyses of the effect of a prescription use only policy versus a combined OTC-prescription use policy on AMU and AMR. Atlantic (AT): PEI, NS, NB, NL. Maritimes (MA): PEI, NS, NB. West: BC, AB, SK, MB. Prairie (PR): AB, SK, MB.

AMR or AMU	Data Source	Sector	Species Sampled	Bacteria	Antimicrobial	n	Ranking (Highest to lowest – relative to QC)
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine	*Salmonella*	Sulfisoxizole		QC, ON, Pr*, AT*, BC*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine	*Salmonella*	All OTC		ON, QC, AT, BC, Pr*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*Enterococcus*	Streptomycin		QC, BC, Pr, AT, ON*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*Campylobacter*	All OTC		QC, Pr*, AT, ON*, BC*
AMR	CIPARS	Clinical	Human	*Salmonella*	Streptomycin		BC, QC, ON, Pr, AT*
AMR	CIPARS	Clinical	Human	*Salmonella*	Tetracycline		BC, QC, ON, Pr, AT*
AMR	CIPARS	Clinical	Human	*Salmonella*	Sulfisoxizole		BC, QC, Pr, ON, AT*
AMR	CIPARS	Clinical	Human	*Salmonella*	All OTC		BC, QC, ON, Pr, AT*
	H_0	OTC AMR in OTC regions = OTC AMR in Rx region (see page 23)					OTC, OTC, Rx, OTC, OTC
	H_a	OTC AMR in OTC regions > OTC AMR in Rx region (see page 23)					OTC*, OTC*, OTC*, OTC*, Rx

*Statistically different from Québec, P ≤ 0.05 using a 2 tailed test.

Table 6. Prescription Antimicrobials: Summary of the non-parametric analyses of the effect of a prescription use only policy versus a combined OTC- prescription use policy on AMU and AMR. Atlantic (AT): PEI, NS, NB, NL. Maritimes (MA): PEI, NS, NB. West: BC, AB, SK, MB. Prairie (PR): AB, SK, MB.

AMR or AMU	Data Source	Sector	Species Sampled	Bacteria	n	Ranking (Highest to Lowest)
AMR	JDS	Farm	Dairy (milk)	*E. coli*, *Staphylococcus*	6	AB, QC-MA (tied), ON
AMR	CIPARS	Farm	Swine	*E. coli*, *Enterococcus*, *Salmonella*	121	QC, ON*, West*
AMR	CIPARS	Abattoir	Chicken, swine[1]	*Campylobacter*, *E. coli*, *Salmonella*	302	QC, BC, ON*, AT*, Pr*
AMR	CIPARS	Retail meat	Chicken[2]	*Campylobacter*, *E. coli*, *Enterococcus*, *Salmonella*	81	BC*, QC, ON*, AT, Pr*
AMR	CIPARS	Human	Human (clinical)	*Salmonella*	246	BC*, ON*, QC, AB, NB*, MB*, NS*, SK*, NL*
AMU	JDS	Farm	Dairy		8	AB, ON, QC, MA
	H_0	Prescription AMR in Rx region = prescription AMR in OTC regions (see p.24)				OTC, OTC, Rx, OTC, OTC
	H_a	Prescription AMR in Rx region > prescription AMR in OTC regions (see p.24)				Rx, OTC*, OTC*, OTC*, OTC*

[1] Samples collect at abattoir are attributed to the region an animal was shipped from. This attribution for AMR samples from beef cattle is questionable given the inter-regional shipment of cattle for backgrounding or feeding. Therefore, the beef cattle abattoir data were excluded from the analysis. Exclusion of the beef abattoir data had no effect on the AMR results for Rx antimicrobials.

[2] Due to concerns with the ability to attribute retail pork or retail beef to production in that region, only results from retail chicken is presented. Exclusion of the beef and pork data had no effect on the ranking of Québec relative to the other regions. Restricting the data to chicken resulted in Québec being statistically different than the region with the highest AMR to Rx products.

*Statistically different from Québec at $P \leq 0.05$ using a 2 tailed test.

Table 7. Prescription Antimicrobials: Summary of the parametric analyses of the effect of a prescription use only policy versus a combined OTC-prescription use policy on AMU and AMR. Atlantic (AT): PEI, NS, NB, NL. Maritimes (MA): PEI, NS, NB. West: BC, AB, SK, MB. Prairie (PR): AB, SK, MB.

AMR or AMU	Data Source	Sector	Species Sampled	Bacteria	Antimicrobial	n	Ranking (Highest to lowest – relative to QC)
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine	*Salmonella*	Chloramphenicol		AT, ON, BC, QC, Pr*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine	*Salmonella*	Ceftiofur		BC*, ON, AT, QC, Pr
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine	*Salmonella*	All Rx		BC*, AT, ON, QC, Pr*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*E. coli*	Amoxicillin Clav		BC*, AT, QC, ON, Pr*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*E. coli*	Ceftiofur		BC*, AT, QC, ON, Pr*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*E. coli*	All Rx		BC, QC, AT, ON, Pr*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*Enterococcus*	Gentamicin		QC, ON*, BC, Pr*, AT*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*Enterococcus*	All Rx		QC, ON*, Pr*, BC*, AT*

AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*Campylobacter*	Ciprofloxacin		BC, QC, AT, Pr*, ON*
AMR	CIPARS	Retail and Abattoir	Poultry, Porcine, Bovine	*Campylobacter*	Nalidixic acid		QC, BC, Pr, AT, ON*
AMR	CIPARS	Clinical	Human	*Salmonella*	Chloramphenicol		BC, QC, ON, Pr*, AT*
AMR	CIPARS	Clinical	Human	*Salmonella*	Amoxicillin Clav		BC, QC, Pr, ON, AT*
AMR	CIPARS	Clinical	Human	*Salmonella*	Ampicillin		BC, QC, Pr, ON, AT*
AMR	CIPARS	Clinical	Human	*Salmonella*	Nalidixic acid		BC*, AT, Pr, QC, ON
AMR	CIPARS	Clinical	Human	*Salmonella*	Trimeth Sulpha		BC*, QC, Pr, AT, ON*
AMR	CIPARS	Clinical	Human	*Salmonella*	All Rx		BC, QC, ON, Pr, AT*
	H_0	Prescription AMR in Rx region = prescription AMR in OTC regions (see p.24)					OTC, OTC, Rx, OTC, OTC
	H_a	Prescription AMR in Rx region > prescription AMR in OTC regions (see p.24)					Rx, OTC*, OTC*, OTC*, OTC*

*Statistically different from Québec at $P \leq 0.05$ using a 2 tailed test.

Table 8. Number of pig herds with reported use of specific active antimicrobial ingredients administered by any route[a], by region; *CIPARS-Swine Farm Surveillance 2009-2012.*

	Antimicrobial Class	**Antimicrobial**	**Region**		
			Prairie	Ontario	Québec
I	Extended-spectrum cephalosporins	Ceftiofur	27	4	47
II	Aminoglycosides	Streptomycin	9	7	1
	Lincosamides	Lincomycin	66	31	20
	Macrolides	Erythromycin	0	0	1
		Tulathromycin	12	6	11
		Tilmicosin	0	0	7
		Tylosin	60	37	53
	Penicillins	Amoxicillin	0	0	0
		Ampicillin	4	9	2
		Penicillin G	60	72	68
		Phenoxymethyl penicillin	0	0	0
	Streptogramins	Virginiamycin	1	2	8
	Trimethoprim-sulfamethoxazole	Trimethoprim-sulfadoxine	7	6	32
III	Aminocyclotols	Spectinomycin	1	3	2
	Aminoglycosides	Neomycin	2	4	10
	Bacitracins	Bacitracin	0	0	1
	Phenicols	Florfenicol	4	3	6
	Pleuromutilins[b]	Tiamulin	13	7	1
	Sulfonamides	Sulfonamide (unspecified)	11	0	3
	Tetracyclines	Chlortetracycline	33	29	68
		Oxytetracycline	14	12	2
		Tetracycline hydrochloride	12	4	2
IV	Flavophospholipids	Bambermycin	0	0	8

Ionophores	Salinomycin	25	6	26
No antimicrobial use in Grow-Finish Period		**27**	**8**	**1**
Total questionnaires submitted		**156**	**107**	**102**

Prairie: AB, SK, MB

Roman numerals I to IV indicate the ranking of antimicrobials based on importance to human medicine as outlined by the Veterinary Drugs Directorate.

[a] Herds with reported use of an antimicrobial class by feed, water, injection, or any combination of these routes are included in each count.

[b] Pleuromutilins are not officially categorized in the current Health Canada Classification System. However, according to the criteria provided by Health Canada, pleuromutilins meet the criteria for Category III.

Table 9. Farm-Swine AMU Summary Table: Logistic regression [1] results for the use of specified antimicrobial classes by region and year. Prairie: AB, SK, MB.

		Odds Ratio (Referent Region: Québec)		Odds Ratio (Referent Year: 2012)			Wald Chi-square Test P-value	
Antimicrobial Category and Class		**Ontario**	**Prairie**	**2009**	**2010**	**2011**	**Region**	**Year**
I	ES Cephalosporins	**0.046***	**0.248***	0.911	1.247	1.236	**<0.0001**	0.8126
II	Licosamides	1.65	**2.984***	0.841	0.769	0.911	**0.0007**	0.8732
	Macrolides	**0.390***	**0.519***	1.529	1.538	1.061	**0.0033**	0.3255
	Penicillins	1.233	**0.297***	0.991	1.196	0.798	**<0.0001**	0.6482
	Potentiated Sulfonamides	**0.130***	**0.103***	2.059	**5.109***	**3.472***	**<0.0001**	**0.0312**
	Streptogramins	**0.186***	**0.064***	0.119	0.233	0.229	**0.0104**	0.0882
II/III	Aminoglycosides	0.974	0.586	0.38	0.52	0.32	0.376	0.0774
III	Phenicols	0.453	0.422	0.211	1.132	0.644	0.3485	0.4531
	Pleuromutilins	6.819	9.255	0.217	0.498	0.877	0.1014	0.2288
	Tetracyclines	**0.285***	**0.229***	0.801	1.017	0.963	**<0.0001**	0.8646
IV	Ionophores	**0.165***	0.541	0.592	0.504	0.787	**0.0007**	0.3824
No Antimicrobial Use		**8.353***	**21.518***	1.57	1.426	1.383	**0.0018**	0.8512

[1] Dependent Variable: Farm Counts of specified antimicrobial class use by any route of administration (Yes/No);
Independent/class variables: Region (West, Ontario and Québec-Referent), and Year (2009, 2010, 2011 and 2012-Referent).
*Statistically different from referent, P ≤ 0.05 using a 2 tailed test. Models did not converge for: Bacitracin, Sulfonamides and Flavophospholipids.

Table 10. Farm-Swine AMU Summary Table: Logistic regression[1] results for the use of specified antimicrobial categories as defined by Health Canada) and route of administration, region and year, classes by region and year. Prairie: AB, SK, MB.

Antimicrobial Category of Importance to Human Medicine	Route of Administration	Odds Ratio (Referent Region: Québec)		Odds Ratio (Referent Year: 2012)			Wald Chi-square Test P-value	
		Ontario	**Prairie**	**2009**	**2010**	**2011**	**Region**	**Year**
I	Injection	**0.046***	**0.253***	0.946	1.248	1.237	**<0.0001**	0.851
II	Feed	**0.434***	1.068	0.959	1.128	1.047	**0.0010**	0.9617
	Water	**0.184***	**0.276***	0.980	0.882	0.556	**<0.0001**	0.4053
	Injection	1.061	**0.209***	0.695	0.908	0.816	**<0.0001**	0.7058
III	Feed	**0.186***	**0.137***	0.923	0.991	1.053	**<0.0001**	0.9834
	Water	1.792	2.160	0.665	0.817	0.369	0.2900	0.3356
	Injection	1.898	1.183	0.406	0.893	0.946	0.3095	0.4003
IV	Feed	**0.117***	**0.379***	0.692	0.456	0.648	**<0.0001**	0.317

[1] Dependent Variable: Farm Counts of antimicrobial use by category of importance to human mediciene and route of administration (Yes/No);
Independent/class variables: Region (Prairie, Ontario and Québec-Referent), and Year (2009, 2010, 2011 and 2012-Referent).
*Statistically different from referent at $P \leq 0.05$ using a 2 tailed test.
There were no reported uses of Category I antimicrobials in feed or water and not reported of Category IV antimicrobial in water or by injection.

Table 11. Regional comparisons in the quantity of specified antimicrobials administered in feed, *CIPARS Farm-Swine 2009-2012*. Prairie: AB, SK, MB

	Antimicrobial (Active Ingredient)	**Québec** (Total Herds = 102)		**Ontario** (Total Herds = 107)		**Prairie** (Total Herds = 156)		**K-W Test**[3]	**Friedman's Chi-square Test:** Controlling for Year
		n[1]	MgAI/TPD[2]	n[1]	MgAI/TPD[2]	n[1]	MgAI/TPD[2]		
II	Lincomycin	18	177	17	136	62	210	0.2109	0.3104
	Penicillin	2	347	8	85	12	83	0.1816	0.4483
	Tilmicosin	7	253					NSD	NSD
	Tylosin	50	123	32	146	58	**237***	**<.0001**	**<.0001**
	Virginiamycin	8	58	2	36	1	146	0.103	0.2077
III	Bacitracin	1	59					NSD	NSD
	Chlortetracycline	68	786	29	**598***	33	627	**0.0087**	**0.0161**
	Oxytetracycline			1	54	4	1557	0.4795	0.1797
	Spectinomycin	2	58	1	14	1	33	0.2592	NSD
	Sulfamethazine					10	135	NSD	NSD
	Tiamulin			6	421	13	85	0.4297	0.7801
IV	Bambermycin	8	9					NSD	NSD
	Salinomycin	26	170	6	132	25	139	0.2518	0.2666

[1] Only herds reporting a specified antimicrobial use were included in the analysis for that antimicrobial use.
[2] Median grams of active ingredient per 1000 pig-days at risk; feed intake was estimated using default values for protein deposition (NRC Swine 2012)
[3] Kruskal-Wallis Test: Significant regional difference
NSD: Not sufficient data or only one Region represented
* Statistically different from Québec, P ≤ 0.05, Wilcoxon Rank Sums and pairwise two-sided multiple comparison analysis, Dwass, Steel, Critchlow-Fligner Method.

Appendix 1

Table 12. Categorization of prescription and OTC veterinary antimicrobials by importance in human medicine.

Category[1]	Antibiotic	Antibiotic Class	Rx	OTC
I	Amoxicillin & clavulanic acid	Combinations of penicillins, including β-lactamase inhibitors	x	
I	Enrofloxacin, danofloxacin, difloxacin, orbifloxacin, marbofloxacin	Fluoroquinolones	x	
I	Ceftiofur, cefpodoxime, cefovecin	Third & fourth generation cephalosporins	x	
I	Polymyxin B	Polymyxins (colistin)		x[2]
II	Cefadroxil, cephalexin, cephapirin	First & second-generation cephalosporins	x	
II	Ampicillin, amoxicillin	Penicillins with extended spectrum	x	
II	Cloxacillin	β-lactamase resistant penicillins	x	
II	Penicillin G	β-lactamase sensitive penicillins		x
II	Neomycin, streptomycin, dihydrostreptomycin, apramycin, gentamicin, amikacin	Aminoglycosides	x	x
II	Fusidic acid	Fusidic acid	x	
II	Clindamycin, lincomycin, pirlimycin	Lincosamides	x	x
II	Erythromycin, tylosin, tylvalosin,tulathromycin, tilmicosin, gamithromycin, tildipirosin	Macrolides	x	x
II	Virginiamycin	Streptogramins		x
II	Trimethoprim, ormetoprim, sulfonamides	Trimethoprim- sulfonamide combinations	x	
III	Spectinomycin	Aminocyclitols		x
III	Neomycin	Aminoglycosides (topical)		x
III	Bacitracin	Bacitracins		x
III	Novobiocin	Coumarins		x
III	Nitrofurantoin	Nitrofurans		x

III	Florfenicol, chloramphenicol	Phenicols	x	
III	A vareity of sulfonamides	Sulfonamides		x
III	Tetracycline, oxytetracycline, chlortetracycline, doxycycline	Tetracyclines	x	x
III	Tiamulin	Pleuromutilins	x	x
IV	Bambermycin	Flavolphospholipols		x
IV	Monensin, lasalocid, narasin, salinomycin, maduramicin	Ionophores		x

[1] Health Canada's categorization of antimicrobials based on importance in human medicine: I - Very High Importance; II - High Importance; III - Medium Importance; IV - Low Importance.

[2] Topical and intramammary products.

Table 13. OTC Antimicrobials: Detailed results of the non-parametric analyses of the effect of a prescription use only policy versus a combined OTC-prescription use policy on AMU and AMR. Atlantic (AT): PEI, NS, NB, NL. Maritimes (MA): PEI, NS, NB. West: BC, AB, SK, MB. Prairie (PR): AB, SK, MB.

							Wilcoxon signed rank count of AMR comparisons between QC and other regions[2]							
AMR or AMU	Data Source	Sector	Species Sampled	Bacteria	n[1]	Regional Ranking (Highest to Lowest)[2]								
							QC>ON	QC<ON	QC>AB	QC<AB	QC>MA	QC<MA		
AMR	JDS	Farm	Dairy (milk)	*E. coli*, *Staphylococcus*	6	MA-QC (tied), AB, ON	5	1	4	2	3	3		
							QC>ON	QC<ON	QC>West	QC<West				
AMR	CIPARS	Farm	Swine	*E. coli*, *Enterococcus*, *Salmonella*	79	QC, ON, West*	47	31	63*	16*				
AMR	CIPARS	Farm	Swine	*Enterococcus*	43	QC, ON*, West*	27*	16*	31*	12*				
AMR	CIPARS	Farm	Swine	*E. coli*	18	QC, ON*, West*	16*	2*	18*	0*				
AMR	CIPARS	Farm	Swine	*Salmonella*	18	ON*, QC, West*	4*	13*	14*	4*				
							QC>ON	QC<ON	QC>BC	QC<BC	QC>Pr	QC<Pr	QC>AT	QC<AT

AMR	CIPARS	Abattoir	Chicken, swine	*Campylobacter, E. coli, Salmonella*	91	QC, BC*, ON*, Pr*, AT*	81*	39*	65*	43*	95*	23*	68*	26*
AMR	CIPARS	Abattoir	Chicken	*Campylobacter*	4	QC, AT, ON, Pr, BC	3	1	3	0	3	1	2	1
AMR	CIPARS	Abattoir	Chicken	*E. coli*	30	QC, BC, Pr*, AT*, ON*	23*	7*	19	11	21*	9*	23*	7*
AMR	CIPARS	Abattoir	Chicken	*Salmonella*	27	QC, BC, Pr, ON*, AT	21*	5*	12	12	16	8	18	7
AMR	CIPARS	Abattoir	Swine	*E. coli*	24	QC, ON, BC, AT*, Pr*	18	12	15	12	26*	4*	19*	8*
AMR	CIPARS	Abattoir	Swine	*Salmonella*	6	QC, ON, Pr*, BC*, AT	16	14	16*	8*	29*	1*	6	3
AMR	CIPARS	Retail meat	Chicken	*Campylobacter, E. coli, Enterococcus, Salmonella*	35	QC, ON*, AT*, Pr*, BC*	103*	34*	34*	14*	67*	33*	23*	9*
AMR	CIPARS	Retail meat	Chicken	*Campylobacter*	6	QC, Pr, ON, AT, BC	15	3	8	0	12	2	5	1
AMR	CIPARS	Retail meat	Chicken	*Enterococcus*	11	BC, Pr, ON, QC, AT	46	21	8	9	26	20	5	3
AMR	CIPARS	Retail meat	Chicken	*E. coli*	9	QC, AT*, ON*, Pr*, BC*	26*	1*	11*	1*	19*	2*	8*	1*
AMR	CIPARS	Retail meat	Chicken	*Salmonella*	9	ON*, QC, AT, BC, Pr	16*	9*	7	4	10	9	5	4

							QC>ON	QC<ON	QC>BC	QC<BC	QC>AB	QC<AB	QC>MB	QC<MB
AMR	CIPARS	Human	Human (clinical)	*Salmonella*	81	BC*, AB*, QC, MB, ON*, NS*, SK*, NB*, NL*	47*	34*	26*	55*	28*	51*	44	35
							QC>NS	QC<NS	QC>SK	QC<SK	QC>NB	QC<NB	QC>NL	QC<NL
							51*	25*	54*	23*	48*	30*	65*	13*
							QC>ON	QC<ON	QC>AB	QC<AB	QC>MA	QC<MA		
AMU	JDS	Farm	Dairy		4	AB, ON-MA(tied), QC,	2	1	0	4	1	2		
	H_0					OTC, OTC, Rx, OTC, OTC	OTC AMR in OTC regions = OTC AMR in Rx region (see page 23)							
	H_a					OTC*, OTC*, OTC*, OTC*, Rx	OTC AMR in OTC regions > OTC AMR in Rx region (see page 23)							

[1] Number of observations for the Friedman test.
[2] The symbol * represents that a region is statistically different than Québec, $P \leq 0.05$ using a 2 tailed test from the Wilcoxon test.

Table 14. Prescription Antimicrobials: Detailed results of the non-parametric statistical analyses of the effect of a prescription use only policy versus a combined OTC-prescription use policy on AMU and AMR. Atlantic (AT): PEI, NS, NB, NL. Maritimes (MA): PEI, NS, NB. West: BC, AB, SK, MB. Prairie (PR): AB, SK, MB.

							Wilcoxon signed rank count of AMR comparisons between QC and other regions[2]							
AMR or AMU	Data Source	Sector	Species Sampled	Bacteria	n[1]	Regional Ranking (Highest to Lowest[2]								
							QC>ON	QC<ON	QC>AB	QC<AB	QC>MA	QC<MA		
AMR	JDS	Farm	Dairy (milk)	*E. coli, Staphylococcus*	6	AB, QC-MA (tied), ON	4	2	2	4	3	3		
							QC>ON	QC<ON	QC>West	QC<West				
AMR	CIPARS	Farm	Swine	*E. coli, Enterococcus, Salmonella*	121	QC, ON*, West*	53*	28*	69*	14*				
AMR	CIPARS	Farm	Swine	*Enterococcus*	15	QC, ON, West*	11	4	12*	3*				
AMR	CIPARS	Farm	Swine	*Escherichia*	53	QC, ON*, West*	31*	11*	37*	7*				
AMR	CIPARS	Farm	Swine	*Salmonella*	53	ON, QC, West*	11	13	20*	4*				
							QC>ON	QC<ON	QC>BC	QC<BC	QC>Pr	QC<Pr	QC>AT	QC<AT

AMR	CIPARS	Abattoir	Chicken, swine	*Campylobacter, E. coli, Salmonella*	302	QC, BC, ON*, AT*, Pr*	137*	77*	107	83	159*	44*	116*	54*
AMR	CIPARS	Abattoir	Chicken	*Campylobacter*	12	BC, AT, ON, Pr, QC	0	4	0	4	0	2	0	3
AMR	CIPARS	Abattoir	Chicken	*E. coli*	100	BC*, QC, AT*, ON*, Pr*	56*	15*	26*	45*	58*	13*	48*	22*
AMR	CIPARS	Abattoir	Chicken	*Salmonella*	90	BC*, QC, AT, ON, Pr*	25	18	12*	26*	27*	8*	19	20
AMR	CIPARS	Abattoir	Swine	*E. coli*	80	QC, ON*, Pr*, BC*, AT*	35*	16*	38*	6*	36*	16*	37*	8*
AMR	CIPARS	Abattoir	Swine	*Salmonella*	20	QC, ON, Pr*, AT*, BC*	21	24	31*	2*	38*	5*	12	1
AMR	CIPARS	Retail meat	Chicken	*Campylobacter, E. coli, Salmonella*	81	BC*, QC, ON*, AT*, Pr*	88*	66*	27*	38*	80*	38*	22	24
AMR	CIPARS	Retail meat	Chicken	*Campylobacter*	18	BC*, ON , Pr, AT, QC	9	20	3*	9*	9	11	1*	7*
AMR	CIPARS	Retail meat	Chicken	*Enterococcus*	3	QC, ON , BC, AT, Pr	14	4	5	1	12	3	3	0
AMR	CIPARS	Retail meat	Chicken	*E. coli*	30	BC, AT, QC, ON*, Pr*	42*	24*	12	17	33*	17*	9	12
AMR	CIPARS	Retail meat	Chicken	*Salmonella*	30	QC, BC, ON, AT, Pr*	23	18	7	11	26*	7*	9	5

							QC>ON	QC<ON	QC>BC	QC<BC	QC>AB	QC<AB	QC>MB	QC<MB
AMR	CIPARS	Human	Human (clinical)	*Salmonella*	246	BC*, ON*, QC, AB, NB*, MB*, NS*, SK*, NL*	99*	87*	67*	101*	87	76	105*	48*
							QC>NS	QC<NS	QC>SK	QC<SK	QC>NB	QC<NB	QC>NL	QC<NL
							108*	38*	118*	30*	97*	55*	121*	25*
							QC>ON	QC<ON	QC>AB	QC<AB	QC>MA	QC<MA		
AMU	JDS	Farm	Dairy		8	AB , ON, QC, MA	4	4	1	6	5	2		
	H_0					OTC, OTC, Rx, OTC, OTC	Prescription AMR in Rx region = prescription AMR in OTC regions (see p.24)							
	H_a					Rx, OTC*, OTC*, OTC*, OTC*	Prescription AMR in Rx region > prescription AMR in OTC regions (see p.24)							

[1] Number of observations for the Friedman test.

[2] The symbol * represents that a region is statistically different than Québec, $P \leq 0.05$ using a 2 tailed test from the Wilcoxon test.

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