Use of Over-the-Counter Antibiotics in BC Livestock and Poultry,

2002 – 2018

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Preamble

The BC Ministry of Agriculture attended the Antimicrobial Stewardship in Canadian Agriculture and Veterinary Medicine Conference: How is Canada doing and what still needs to be done?[1], held October 30 to November 2, 2011 in Toronto. A reoccurring theme of the conference was the need for more monitoring of antimicrobial use (AMU) in animals. It was recognized at the conference that the BC Ministry of Agriculture's information on aquaculture's use of antibiotics was one of the few existing sources of animal AMU data in Canada. Following the conference, the Ministry reviewed and analyzed its other AMU data which resulted in this report. The goal of this report is to present and analyze the animal AMU information with full transparency.

Summary

This report analyzes the annual purchases of veterinary antibiotics by licensed over-the-counter retailers from 2002 to 2018, and does not include purchases by pharmacists or veterinarians. The purchase data is combined with product label information including active antibiotic ingredient concentration, animal species, administration method and usage category (therapeutic, disease prevention, or growth promotion) and also incorporates Health Canada's categorization of antimicrobial class based on importance in human medicine. Antibiotic use is measured on a steady state biomass basis (gm of active antibiotic ingredient/tonne of steady state livestock biomass).

Some of the report's key findings include:

- Over the 17 year span from 2002 to 2018, total antibiotic use, on a population biomass basis, has fluctuated. It peaked in 2008, and then trended downward to 2014 resulting in usage less than 2002. The amount of antibiotics increased in 2016 to surpass the 2002 level, before decreasing in 2017 and 2018. Total antibiotic use declined 7.3% from 2017 to 2018. The overall 17 year change is less than a 5% increase and likely closer to 0%.
- Antibiotic usage by category of importance in human medicine fluctuated; however, the average annual use of categories I, II, III, and IV are 0%, 12%, 40%, 48%, respectively. Health Canada's categorization of antibiotics on their importance in human medicine ranges from very high importance (category I) to products which aren't used in humans and have a low importance (category IV).
- The temporal pattern of usage and the pattern of diminishing use of antibiotics as their importance in human medicine increases is consistent with judicious use of over-the-counter antibiotics.

- In 2018, approximately 88% of the antibiotics were administered in feed, 11% in water and all other methods of administration account for less than 1% of total usage. Effective December 1, 2018 all veterinary antibiotics, except for category IV products, required a veterinary prescription. The data suggests producer stockpiling of a water medication in advance of its shift to prescription status. Without this stockpiling, total antibiotic use in 2018 would have declined 11.5% from 2017.
- Less than one third of the antibiotics used are labelled for use in a single animal species. The majority of antibiotics used are approved for use in more than one species. Those labelled for poultry, cattle or swine, or some combination of these, accounted for approximately 89% of total usage.
- Penicillin G accounts 45% of that category's use from 2002 to 2018, and over half of the category II usage since 2011. The report examines Health Canada's classification of Penicillin G as high importance in human medicine.

In addition to the evaluation of the judiciousness of the over-the-counter antibiotic usage, this data presents evidence about the policy option of requiring prescriptions for all veterinary antibiotics. For example, the data collected from over-the-counter retailers is evidence that prescriptions are not necessary for the collection of antibiotic use data. Also, the evidence that virtually no category I antibiotics are sold in BC's over-the-counter products, combined with the realization that current veterinary prescription products are typically category I or II, means that shifting to a prescription-use-only policy and requiring producers to interact with veterinarians would likely increase the amount of category I products used in animals. Category I products are defined by Health Canada as very high importance to human medicine. An increase in the usage of antibiotics of greatest importance to human medicine would be an unexpected result for a policy that is typically considered to foster judicious use. Consideration should also be given to assessing the judiciousness of human over-the-counter antibiotic use.

Introduction

The primary scientific concern with AMU in animals is with the development of resistance to the antimicrobials. The importance of the resulting antimicrobial resistance (AMR) to animal health is equivocal; the primary worry is the AMR could result in more AMR in human infections which could have negative implications for treatment of those infections. Debate continues as to the respective contributions of human AMU and animal AMU to AMR among human infections. A general, but not universal, consensus is that antibiotic use in humans is the main force behind development of antimicrobial resistance impacting humans[2]. This does not mean interspecies transmission of resistant bacteria isn't important. Transmission of resistant bacteria from animals to humans is an important concern. Similarly, transmission or resistant bacteria from humans to animals is also a concern. The

AMU results in this report are then largely presented from a public health, as opposed to an animal health, perspective.

The report begins with a review of the legislative basis for the sale of animal antibiotics without a prescription, including the federal legislative changes effective December 1, 2019 that severely limited these sales. This is followed by a description of the AMU data including the source of the data and the calculation of animal biomass. The results begin with comparing antibiotic use and animal biomass, before comparing 2 measures of annual AMU: 1) AMU mass; and 2) AMU mass on a biomass basis. AMU categorized by importance in human medicine is presented before separately reviewing annual AMU of category IV, III and II products. Categorization of AMU by importance in veterinary medicine is then considered. This is followed by the label method of administration, label usage category, and species label use. Then the need for caution in assessing the AMU results and their fluctuations is discussed. This is followed by a discussion of the appropriate categorization of the importance of penicillin G to human medicine. The AMU data is then reviewed in light of judicious use. The report concludes with a critical analysis of the need for veterinary prescriptions to collect AMU data and the implications of this AMU data for veterinary prescription use only policies.

The legislative basis for the sale of antimicrobials for use in animals without a prescription

The federal government's Prescription Drug List[3] contains the pharmaceutical products, including antibiotics, which require a prescription in order to be sold. The federal Feeds Regulations' Compendium of Medicating Ingredients Brochures[4] (CMIB) lists the medicating ingredients, including antibiotics, which can be added to livestock feeds. The Compendium specifies whether a veterinary prescription is required, the species of livestock, the level of medication, the directions for feeding and the purpose for which each medicating ingredient may be used, as well as the brand of each medicating ingredient that is approved for use in Canada.

Concerns that AMR is a complex and evolving public health issue motivated a number of changes in veterinary antibiotics in 2018 by the federal government[5]. These changes included, as of February 2018, veterinary pharmaceutical companies' voluntary removal of growth promotion or production enhancement claims from labels of medically important antibiotics. The deadline for ceasing the use of medically important antibiotics as growth promoters or production enhancers was December 1, 2018. Non-medically important antibiotics (Category IV products such as the ionphores and flavophospholipols), can continue to be used in feed for growth promotion or production enhancement. The federal government considers having appropriate veterinary oversight to be a key measure to promote the prudent use of antimicrobials and minimizing the development and spread of AMR. Effective December 1, 2018, the federal government added most medically important veterinary antibiotics to the Prescription Drug List[6]. This applied to all dosage forms (that is, all methods of administration) of the affected antibiotics. As of December 1, 2018 the only veterinary antibiotics which don't require a veterinary prescription and are available OTC are: nitrofurans products which are applied topically; ionophores and flavophospholipols (bambermycin) which are administered in feed.

Nitrofurans are Category III Medium Importance in human medicine and the ionophores and flavophospholipols are Category IV Low Importance to human medicine.

The Drug Schedules Regulation[7] of BC's Pharmacy Operations and Drug Scheduling Act notes which drugs, including antimicrobials, can be sold without a prescription for use in animals. Provincial legislation must be consistent with the federal Prescription Drug List, with the option of requiring prescriptions for products not listed on the federal List. The BC Veterinary Drug and Medicated Feed Regulation[8] permits the sale without a prescription of medicated feed as listed in the CMIB. Medications sold without a prescription are commonly referred to as over-the-counter (OTC) products.

The BC Ministry of Agriculture issues licences under the BC Veterinary Drugs Act[9] and Veterinary Drug and Medicated Feed Regulation for the sale of OTC veterinary drugs. The classes of licence are: 1) medicated feed for the manufacture and sale of medicated feeds; 2) limited medicated feed for the sale, but not manufacture, of medicated feeds; and 3) veterinary drug for the sale of non-feed products containing veterinary medications including products that are injectable, water soluble, oral, topical, intrauterine, and intramammary. The BC legislation also licenses veterinary drug dispensers. A licensed dispenser is required to be present when medicated feeds are being manufactured and when a veterinary drug licensee is open for business. Pharmacies and veterinarians can also sell OTC veterinary drugs and are exempt from the BC Veterinary Drugs legislation licensing requirements. Commercial feed mills are considered wholesale druggists under the federal Food and Drugs Regulations, which allows them to import and buy prescription drugs. Medicated feed licensees can manufacture and sell prescription feeds under the order of a registered veterinarian. As a condition of licensing, medicated feed licensees and veterinary drug licensees annually submit veterinary drug purchase records to the Ministry. The purchase records include the date of purchase, name of supplier, quantity purchased, the generic name, trade name and name of the manufacturer of the drug.

Methods

Antibiotic Usage – The annual purchase records of medicated feed licensees and veterinary drug licensees are reviewed and all antibiotic purchases are entered into an Excel spreadsheet. The spreadsheet contains data from 2002 to 2018. For 2002 and 2003, the purchase records of medicated feed licensees, but not veterinary drug licensees, are included. Part of the 2006 purchase record of at least one medicated feed licensee is missing so antimicrobial usage in that year is underestimated and must be interpreted with caution. The spreadsheet also contains veterinary product label information including: active antibiotic ingredient concentration, animal species, administration method and usage category (therapeutic, disease prevention, or growth promotion). In addition, the spreadsheet contains information on the antimicrobial class of the active antibiotic ingredient, and Health Canada's categorization of antimicrobial drugs based on importance in human medicine[10] and the World Organization for Animal Health's (i.e., the OIE's) categorization of antimicrobials based on importance in veterinary medicine[11]. Antimicrobial use by BC aquaculture is excluded from this OTC analysis because that usage is under veterinary prescription and has been previously reported[12].

In summary, the BC Ministry OTC data includes purchases of veterinary antibiotics by licensed retailers. It does not include OTC sales by pharmacies or veterinarians. Retailers' purchases are expected to closely reflect sales; however, the two can vary based on changes in inventory between the beginning and end of a year. Antibiotics for prescription feeds are included in the data; however, anecdotally, medicated feed licensees indicate the manufacture of prescription feeds was rare (with the exception of aquaculture which is excluded from this report) prior to the December 1, 2018 addition of all veterinary antibiotics, with the exception of category IV products, to the federal Prescription Drug List. Therefore, the data analyzed in this report reflect the sale of OTC veterinary antibiotics by licensed retailers.

Biomass – The annual steady state biomass of the following agricultural livestock commodities is calculated: beef cattle, dairy cattle, poultry (broilers, layers, broiler breeders, and turkeys), hogs, sheep, goats, and horses. The resulting steady state biomass estimates the total weight of BC livestock averaged over a year, that is, the biomass for an average day in the year. Technically, the biomass measure used is Adjusted Population Correction Unit[13]. The biomass is calculated using a variety of data sources including Statistics Canada Census of Agriculture data, livestock commodity group data and Agriculture and Agri-Food Canada slaughter data. Briefly, the calculation for a given commodity includes the estimated number, weights and lifetimes of the various production classes. Typically, both breeding livestock and slaughter animals are included for a given commodity. The biomass calculation considers how many days in a year a given type of animal is alive and any weight change during that time is also considered. An animal's steady state mass is the product of its average mass and the portion of the year it is alive. A broiler is an example of a slaughter animal. A broiler that hatches at 0.04 kg and over the span of 35 days grows to its slaughter weight of 1.98 kg has an average mass of 1.01 kg = (0.04 kg+1.98 kg)/2 over its lifespan of 0.096 = (35/365) of a year. So a broiler's steady state mass is 0.097 kg = 1.01 kg x 0.096. (For simplicity, the units of the steady state biomass are noted as mass; however, more accurately the measure is a density function with units mass·time.) In contrast, breeding livestock are typically animals which have finished growing and achieved a constant mature mass. For example, a beef cow has a constant mass of 590 kg for the entire year and therefore has a steady state mass of 590 kg = ((590 kg +590 kg)/2)*(365/365). So the combined steady state mass of 1 broiler and 1 cow is 590.097 kg = is 0.097 kg + 590 kg. Where growth curves are readily available, the area under the curve is integrated to determine the average mass of an animal, instead of using the arithmetic mean of a beginning and ending mass.

Results

Figure 1 shows the total mass of antimicrobial active ingredient (AI) per year and the commodity composition of total biomass. The line in figure 1 is the total amount of antibiotics. The effect of not including the non-feed antibiotic in 2002 and 2003 is expected to be small as in the other years this non-feed method of administration typically accounts for approximately 5% of total AMU. Also, as noted in the figure the AMU in 2006 is underestimated due to missing records.

OTC total antibiotic use peaked in 2007, slightly surpassing usage in 2005. After 2007, total antibiotic use generally declined to 2014 when it reached the lowest point over the 15 years. OTC total antibiotic usage then increased from 2015 to 2017, then declined in 2018.

The bars in figure 1 show the annual commodity composition of animal biomass. The total biomass fluctuates over the time period, peaking in 2005 and then declining until 2010. Since 2010 the biomass has slowly risen. From 2007 to 2012 AI mass and biomass follow similar trends. After 2012 AI mass has fluctuated while the biomass has slowly risen. The pattern of total biomass changes over the 17 years mirrors the beef biomass which is the largest contributor to the total biomass. The biomasses of dairy cattle, which is the second largest contributor to total biomass, has slowly increased over the 17 years. The biomasses of hogs and especially sheep, goats and horses have declined over the 17 years. Overall, the poultry biomass has increased slightly over time; however, it declined in 2004 associated with BC outbreak of avian influenza. This outbreak resulted in a significant depopulation with cessation of production and importation of poultry products to replace the lost production.

The effect, if any, of the biomass' changing commodity composition on AMU is unclear.

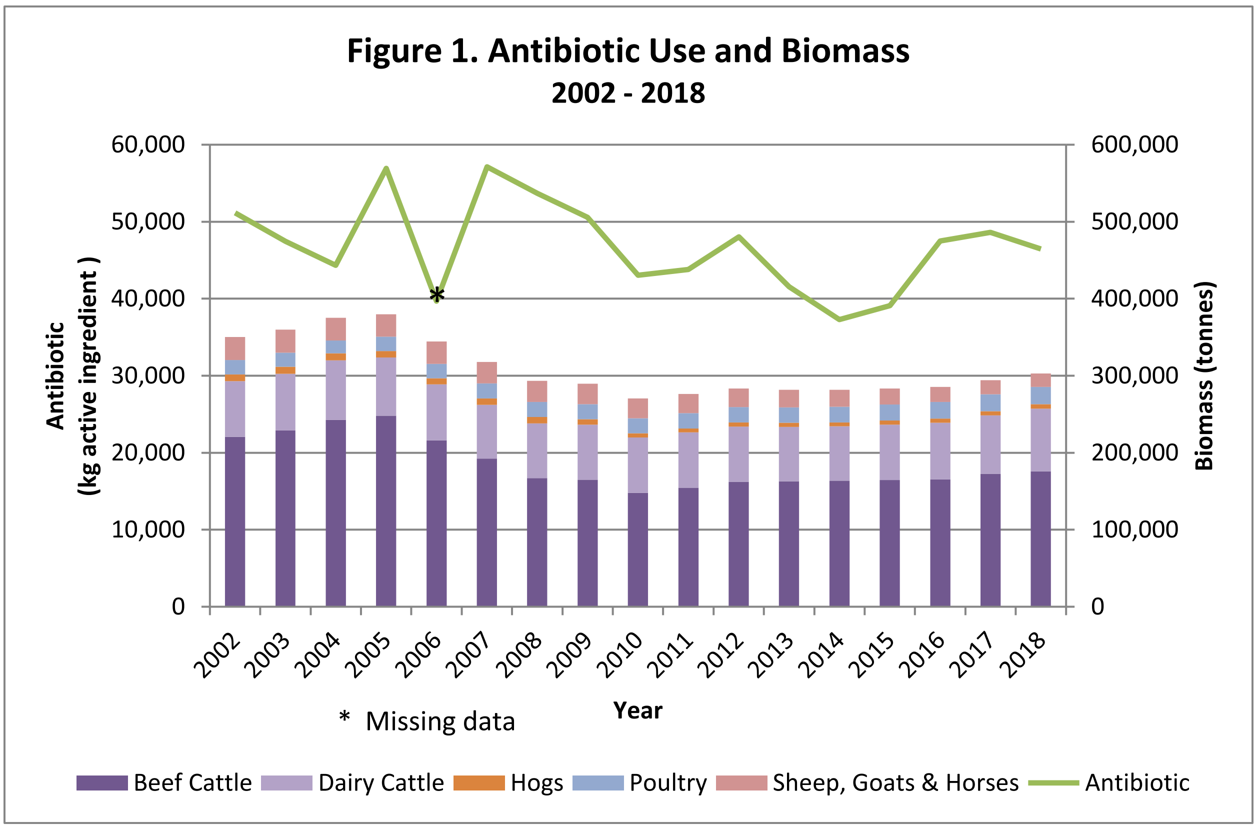


Figure 2 compares total mass of AI with another measure of AMU. The light green line in figure 2 reproduces the total mass of AI line from figure 1. The second measure, the darker line, is antibiotic mass on a biomass basis, specifically gram of active ingredient per tonne of biomass. Figure 2 reveals the two measures of AMU are similar, with the biomass correction serving to dampen the fluctuations in AMU, especially in the first 10 years. For example, the mass of antibiotics is similar in 2005 and 2007. Yet AMU in 2007 is discernably greater than 2005 when measured on a biomass basis due to the larger 2005 biomass. Since 2010 the biomass has been relatively constant, so the two measures track similarly. In assessing antibiotic usage it is helpful to remove the effect of changes in the mass of the underlying animal population, and this is accomplished by measuring usage on a biomass basis. Such a population based measure is consistent with human AMU monitoring, although with humans the AMU denominator is typically population-days[14]. Hereafter, OTC antibiotic use will be presented on a per biomass basis (gm of antibiotic active ingredient per tonne of steady state biomass measured as adjusted population correction unit).

Figure 2. Antibotic Use and Antibiotic Use on a Biomass Basis
2002 - 2018

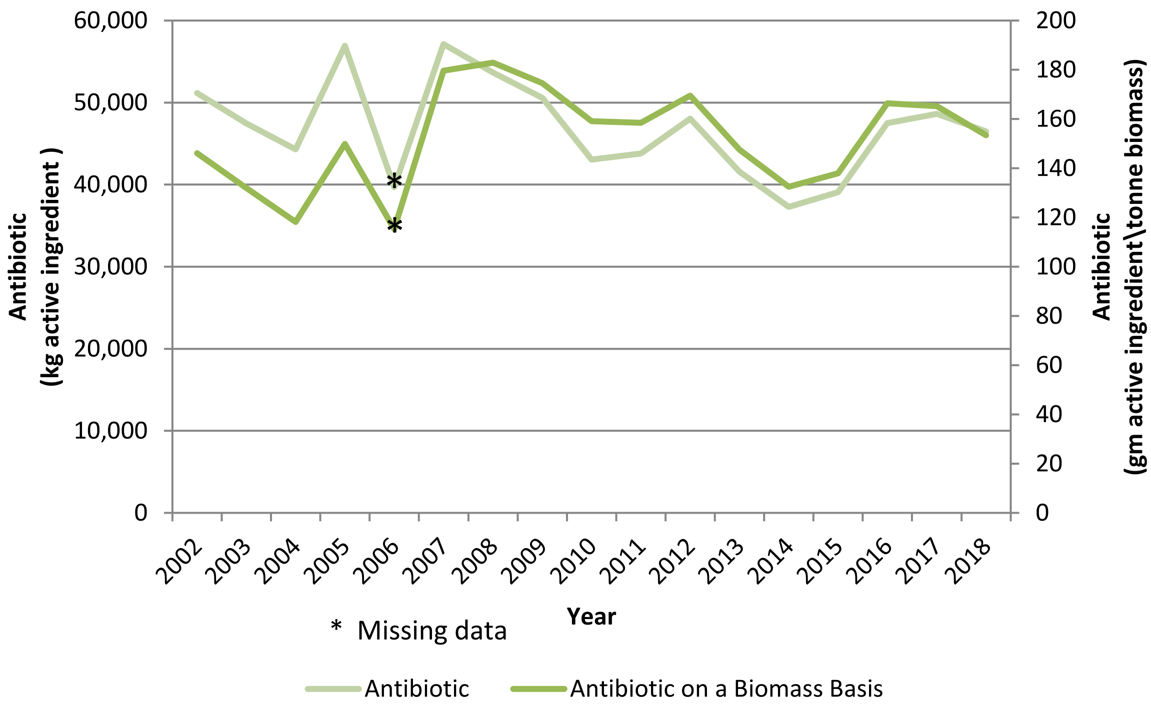
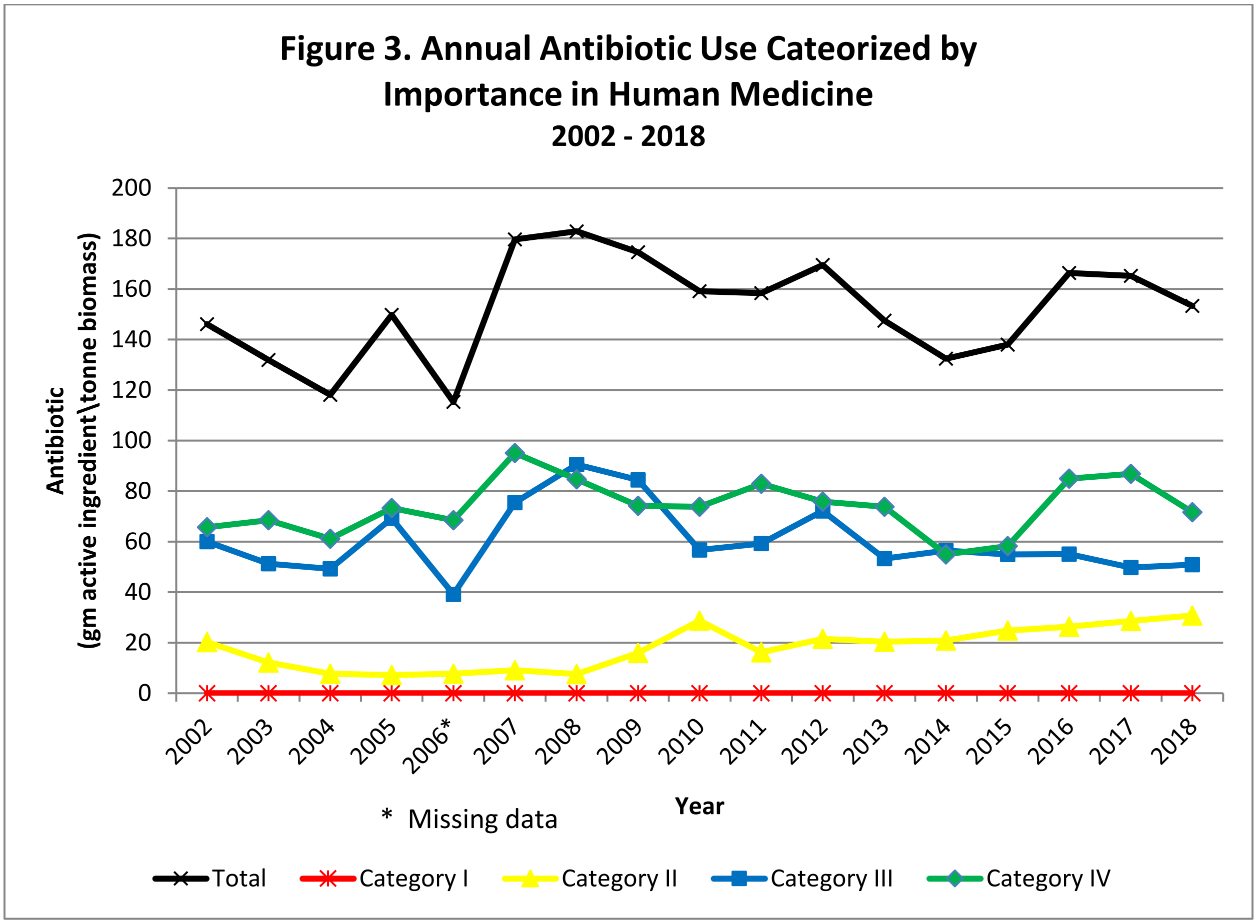


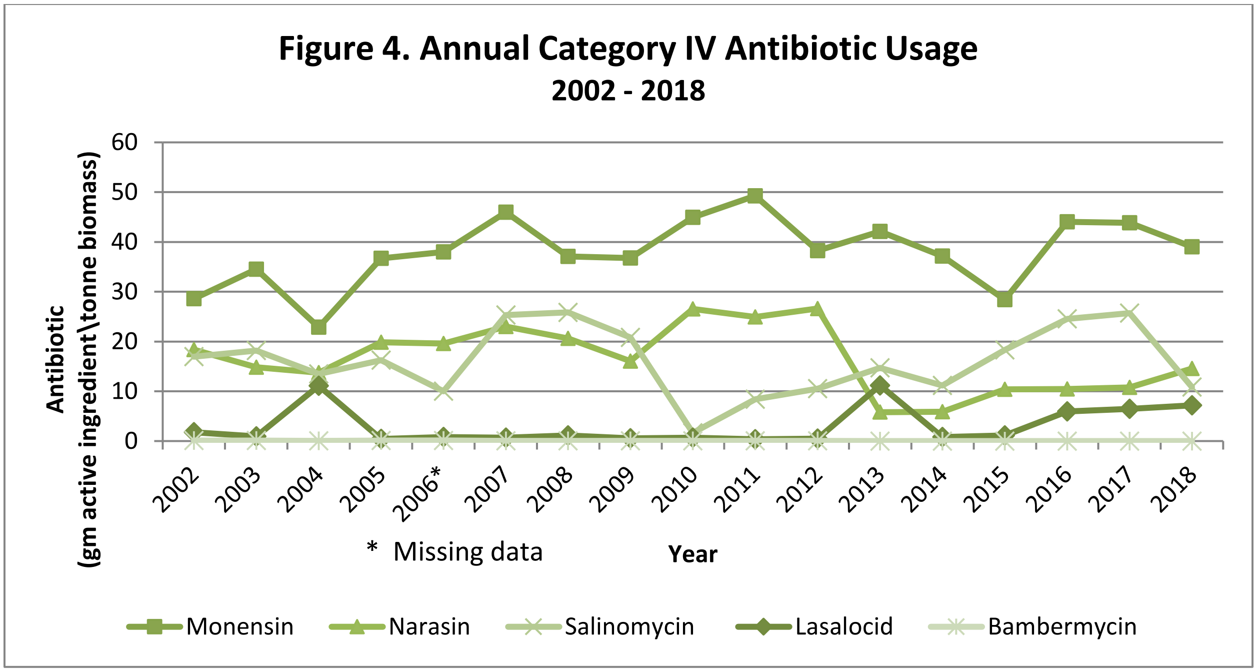
Figure 3 shows the annual antibiotic use categorized by Health Canada's importance in human medicine.



The data in Figure 3 is also presented in Table 1 in the Appendix. Over the 17 year span, total usage has changed from 146 gm of active antibiotic ingredient/tonne of biomass in 2002 to 153 gm of active ingredient/tonne of biomass in 2018, a 5% increase. However, the 2002 usage does not include antibiotics administered via methods other than feed. Typically, these alternative methods of administration account for approximately 5% of usage, so the overall 17 year increase is less than 5% and likely closer to 0%. The peak antibiotic usage on a biomass basis occurred in 2008 at 183 gm/tonne of biomass. Total usage in 2018 declined 7.3% from 2017. This decrease was primarily due to decreased category IV (ionophore) usage with small increases in category II and III usages.

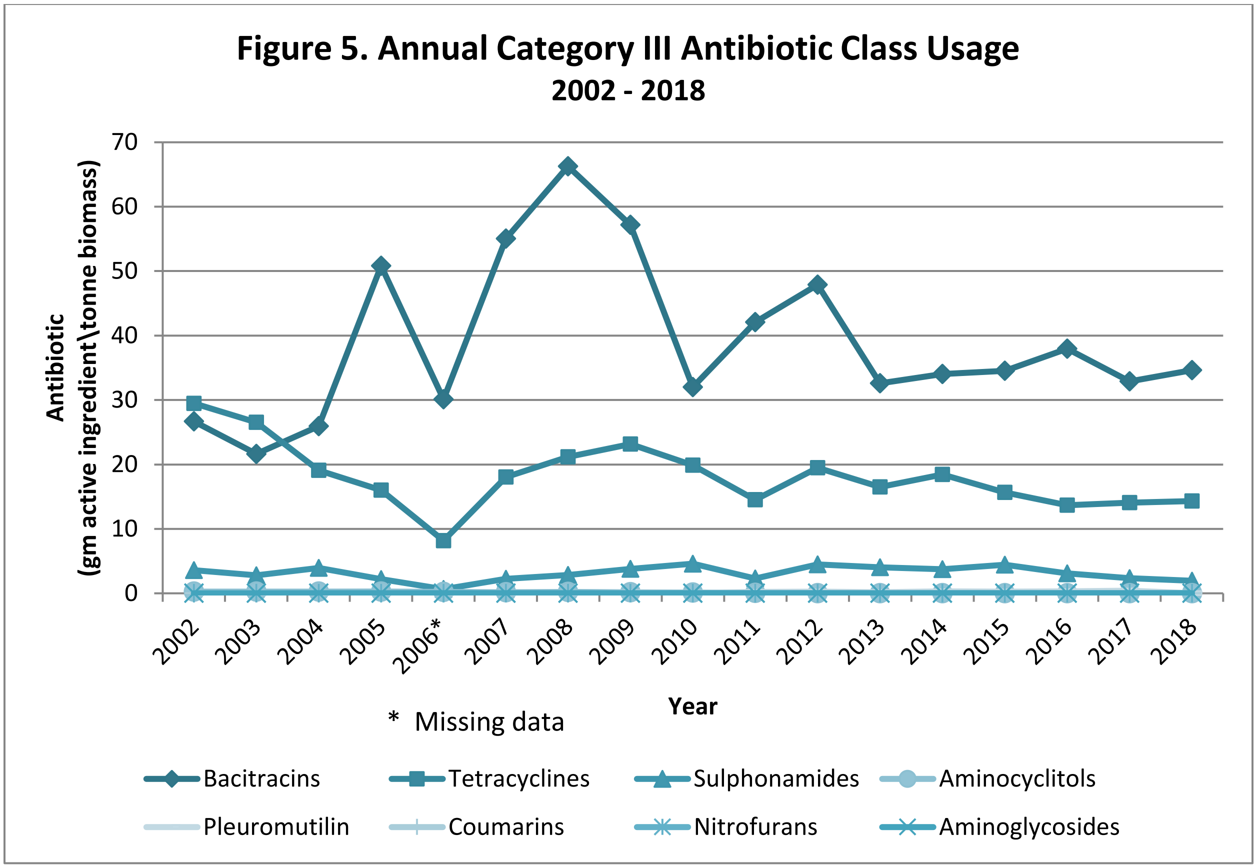
Generally, the category of greatest use is IV which is considered not medically important by Health Canada because the antibiotics aren't used in human medicine. Annually, category IV products range from 42% to 59% of total AMU and average 48% over the 17 years. Category IV use peaks in 2007. Category IV usage rose substantially in 2016, and its decrease in 2018 accounts for the majority of decreased total use of antibiotics in 2018. Annually, category III products range from 33% to 50% of the total usage (33% in 2018) and average 40% over the 17 years. The use of category III products peaked in 2008 and thereafter has been trending down, with a slight increase in 2018 (Table 1). The use of category II products, high importance in human medicine, is variable over time and peaked in 2018, slightly surpassing its previous high in 2010. Annually category II products range from 4% to 20% of the total usage (20% in 2018) and average 12% over the 17 years. Except for 2004 to 2006, there is no category 1 antibiotics used. In 2004, 2005, and 2006, polymyxin B, a category I (very high importance in human medicine), was used on the order of 0.000004 gm/biomass tonne. These amounts are less than 0.00001% of the total annual antibiotic use. Over the three years, the total amount of polymyxin B is 4.5 grams. The polymyxin B was in an intramammary preparation for the treatment of mastitis in dairy cows. Interestingly, Polysporin®, a human OTC skin ointment, also contains polymyxin B.

Figure 4 shows the usage of category IV antibiotic active ingredients over time. Table 2 (Appendix) reports the same information but in greater detail.



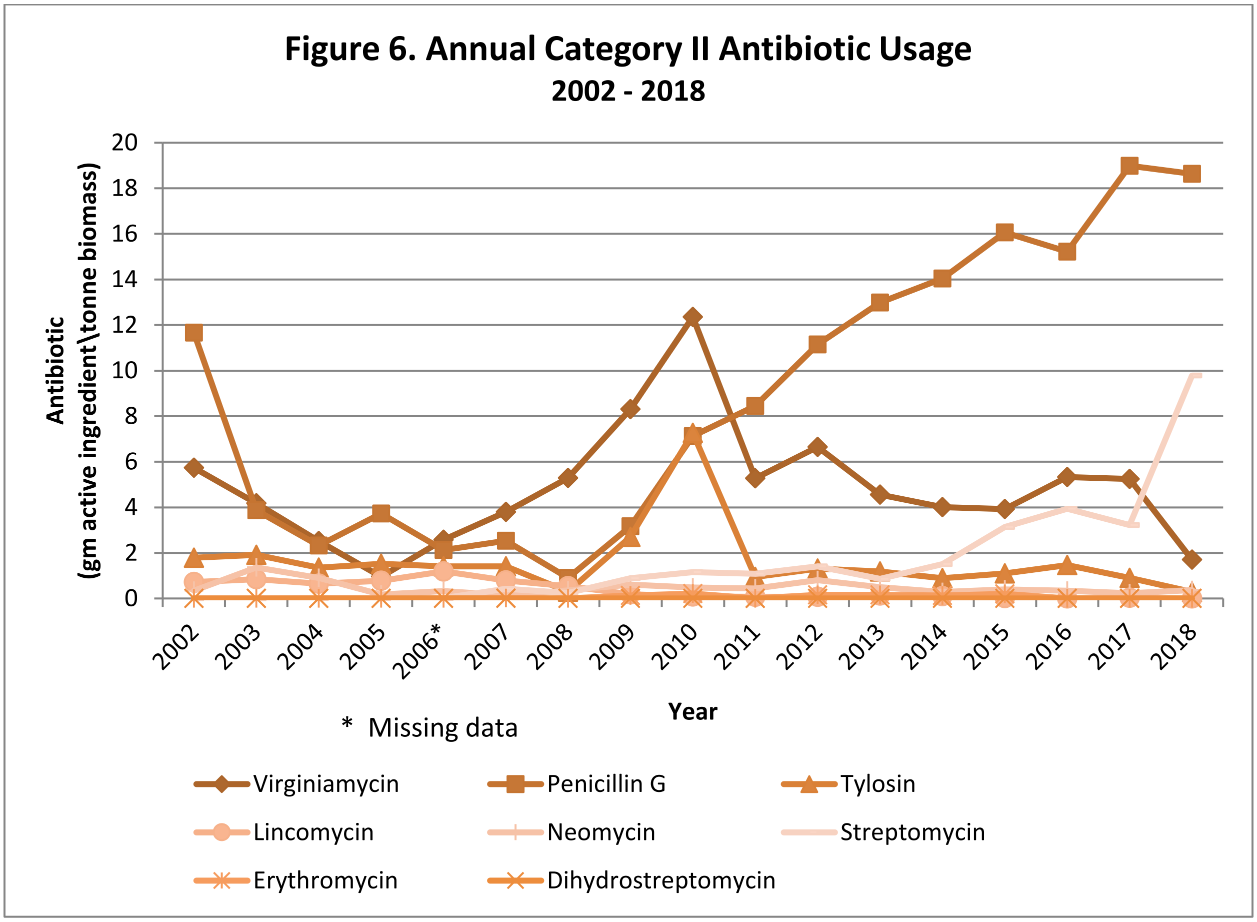
Category IV antibiotics are not used in human medicine and are available without a veterinary prescription. Health Canada considers category IV antibiotics to be of low importance in human health and not medically important, therefore, potential use of this category for growth promotion/production enhancement is permitted. Yet, the public health implications of ionophore use have been noted[15]. Monensin accounts for approximately half of the category IV usage followed by narasin, salinomycin, lasalocid. Monensin, narasin, salinomycin and lasalocid belong to the ionophore antibiotic class, and bambermycin belongs to the flavophospholipols class. The 2018 decline in total category IV use was driven by substantially decreased use of salinomycin, decreased use of monesin, and mitigated by the slight increases in narasin and lasalocid. The salinomycin products used in BC (Bio-Cox and Sacox) are the only category IV antimicrobials that don't have a growth promotion/production enhancement label. Bambermycin is the only category IV antibiotic with only a growth promotion label. Its use has been very small from 2002 to 2012 and nil since (Table 2).

Figure 5 shows the usage of category III antibiotic active ingredients over time. Table 3 in the Appendix reports the same information but in greater detail.



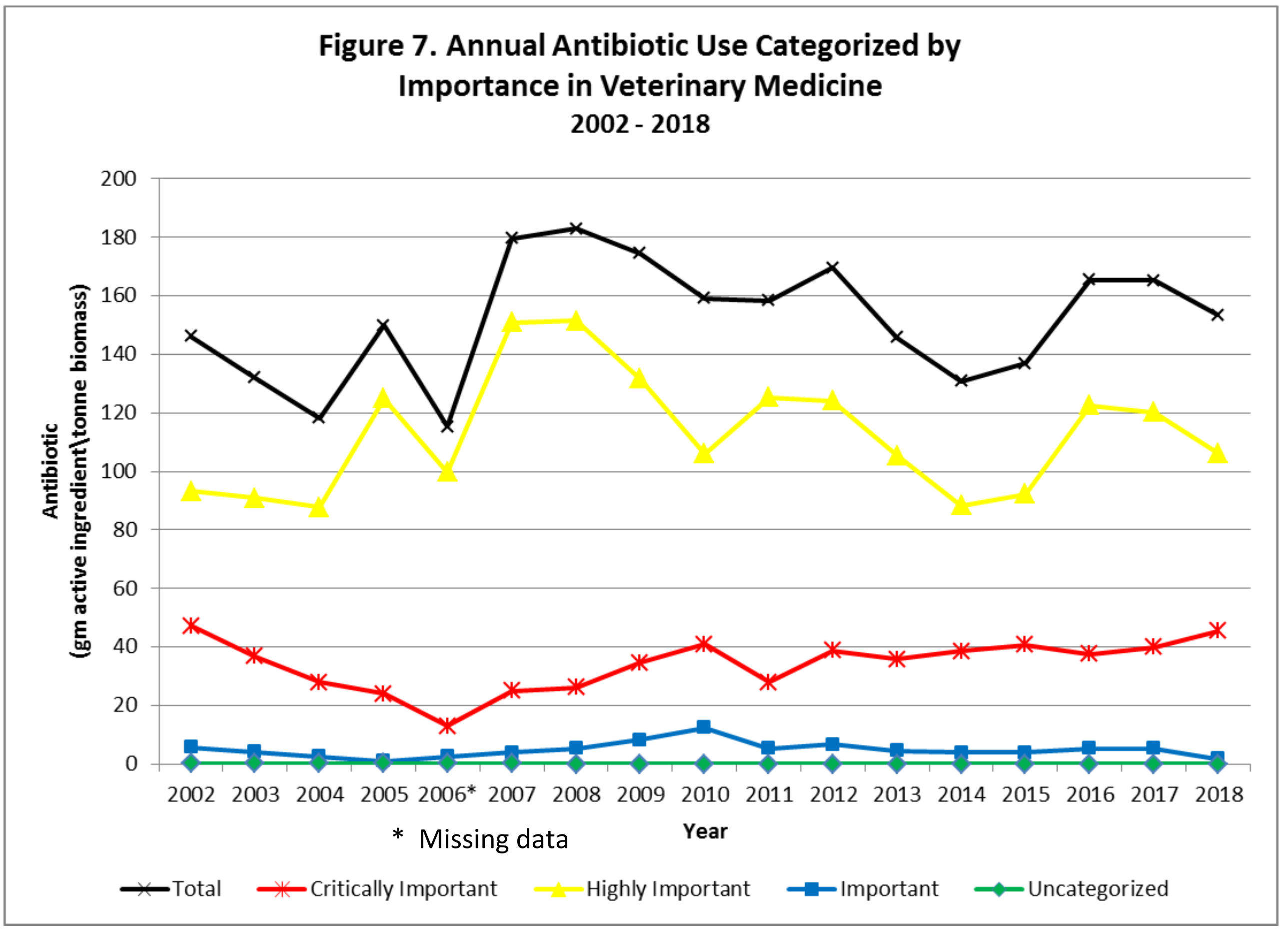
Health Canada considers category III antibiotics to be of medium importance in human medicine. Bacitracin usage fluctuates over the 17 years, particularly 2004 to 2013, and has accounted for over half of the category III usage. In 2017, the United States required prescriptions for most antibiotics administered in feed and water[16]. In the US, bacitracin is not considered medically important and it maintains its non-prescription status in that country[17]. Polysporin®, the human OTC antibiotic skin ointment which contains polymyxin B also contains bacitracin. Usage of the tetracycline class also fluctuates. As of 2004, tetracycline is the category III antibiotic class with the second highest usage, and accounts for approximately 20% to 40% of the category's active ingredients. The antibiotics used in this class are tetracycline, chlortetracycline and oxytetracycline. Combined, bacitracin and tetracyclines account for over 90% of the annual category III usage. Non-potentiated sulphonamides is the category III antibiotic class with the third highest level of usage, averaging approximately 5% from 2002 to 2018. Usage of this class peaked in 2010 at 8% of the category III class usage. Other category III antibiotic classes that were used from 2002 to 2018 had very small or zero usages, each accounting for less than 1% of the annual category usage. These antibiotic classes (and the antibiotic) included aminocyclitols (spectinomycin), pleuromutilin (tiamulin), coumarins (novobiocin), nitrofurans (nitrofurantoin, nitrofurazone), and topical aminoglycosides (neomycin). Category III usage slightly increased from 2017 to 2018 due to small increases in bacitracin and tetracycline, while the use of the other category III compounds decreased. The December 1, 2018 movement of all category III veterinary antibiotics, except for nitrofurans, to the federal Prescription Drug List means these antibiotics can no longer be sold by those licensed under the BC Veterinary Drugs Act and whose data contributes to this report. As of December 1, 2018, sales of these antibiotics are limited to veterinarians and pharmacists.

Figure 6 shows the usage of category II antibiotic active ingredients over time. Table 4 reports the same information but in greater detail.



Health Canada classifies category II antibiotics to be of high importance in human medicine. The category II antibiotic classes streptogramins (virginiamycin) and penicillins (penicillin G) account for approximately 60 to 87% of annual category II usage. Penicillin G decreases from 2002 to 2008 and then rises from 2009 to 2017 with downturns in 2016 and 2018. Over the seventeen years, penicillin G averages 45% of annual category II usage, and since 2011 accounts for 50 to 65% of the category II usage. Virginiamycin use increases from 2005 to a peak in 2010 when it accounted for 43% of the category II usage. Thereafter, virginiamycin use trends lower, including a marked decrease in 2018. Tylosin (macrolide class) use is relatively low over the seventeen years except for 2009 and 2010 when it peaked. Streptomycin (aminoglycoside class) use generally increases over time and as of 2011 replaces tylosin as the third most used antibiotic in the category. Streptomycin use has been trending up as of 2014 with an almost tripling of use in 2018. As further discussed in the section on method of administration, the large increase in streptomycin is suggestive of stock piling of this antibiotic by producers in advance of its shift to prescription status. Use of the remaining category II antibiotics has been low over the seventeen years. This includes neomycin (aminoglycoside class), lincomycin (lincosamide class), erythromycin (macrolide class) and, dihydrostreptomycin (aminoglycoside class). Their combined annual usage averaged 7.5% over the seventeen years and was 1% in 2018 with zero usage of dihydrostreptomycin, lincomycin, erythromycin. Category II usage increased from 2017 to 2018 due to the large increase in streptomycin, which was largely mitigated by the large decrease in virginiamycin use. The December 1, 2018 movement of all category II veterinary antibiotics to the federal Prescription Drug List means these antibiotics can no longer be sold by those licensed under the BC Veterinary Drugs Act and whose data contributes to this report. As of December 1, 2018, sales of these antibiotics are limited to veterinarians and pharmacists.

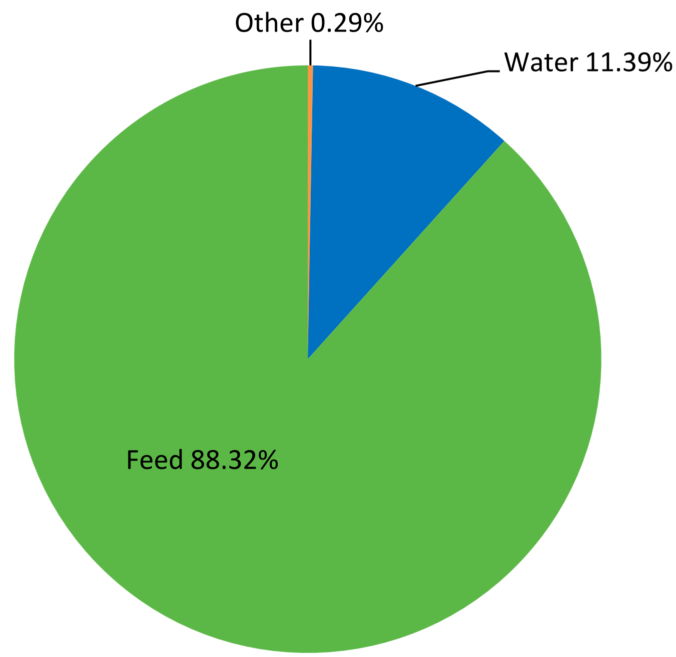
Figure 7 shows the categorization of antibiotic usage by their importance in veterinary medicine.



The OIE's international categorization is used as Canada does not have a national veterinary categorization system. Every year the majority of antibiotics used are highly important in veterinary medicine, ranging from 64% to 86% of the total active ingredient on a biomass basis. The critically important antibiotics in veterinary medicine are consistently the second largest category, ranging from 11% to 32% of the total. Antibiotics important in veterinary medicine account for between 1% and 8% of usage annually. Antibiotic active ingredients used in BC but not categorized by OIE include bambermycin, nitrofurantoin and nitrofurazone. These uncategorized antibiotics are less than 1% of annual usage.

Figure 8 shows, for 2018, the method of administration for OTC antibiotic purchases based on the product labels.

Figure 8. Label Method of Administration, 2018
(% of active ingredient)

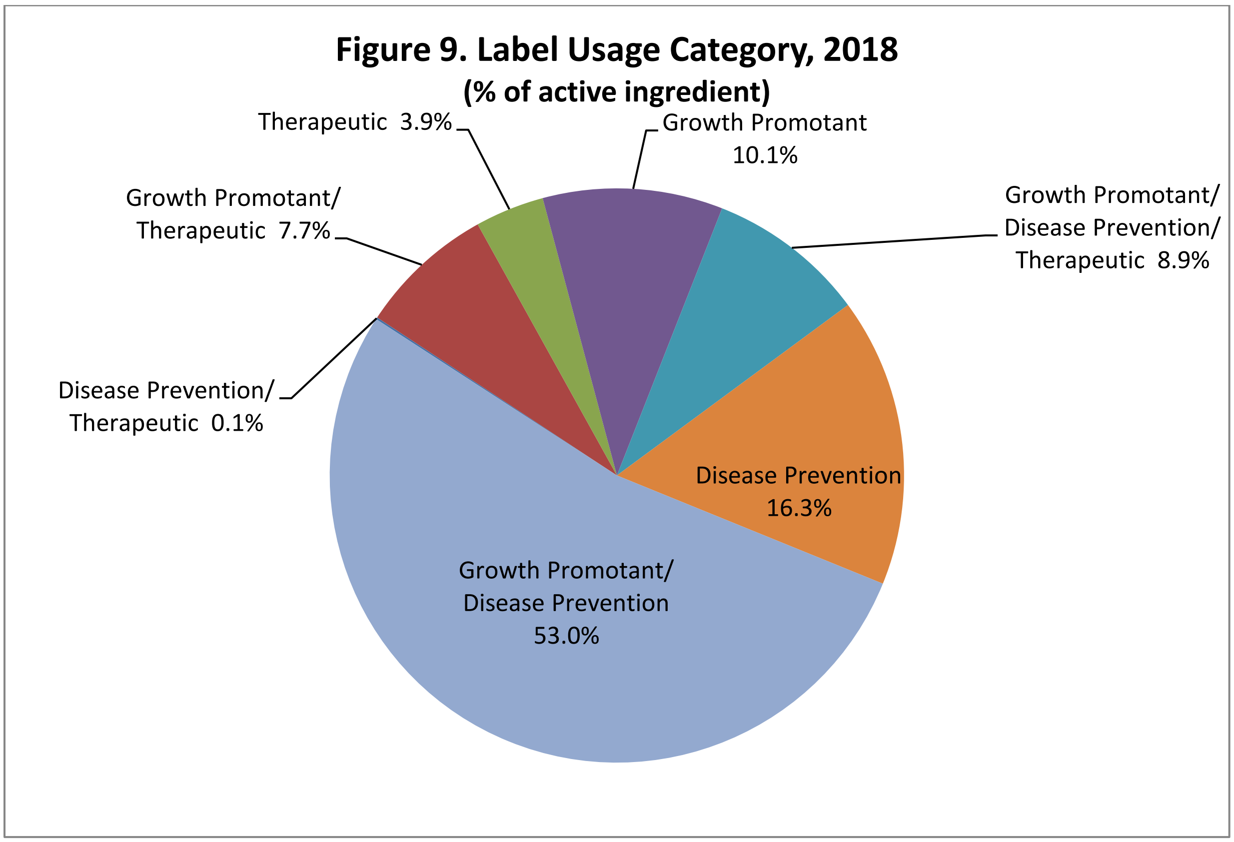


In 2018, as previously, the vast majority of the active antibiotic ingredients are administered via feed. From 2004 to 2017, feed administration ranges from 92% to 98% of total use. Less than 1% was administered via non-feed and non-water methods and this is consistent with the with the range of 0.3% to 1.1% from 2004 to 2017. Methods of administration included in the other category (and the respective percentage of active ingredient) are: injectable (0.16%), oral tablet (0.10%), palatable suspension (0.01%), topical (0.004%), intrauterine (0.003%), and zero intramammary use. However, in 2018, 11.39% of the active antibiotics ingredients were administered water. This is almost double the 2017 amount, and from 2004 to 2017 the average annual amount was administered in water was 4%.

Further analysis of the purchase data, revealed a 213% increase in the weight of Super Booster purchases. This product is labelled for administration in water to: chickens and turkeys for growth promotion/production enhancement; and to swine and calves for treatment of diarrhea. Super Booster's primary active ingredient is spreptomycin, and it is the only product purchased by OTC licensees that contains streptomycin. Super Booster contains a minor amount of Penicillin G. The increased sales of Super Booster occurred from Sept to November. Animal Health Centre staff are unaware of any disease or management conditions in BC's livestock that would warrant such an increased use of Super Booster. This combined with increased purchases occurring just prior to the move of this and most other antibiotics to the prescription drug list suggest producers might have purchased this product to stockpile in advance of the regulatory changes.

With this apparent stockpiling included in the 2018 antibiotic usage, in 2018 use of category II products increased 7.5% and total antibiotic usage decreased 7.3%. Removing the effect of the stockpiling results in category II produce usage in 2018 declining 20.0% and total usage declining 11.5% relative to 2017.

Chart 9 summarizes for 2018, the usage categories for OTC antibiotic purchases based on the product labels.

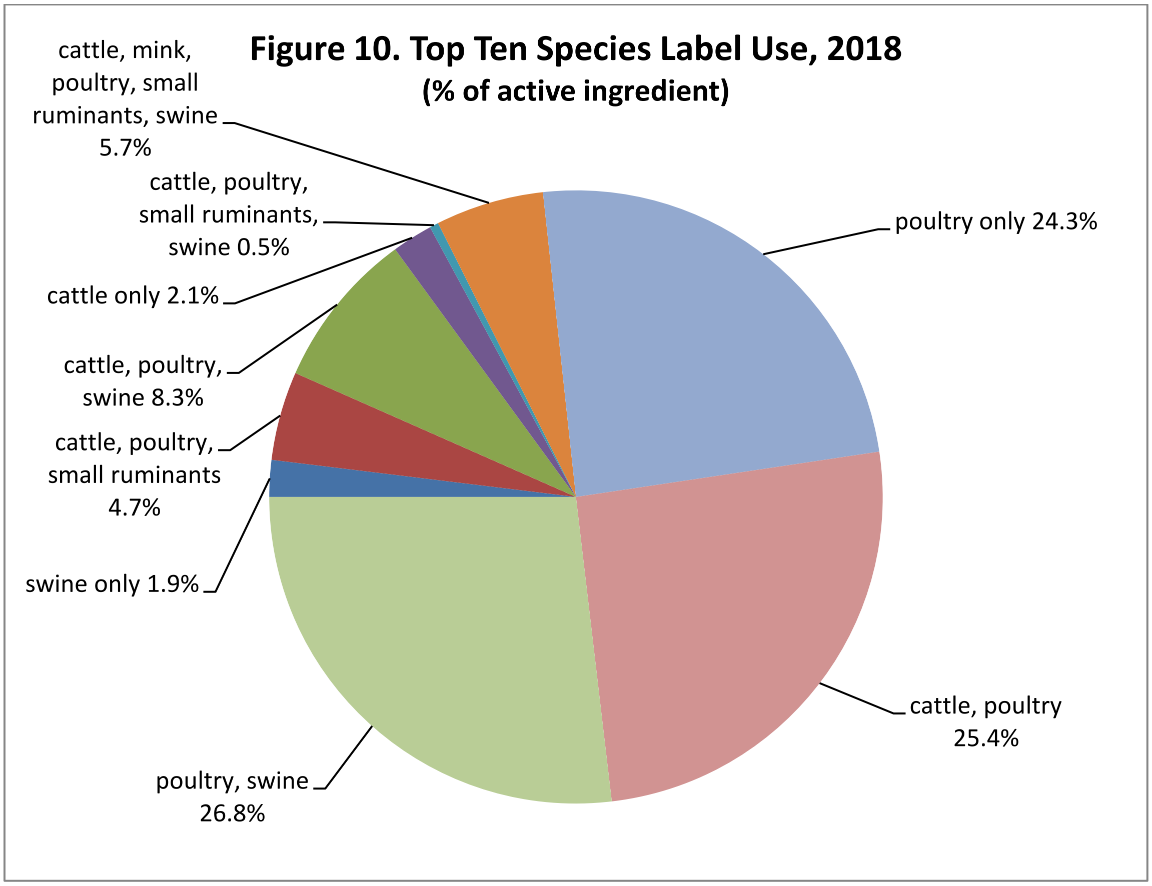


The three label usage categories are: therapeutic, disease prevention and growth promotant. The majority of products have more than one label usage category. For example, monensin, a category IV ionophore, is labelled as a growth promotant and for disease prevention. It and similarly labelled products account for 53.0% of the total active antibiotic ingredients used in 2018. Thirty percent of the 2018 antibiotic active ingredients are labelled for a single usage: 16.3% disease prevention; 10.1% growth promotion and 3.9% therapeutic. The three label usage category combinations: Growth Promotant/Disease Prevention/Therapeutic; Disease Prevention; Growth Promotant/Disease Prevention account for 78.2% of the total 2018 antibiotic usage. The usage categorization results for previous years are substantially similar to those for 2018.

For products with more than one label usage, it is not possible to parse the usage into the different individual categories. Due to 70% of the active ingredients having labels with more than one label usage category, this data is not informative with respect to assessing antibiotic usage for therapy versus growth promotion versus disease prevention.

Effective December 1, 2018 category II and III products can no longer be used for growth promotion. Category IV products can continue to be used for growth promotion as they are not medically important, and category I products have never been approved for growth promotion.

Figure 10 summarizes, for 2018, the top nine combinations of species based on the product labels.



Twenty-eight percent of AMU in 2018 is labelled for use in a single species. The majority of products are labelled for use in more than one species. For example, monensin, a category IV ionophore, is labelled for use in cattle and poultry. That product and others labelled for use in cattle and poultry account for 25.4% of active antibiotic ingredients purchased in 2018. And products labelled for use solely in poultry account for 24.3% of the active ingredients. Figure 10 shows the nine label species combinations with the greatest use. The remaining 15 species labels, in total, account for less than 1% of the total active ingredient. Products labelled for: poultry, cattle or swine, or some combination of these, accounted for 88.8% of the total active ingredients. These 2018 results are substantially similar to the previous years.

For products with more than one label species, it is not possible to parse usage among the species. Due to the large number of label species combinations, and each species being included in at least two combinations, this data is not informative with respect to assessing individual species usage.

Caution in assessing usage amounts and their fluctuations

Incomplete 2006 purchase record data for at least one medicated feed licensee results in an underestimation of usage for that year and likely overstates the fluctuation in AMU. A less obvious potential source of annual AMU fluctuations are substituting between products that vary in dosage rate. For example, salinomycin, monensin, and narasin and are all category IV ionophores approved for coccidiosis prevention in broilers. For this label indication, salinomycin is included at a rate of 60 mg/kg of feed and monensin's inclusion rate is 99 mg/kg. Narasin's inclusion rate is 40 mg/kg for a combination product and 70 mg/kg when narasin is the only active ingredient. Substituting monensin for salinomycin in the prevention of broiler coccidiosis would result in a 65% increase in AMU.

AMU measures such as defined doses remove the effect of dosage rate[18]. Such measures require information on the species the product is being administered to and therefore can not be calculated with the current data. Steady state biomass, corrected for the animal species' lifespans, has been used to put the OTC AMU into a population context. The effect on usage and its fluctuations of changes in the commodity composition of the biomass is unknown.

Is penicillin G of high importance to human medicine?

Health Canada categorizes the penicillin class of antimicrobials as high importance in human medicine (category II) and the penicillin-beta-lactamase inhibitor combinations (amoxicillin-clavulanate, piperacillin-tazobactam) are categorized as very high importance in human medicine (category I). The penicillin class then includes 3 subclasses: 1) extended spectrum penicillins (amoxicillin, ampicillin, piperacillin); 2) beta-lactamase resistant penicillins (cloxacillin); and 3) beta-lactamase sensitive penicillins (penicillin V and penicillin G). All OTC use of this class had been penicillin G until December 1, 2018 when penicillin G was added to the federal Prescription Drug List. It is unclear whether penicillin G is of high importance in human medicine (category II) because beta-lactamase sensitive penicillins are seldom used in human medicine in favour of other penicillins. And it's unclear to what degree resistance to beta-lactamase sensitive penicillins would impact the resistance to other penicillin products.

The beta-lactamase sensitive penicillins have a narrow spectrum of activity, specifically against gram positive organisms, including the human pathogens *Staphylococci*, *Streptococci* and *Pneumococci*. The extended spectrum penicillins have broader activity including gram-negative organisms such as the human pathogens *Neisseria meningitides*, *E. coli* and *P. mirabilis*. The beta-lactamase resistant penicillins and penicillins combined with beta-lactamase inhibitors do not succumb to the beta-lactamase enzyme which is one of the two main mechanisms of penicillin resistance. Alteration of the penicillin-binding protein is the other main mechanism of penicillin resistance.

In BC almost 80% of human penicillin use, as measured by daily defined dose/1000 population/day, is extended spectrum penicillins[14]. The remaining 20% of human use is approximately equally split between the remaining 2 penicillin subclasses and penicillin-β-lactamase inhibitor combinations. In 2016, amoxicillin was the most prescribed and most consumed drug in BC[19]. Judicious antibiotic use requires targeting antibiotics for the infection being treated. So extended spectrum penicillins should be used when their extended spectrum is required such as gram negative or mixed infections. Gram negatives are inherently resistant to beta-lactamase sensitive penicillins so penicillin G use, and any associated resistance expression, should have little impact on the effectiveness of extended spectrum penicillins to treat gram negatives. Similarly, if use of penicillin G resulted in expression of the beta-lactamase enzyme this would not impact the efficacy of the beta-lactamase resistant penicillins or penicillin-β-lactamase inhibitor combinations. Penicillin G mediated resistance via penicillin-binding proteins could impact the effectiveness of the other penicillin subclasses.

Prescott, Bagger & Walker[20] report, despite the extensive use of penicillin in veterinary medicine for many years, most gram positive bacteria remain susceptible to the drug, with the exception of Staphylococcus aureus. They note its resistance is primarily via beta-lactamase production. This supports the reconsideration of whether the use of penicillin G in animals is of high importance in human medicine. In BC data from 2007 to 2015, approximately 20% or less of *Staphylococcus* species isolated from broilers (including *Staph. aureus*) are resistant to penicillin G, with no trend of increasing resistance[21]. Over the same time period, approximately 25% of *Staph. aureus* and coagulase negative staphylococci isolated from bovine milk samples were resistant to penicillin G. Penicillin G resistance averaged four and zero percent respectively to milk isolates of *Streptococcus uberis* and *Streptococcus dysgalactiae*[21].

The European Medicines Agency in 2019 recommended penicillins, including natural narrow spectrum penicillins (penicillin G); and aminopenicillins, without β-lactamase inhibitors (amoxicillin, ampicillin, cloxacillin) be moved to the lowest of the four categories of importance for use in human medicine[22]. The EU doesn't consider ionophores as antibiotics and therefore doesn't include this class of drugs in their categorization of importance to human medicine. Their lowest category includes the following antibiotics: bacitracin, nitrofurans, sulfonamides, tetracyclines, trimethoprim, trimethoprim – sulfamethoxazole, fusidic acid, and nitroimidazoles. The first 5 antibiotics are currently classified by Health Canada as category III medium importance, trimethoprim–sulfamethoxazole, fusidic acid are category II high importance and the final antibiotic as category I very high importance. The European Medicines Agency ranking in their lowest category of importance to human medicine is equivalent to Canada's category III medium importance .

Judicious use

The data indicate from 2002 to 2018 total AMU measured on a biomass basis increased 5%. This estimate is inflated due to missing data in 2002, and the 17 year change is likely closer to 0%. Furthemore, after removing the effect of the apparent Super Booster stockpiling, the usage in 2018 was likely about 5% lower than usage in 2002. Preferably usage on a biomass basis would remain constant if not decrease over time.

Generally, assessment of judicious use is difficult for two reasons. First, a practical, clear definition of judicious (or prudent) use is lacking. The standard definition of judicious use is the optimal section of drug, dose and duration combined with the reduction of inappropriate and excessive use, as a means of achieving the best clinical outcome while slowing the emergence of resistance[23]. It is recognized that such a definition provides minimal practical guidance to prescribers, and is not helpful for assessing antibiotic use data. In addition, the definition provides little insight into antibiotic use issues such as the judiciousness of their use to prevent disease versus treating disease after it has occurred. The second difficulty with assessing judicious use is a lack of consensus on whether antibiotics should be prioritized, this despite the categorization of antibiotics' importance in human medicine by such organizations as Health Canada and the World Health Organization's. Notwithstanding this lack of consensus, judiciousness of OTC usage is evaluated in this report using categorization by importance in human medicine.

Total usage on a biomass basis is a crude measure; from a public health perspective it is informative to consider the categorization of that usage by importance in human medicine. The change from 2002 to 2018 in the amount of antibiotics from each category of importance to human medicine is an indication of the judiciousness of OTC usage. From 2002 to 2018 there was a 9% increase in category IV products which are considered not medically important. Use of category III (medium importance in human medicine) decreased 15%. OTC use of category I products is negligible and total use of category II products increased 55% over the 17 years (removing the effect of the Super Booster stockpiling resulted in a 15% increase since 2002).

Each categories' percentage of total use in another indicator of judiciousness of OTC usage. Approximately half of the active ingredients used are not used in human medicine and therefore are not considered as medically important (category IV). Average annual usage of category III products was 40% of total usage, and use of category II products (including Penicillin G) products averaged 12% of total use from 2002 to 2018. In 2018, the each categories percentage of total use was 47%, 33%, 20% respectively for categories IV, III, and II. This pattern of diminishing use of products as their importance to human medicine increases in consistent with judicious use of OTC antibiotics. Category I and II products are of greatest importance in human medicine.

<u>Prescriptions and prescription use only policy as sources of AMU data</u>

A common refrain in the discussion about animal AMU is the need for a prescription use only policy to facilitate data collection. Antibiotics dispensed by BC veterinarians and pharmacists, either by prescription or OTC, would complement the AMU data presented in this report to provide a complete picture of animal AMU in BC. However, the evidence does not support prescriptions, or associated policies, as AMU data sources. All Canadian provinces and territories have had veterinary prescriptions for decades and some provinces are prescription use only. Yet, none of the provinces or territories have produced animal prescription AMU data. BC in the only province to generate AMU data, its aquaculture data is from prescriptions and this report is OTC sales, and all of the data is collected from the dispensers not the prescribers. Similarly, dispensers (pharmacists) are the primary source of human prescription AMU data (human OTC AMU data is not currently collected). A foreseeable consequence of the additional of virtually all category II and III products to the federal Prescription Drug list is the loss of data collection and analysis for non-feed antibiotics sold by BC's Veterinary Drug licencees.

Implications of a prescription use only policy

This AMU data is unique in that is restricted to OTC sales by non-veterinarians and non-pharmacists. This data provides interesting insights into OTC usage and the implications of changing to a prescription use only policy. For example, there are varying definitions of prescription use only and this data set can illustrate which products and their amounts would be affected by a given definition of prescription use only.

This data illustrates that in so far as virtually no category I products are sold in BC's OTC products, shifting to a prescription use only policy and requiring producers to interact with veterinarians would likely increase the amount of category I products used in animals. Veterinary prescription products are typically category I and II products, very high importance and high importance to human medicine, respectively. An increase is the usage of antibiotics of greatest importance to human medicine is an unexpected result for a policy that is typically considered to foster judicious use. OTC sales of antibiotics are not limited to animals. For example, the human antibiotic skin ointment Polysporin® contains an antibiotic of the highest importance to human medicine. The judiciousness of human over-the-counter antibiotic use should be reviewed, and this would start with collecting human OTC AMU data.

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Appendix - Tables

Table 1. Annual Antibiotic Use Categorized by Importance in Human Medicine (gm active ingredient/tonne biomass)

	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Category I	0	0	4.5E-06	4.3E-06	3.5E-06	0	0	0	0	0	0	0	0	0	0	0	0
Category II	20	12	8	7	8	9	8	16	29	16	22	20	21	25	26	29	31
Category III	60	51	49	69	39	75	91	84	57	59	72	53	56	54	55	50	51
Category IV	66	69	61	73	68	95	85	74	74	83	76	73	54	58	85	87	72
Total	146	132	118	150	115	180	183	175	159	158	170	146	131	137	165	165	153

* missing data

Table 2. Annual Antibiotic Use of Category IV Importance in Human Medicine (gm active ingredient/tonne biomass)

Antibiotic	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Bambermycin	0.08	0.08	0.07	0.13	0.13	0.07	0.01	0.02	0.01	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Lasalocid	1.77	0.91	11.08	0.42	0.78	0.69	1.14	0.53	0.69	0.36	0.46	11.06	0.79	1.09	5.92	6.48	7.17
Salinomycin	16.93	18.18	13.45	16.25	10.03	25.34	25.85	20.79	1.65	8.38	10.51	14.55	11.00	18.17	24.41	25.70	10.87
Narasin	18.40	14.81	13.72	19.85	19.56	23.01	20.62	16.06	26.52	24.95	26.63	5.73	5.79	10.33	10.41	10.78	14.60
Monensin	28.58	34.53	22.87	36.71	37.97	45.99	37.11	36.77	44.91	49.27	38.27	41.62	36.69	28.13	43.79	43.84	39.00
Total	65.76	68.51	61.18	73.37	68.47	95.10	84.73	74.17	73.78	82.96	75.86	72.95	54.27	57.72	84.53	86.79	71.64

* missing data

Table 3. Annual Antibiotic Use of Category III Importance in Human Medicine (gm active ingredient/tonne biomass)

Antibiotic	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Aminoglycosides	- **	-	6.3E-05	1.4E-05	1.3E-05	-	-	-	-	-	-	2.7E-04	2.1E-05	5.2E-05	1.7E-05	3.7E-05	1.2E-04
Nitrofurans	-	-	1.7E-04	0.001	3.8E-04	4.2E-04	2.1E-04	1.7E-04	2.3E-04	3.3E-04	2.6E-04	7.6E-04	9.8E-04	1.8E-03	1.1E-03	6.6E-04	6.2E-04
Coumarins	-	-	0.004	0.003	0.002	-	-	-	-	-	-	-	-	-	-	-	-
Pleuromutilin	0.026	0.004	0.001	0.001	-	-	0.027	0.103	0.069	0.198	0.251	0.156	0.290	0.282	0.298	0.412	0.007
Aminocyclitols	0.264	0.267	0.277	0.285	0.224	0.159	0.208	0.184	0.091	0.070	0.035	0.039	0.033	0.008	0.008	0.038	0.000
Sulphonamides	3.574	2.808	3.919	2.188	0.641	2.259	2.844	3.811	4.600	2.314	4.488	3.993	3.706	4.408	3.088	2.351	1.966
Tetracyclines	29.486	26.515	19.088	15.983	8.176	18.041	21.193	23.139	19.893	14.537	19.465	16.295	18.184	15.525	13.584	14.086	14.337
Bacitracins	26.697	21.636	25.932	50.836	30.114	55.014	66.264	57.167	32.010	42.079	47.901	32.193	33.582	34.229	37.743	32.866	34.609
Total	60.0	51.2	49.2	69.3	39.2	75.5	90.5	84.4	56.7	59.2	72.1	52.7	55.8	54.5	54.7	49.8	50.9

* missing data

** no usage

Table 4. Annual Antibiotic Use of Category II Importance in Human Medicine (gm active ingredient/tonne biomass)

Antibiotic	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Dihydrostreptomycin	-**	-	7.5E-05	7.2E-05	5.9E-05	-	-	-	-	-	-	-	-	-	-	-	-
Erythromycin	-	-	0.008	3.3E-04	4.1E-04	0.015	0.008	0.128	0.214	4.6E-04	0.156	0.155	0.123	0.205	0.001	0.008	-
Streptomycin	-	-	0.023	0.021	0.023	0.422	0.240	0.893	1.159	1.085	1.407	0.857	1.487	3.109	3.918	3.217	9.778
Lincomycin	0.722	0.848	0.644	0.781	1.190	0.790	0.531	0.184	0.091	0.070	0.078	0.123	0.102	0.023	0.008	0.037	-
Neomycin	0.345	1.360	0.900	0.176	0.328	0.138	0.359	0.612	0.485	0.441	0.801	0.483	0.274	0.396	0.338	0.234	0.375
Tylosin	1.790	1.913	1.352	1.514	1.412	1.403	0.292	2.706	7.268	0.946	1.305	1.170	0.877	1.093	1.457	0.899	0.290
Penicillin G	11.663	3.872	2.319	3.731	2.132	2.534	0.903	3.164	7.128	8.446	11.144	12.826	13.855	15.922	15.137	18.988	18.638
Virginiamycin	5.736	4.181	2.516	0.955	2.575	3.798	5.293	8.302	12.357	5.276	6.655	4.508	3.957	3.884	5.302	5.243	1.706
Total	20.258	12.176	7.762	7.177	7.661	9.100	7.627	15.990	28.703	16.264	21.546	20.123	20.676	24.632	26.160	28.626	30.787

* missing data

** no usage