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

2002 – 2012

Brian R Radke DVM PhD

Public Health Veterinarian

Plant and Animal Health Branch

BC Ministry of Agriculture

brian.radke@gov.bc.ca

January 7, 2014

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[2] 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 2012, 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 (mg of active antibiotic ingredient/tonne of steady state livestock biomass).

Some of the report's key findings include:

- Over the 11 year span, total antibiotic usage increased by an estimated 11% (approximately 1% annually). This small increase is due to slight increases in the usage of antibiotics categorized as the least important to human medicine. This temporal pattern of usage and the pattern of diminishing use of antibiotics as their importance to human medicine increases is consistent with judicious use of over-the-counter antibiotics.
- Approximately 95% of the antibiotics are administered in feed, 5% in water and all other methods of administration account for less than 1% of total usage.
- Approximately one-third of the antibiotics used have a single label usage category and the majority are labelled for two or more of these usages. The majority of antibiotics used are approved for use in more than one species. Those labelled for poultry, cattle & poultry or poultry & swine accounted for 83% of total usage.
- Antibiotic usage by category of human importance fluctuated; however, the average annual use of categories I, II, III, and IV are 0%, 9%, 42%, 49%, respectively. Health Canada's categorization of antibiotics on their importance to human medicine ranges from very high importance (category I) to products which aren't used in humans and have a low importance (category IV).
- Penicillin G accounted for over half of the category II usage in 2011 and 2012, and 35% of that category's use from 2002 to 2012. 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 interesting 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. 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. 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. 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

Part I of Schedule F of the federal Food and Drug Regulations[3] includes the pharmaceutical products, including antibiotics, which require a prescription in order to be sold. Part II of Schedule F lists those products, including antibiotics, which can be sold without a prescription for use in animals. The federal Feeds Regulations' Compendium of Medicating Ingredients Brochures[4] (CMIB) lists the medicating ingredients, including antibiotics, which can be added to livestock feeds without a prescription from a veterinarian. The Compendium specifies 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.

The Drug Schedules Regulation[5] of BC's Pharmacy Operations and Drug Scheduling Act notes which drugs, including antimicrobials, can be sold without a prescription for use in animals. This list is consistent with Part II of Schedule F. The BC Veterinary Drug and Medicated Feed Regulation[6] 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[7] 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. 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 2012. 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[8] and the World Organization for Animal Health's (i.e., the OIE's) categorization of antimicrobials based on importance in veterinary medicine[9]. Antimicrobial use by BC aquaculture is excluded from this OTC analysis because that usage is under veterinary prescription and has been previously reported[2,10].

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 is rare (with the exception of aquaculture which is excluded from this report). 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. 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 included 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 the 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 less than 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, which was slightly higher than 2005. After 2007, total antibiotic use decreased to 2010 and increased thereafter. Over the 11 years, AMU fluctuated, and there is little discernible trend in antibiotic use as measured by kilogram of active ingredient -- usage in 2012 is slightly less than that in 2002.

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. In 2011 and 2012 the total biomass increases slightly. From 2007 to 2012 AI mass and biomass follow similar trends. The biomass of beef cattle follows a similar pattern as the total biomass. The biomass of dairy cattle remains constant over the time period. The poultry biomass remains constant over the time period with the exception of 2004 when the BC poultry industry experienced an 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 biomasses of hogs, and sheep, goats and horses steadily decline over the 11 years.

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

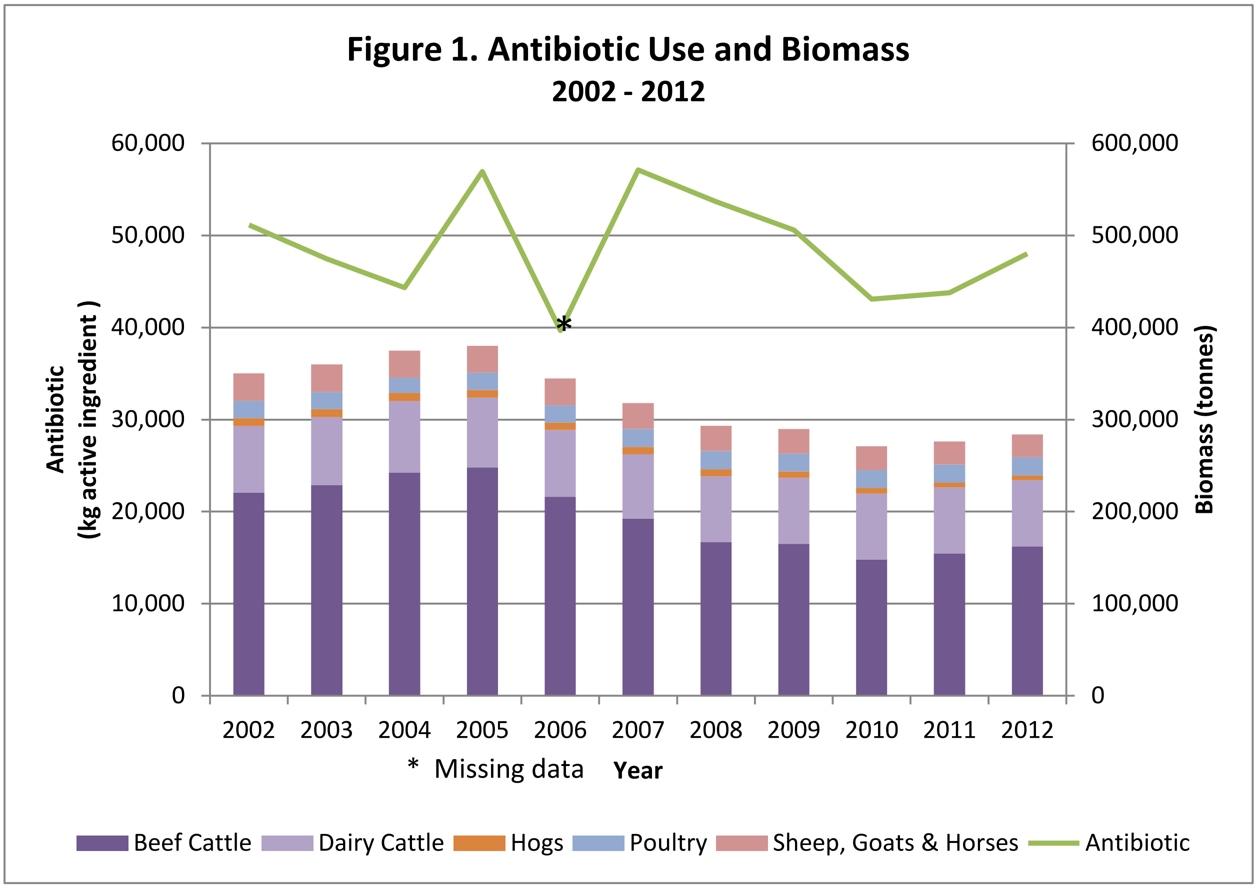


Figure 2 compares total mass of AI with another measure of AMU. The light green line in figure 2 reproduces the total mass of AI line from figure 1. The second measure, the darker line, is antibiotic mass on a biomass basis, specifically gram of active ingredient per tonne of biomass. Figure 2 reveals the two measures of AMU vary. There is little discernable trend in antibiotic mass over the 11 year period; however, when measured on a biomass basis, AMU increases over that period. Also, the biomass basis measure peaks in 2008 as opposed to 2007. While there is little difference in antibiotic mass between 2005 and 2007, AMU in 2007 is discernably greater than 2005 when measured on a biomass basis. 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[11]. Hereafter, OTC antibiotic use will be presented on a per biomass basis (gm of antibiotic active ingredient per tonne of steady state biomass).

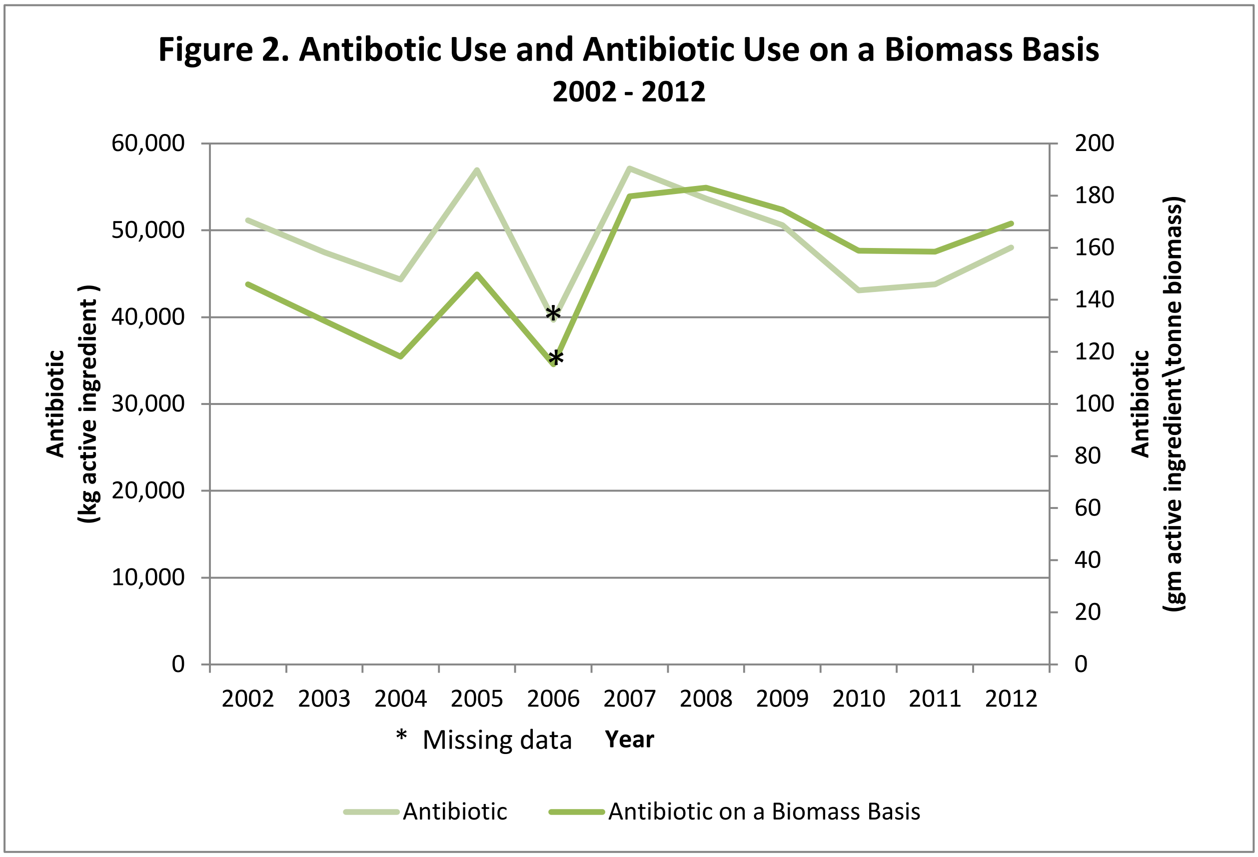


Figure 3 shows the annual antibiotic use categorized by Health Canada's importance in human medicine. Table 1 reports the same information but in greater detail. Categories I, II and III are considered as "medically important antimicrobials".

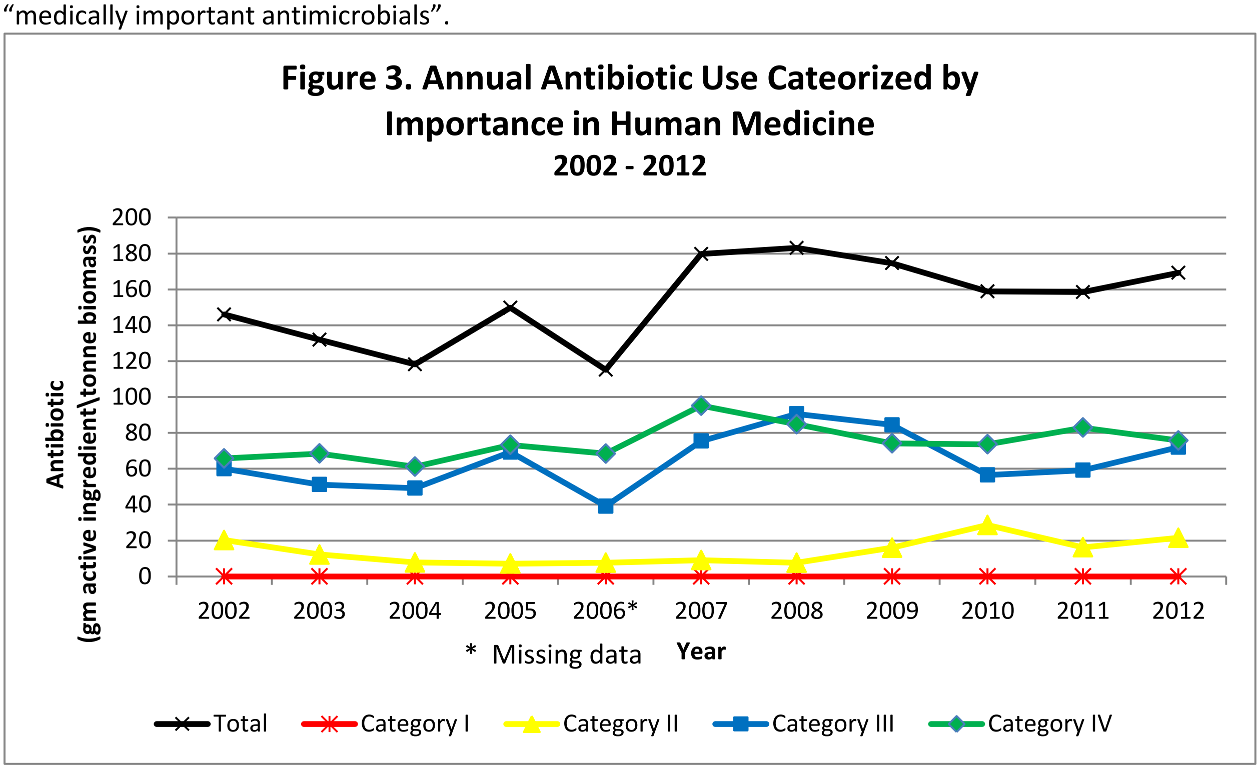


Table 1. Annual Antibiotic Use Categorized by Importance in Human Medicine (gm active ingredient/tonne biomass)

	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011	2012
Category I	0	0	4.5E-06	4.3E-06	3.5E-06	0	0	0	0	0	0
Category II	20	12	8	7	8	9	8	16	29	16	22
Category III	60	51	49	69	39	75	91	84	57	59	72
Category IV	66	69	61	73	68	95	85	74	74	83	76
Total	146	132	118	150	115	180	183	175	159	158	169

* missing data

Over the 11 year span, total usage increases from 146 mg of active antibiotic ingredient/tonne of biomass to 169 mg of active ingredient/tonne of biomass, a 16% 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 11 year increase is less than 16% and likely closer to 11%. This small increase in total use is driven by the slightly increasing use of category IV (low importance to human medicine) and category III (medium importance to human medicine) products. Usage of categories IV and III peak in 2007 and 2008, respectively. Annually, category IV products range from 42% to 59% of total AMU and average 49% over the 11 years. Annually, category III products range from 34% to 50% of the total and average 42% over the 11 years. The use of category II products, high importance in human medicine, is variable over time and peaks in 2010. Use of category II products trends downward from 2002 to 2008 and then increases. Annually category II products range from 4% to 18% of the total usage and average 9% over the 11 years. With the exception of 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), is 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 reports the same information but in greater detail.

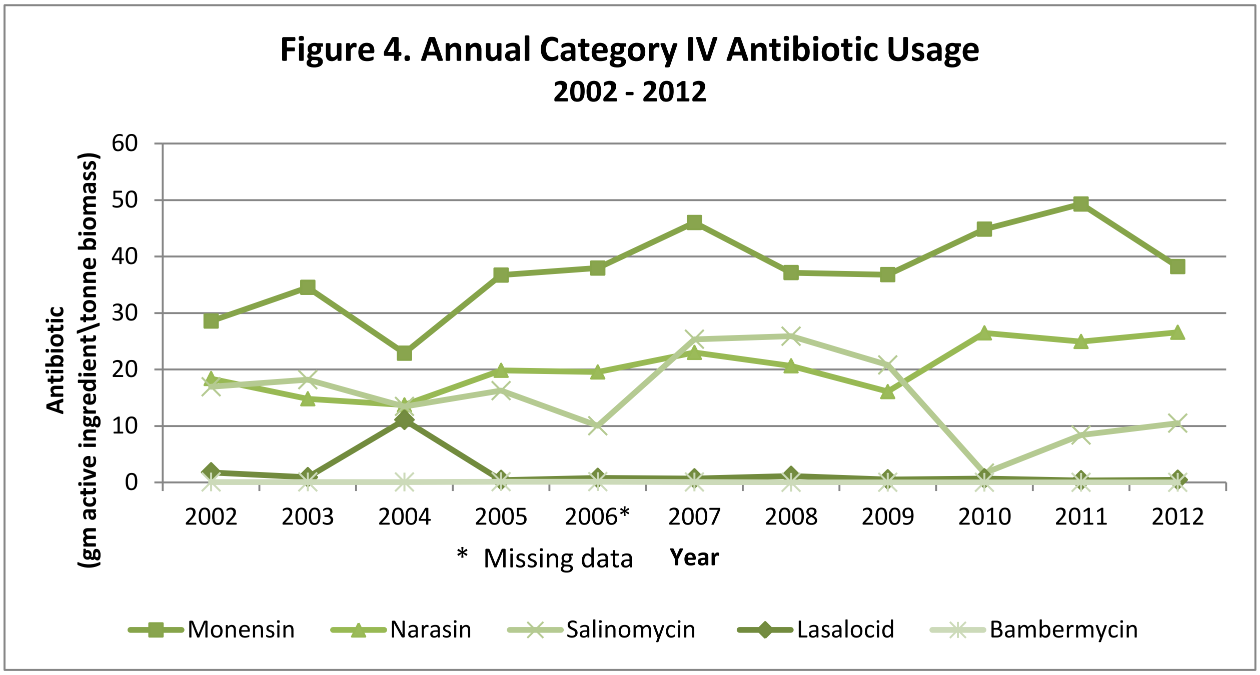


Table 2. Annual Antibiotic Use of Category IV Importance in Human Medicine (gm active ingredient/tonne biomass)

Antibiotic	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011	2012
Bambermycin	0.08	0.08	0.07	0.13	0.13	0.07	0.01	0.02	0.01	0.01	0.01
Lasalocid	1.77	0.91	11.08	0.42	0.78	0.69	1.14	0.53	0.69	0.36	0.45
Salinomycin	16.93	18.18	13.45	16.24	10.02	25.35	25.88	20.79	1.65	8.38	10.49
Narasin	18.39	14.81	13.72	19.84	19.55	23.01	20.64	16.07	26.47	24.95	26.58
Monensin	28.56	34.53	22.87	36.70	37.94	46.00	37.14	36.78	44.83	49.28	38.20
Total	65.72	68.51	61.18	73.33	68.42	95.12	84.81	74.19	73.66	82.98	75.73

* missing data

Category IV antibiotics are not used in human medicine. Health Canada considers category IV antibiotics to be of low importance in human health and not medically important. Monensin accounts for approximately half of the category IV usage followed by narasin, salinomycin, lasalocid, and bambermycin. Monensin, narasin, salinomycin and lasalocid belong to the ionophore antibiotic class, and bambermycin belongs to the flavophospholipols class.

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

Figure 5. Annual Category III Antibiotic Class Usage
2002 - 2012

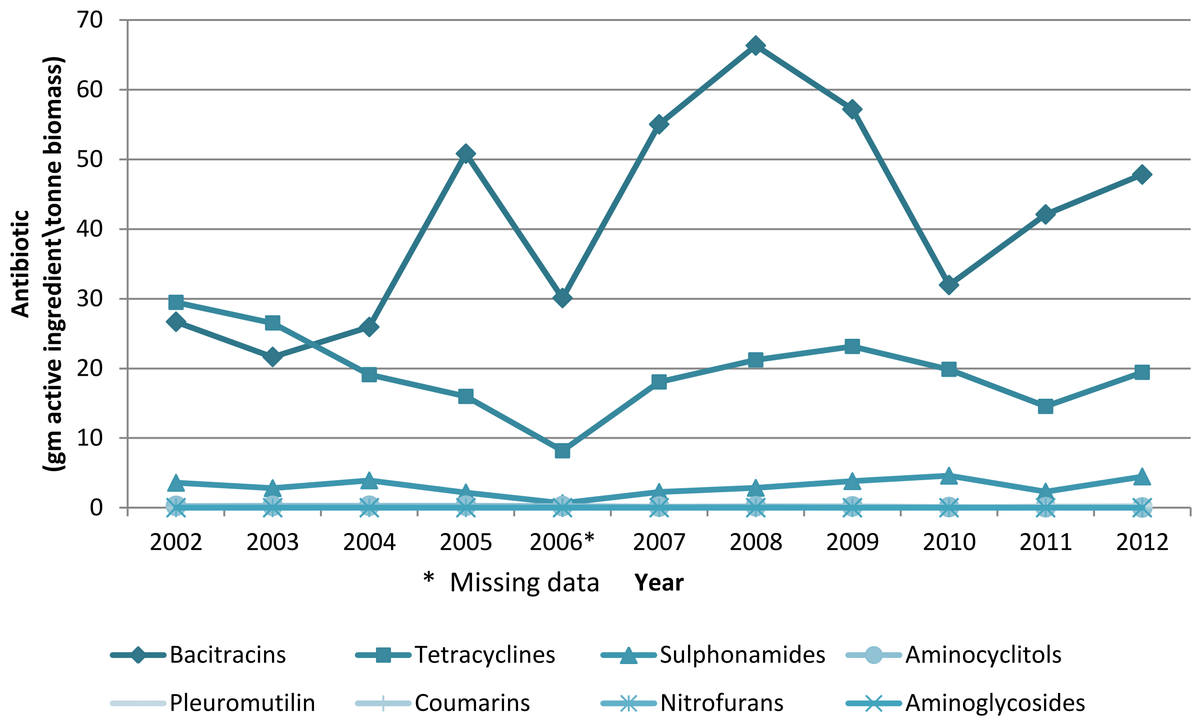


Table 3. Annual Antibiotic Use of Category III Importance in Human Medicine (gm active ingredient/tonne biomass)

Antibiotic Class	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011	2012
Aminoglycosides	- **	-	6.3E-05	1.4E-04	1.3E-04	1.8E-04	1.7E-04	1.4E-04	1.5E-04	1.6E-04	7.0E-05
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
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
Aminocyclitols	0.264	0.268	0.277	0.285	0.223	0.159	0.208	0.184	0.091	0.070	0.035
Sulphonamides	3.572	2.808	3.919	2.187	0.641	2.260	2.847	3.812	4.593	2.315	4.480
Tetracyclines	29.472	26.516	19.090	15.975	8.170	18.045	21.212	23.145	19.860	14.541	19.431
Bacitracins	26.684	21.637	25.934	50.810	30.092	55.026	66.324	57.181	31.956	42.091	47.817
Total	60.0	51.2	49.2	69.3	39.1	75.5	90.6	84.4	56.6	59.2	72.0

* missing data

** no usage

Health Canada considers category III antibiotics to be of medium importance in human medicine. Since 2004, bacitracin has accounted for over half of the category III usage. Its usage fluctuates with an overall trend of increased use. 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 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 2012. Usage of this class peaks in 2010 at 8% of the category III class usage. Other category III antibiotic classes that were used from 2002 to 2012 had very small 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).

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

Figure 6. Annual Category II Antibiotic Usage
2002 - 2012

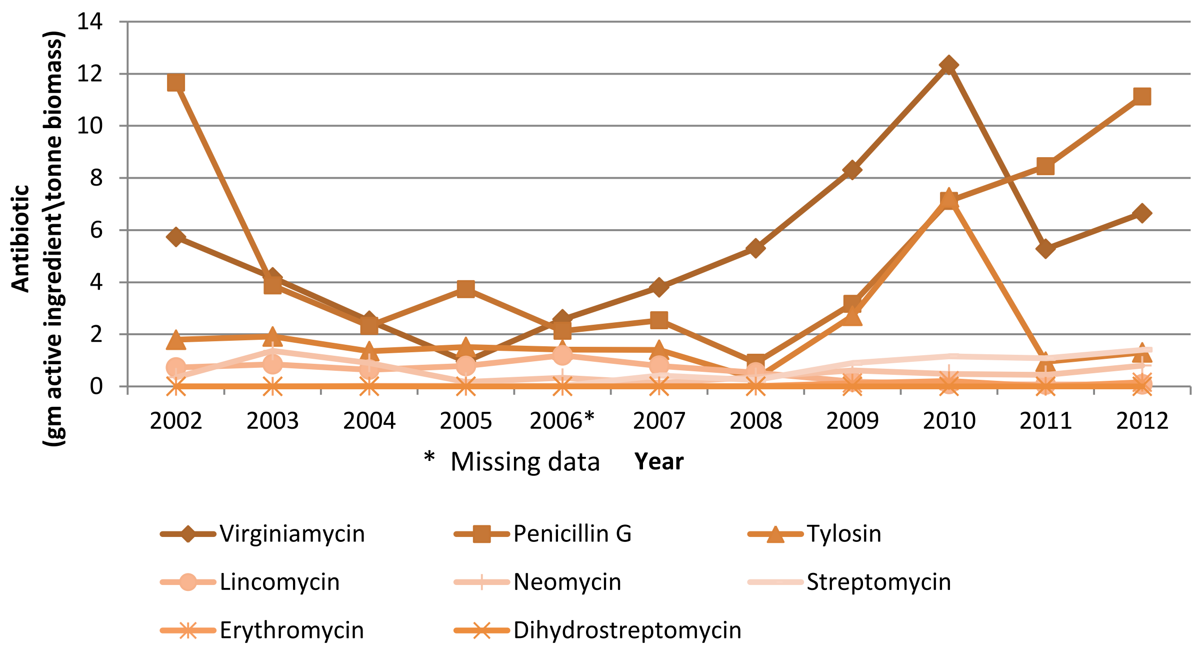


Table 4. Annual Antibiotic Use of Category II Importance in Human Medicine (gm active ingredient/tonne biomass)

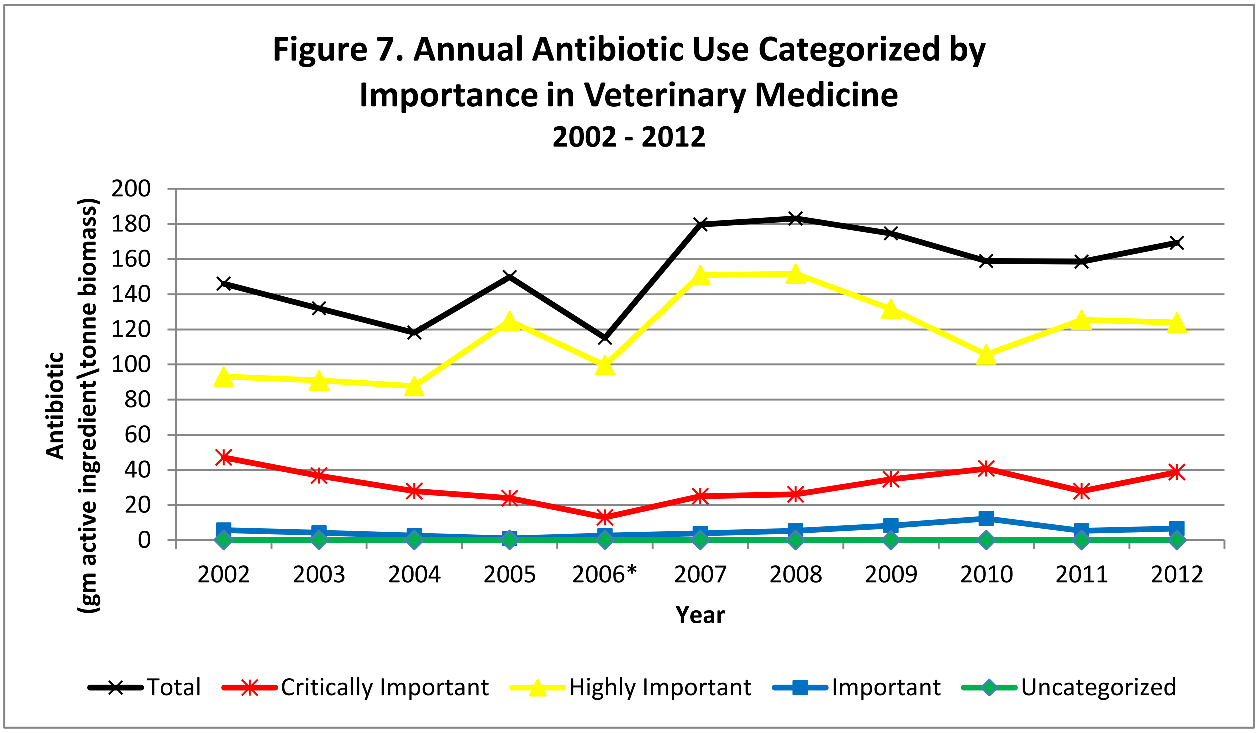
Antibiotic	2002	2003	2004	2005	2006*	2007	2008	2009	2010	2011	2012
Dihydrostreptomycin	** -	-	7.5E-05	7.2E-05	5.9E-05	-	-	-	-	-	-
Erythromycin	-	-	0.008	3.3E-04	4.1E-04	0.015	0.008	0.128	0.214	4.6E-04	0.156
Streptomycin	-	-	0.023	0.021	0.022	0.422	0.240	0.894	1.158	1.085	1.405
Lincomycin	0.722	0.848	0.644	0.780	1.189	0.790	0.531	0.184	0.091	0.070	0.078
Neomycin	0.345	1.360	0.900	0.176	0.328	0.138	0.360	0.612	0.485	0.441	0.800
Tylosin	1.789	1.913	1.352	1.514	1.411	1.403	0.293	2.707	7.255	0.946	1.303
Penicillin G	11.658	3.873	2.320	3.729	2.130	2.535	0.904	3.165	7.116	8.449	11.124
Virginiamycin	5.733	4.182	2.517	0.955	2.573	3.799	5.298	8.304	12.336	5.278	6.644
Total	20.248	12.176	7.763	7.174	7.655	9.102	7.634	15.994	28.654	16.268	21.508

* missing data

** no usage

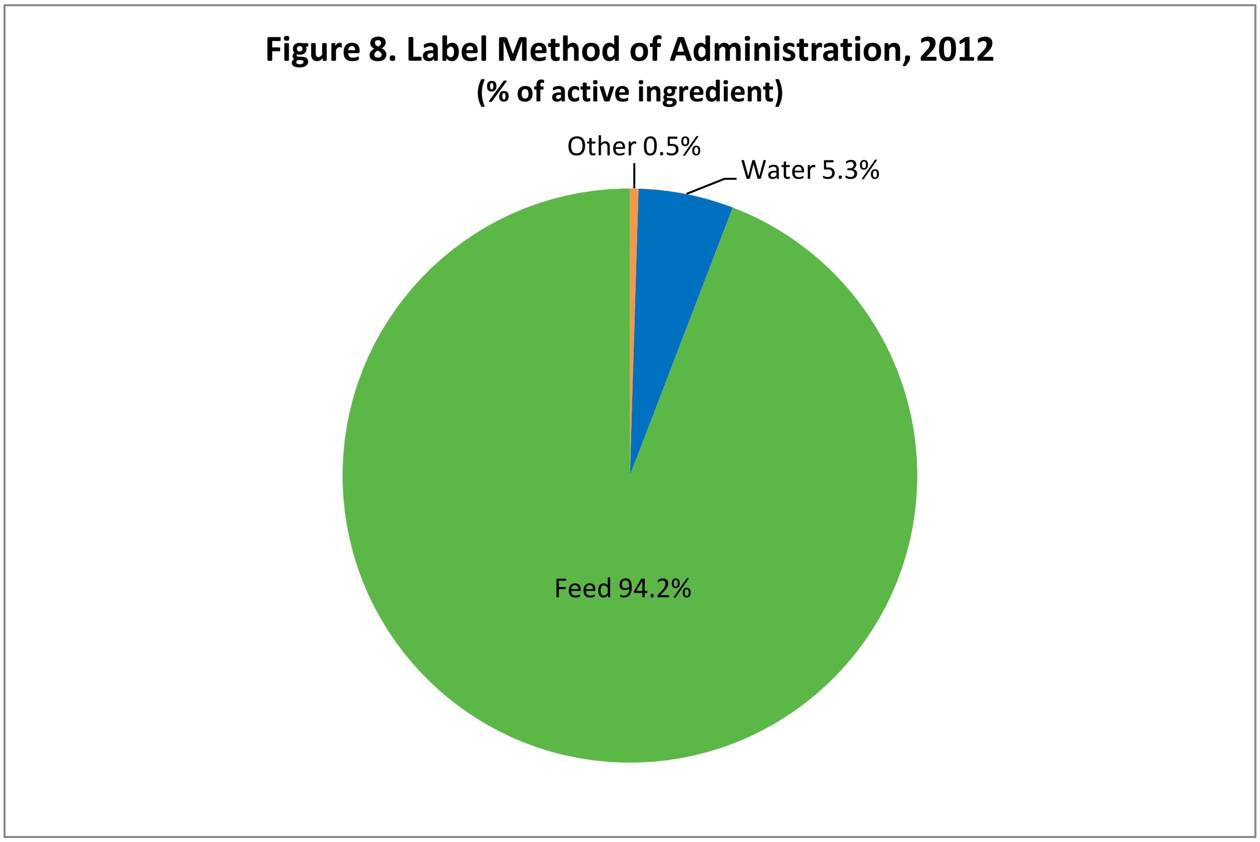
Health Canada considers category II antibiotics to be of high importance in human medicine. The category II antibiotic classes streptogramins (virginiamycin) and penicillins (penicillin G) account for approximately 60 to 85% of annual category II usage. Penicillin G decreases from 2002 to 2008 and then rises from 2009 to 2012, nearly reaching the same usage as 2002. Over the eleven years, penicillin G averages 35% of annual category II usage. In 2011 and 2012, penicillin G accounts for over half of the category II usage. Virginiamycin use increases from 2005 to a peak in 2010 then declines. In 2010 virginiamycin accounts for 43% of the category II usage. Tylosin (macrolide class) is typically the third most used antibiotic in this category, peaking in 2010 before returning to lower levels. Streptomycin (aminoglycoside class) use increases over time and in 2011 and 2012 replaces tylosin as the third most used antibiotic in the category, although significantly less than penicillin G or virginiamycin. Neomycin (aminoglycoside class) use peaks in 2003 and then fluctuates, almost regaining its peak level in 2012. After peaking in 2006, lincomycin (lincosamide class) use declines. Erythromycin (macrolide class) and, dihydrostreptomycin (aminoglycoside class) use is very limited, and combined, are less than 1% of category II usage.

Figure 7 shows the categorization of antibiotic usage by their importance to 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.

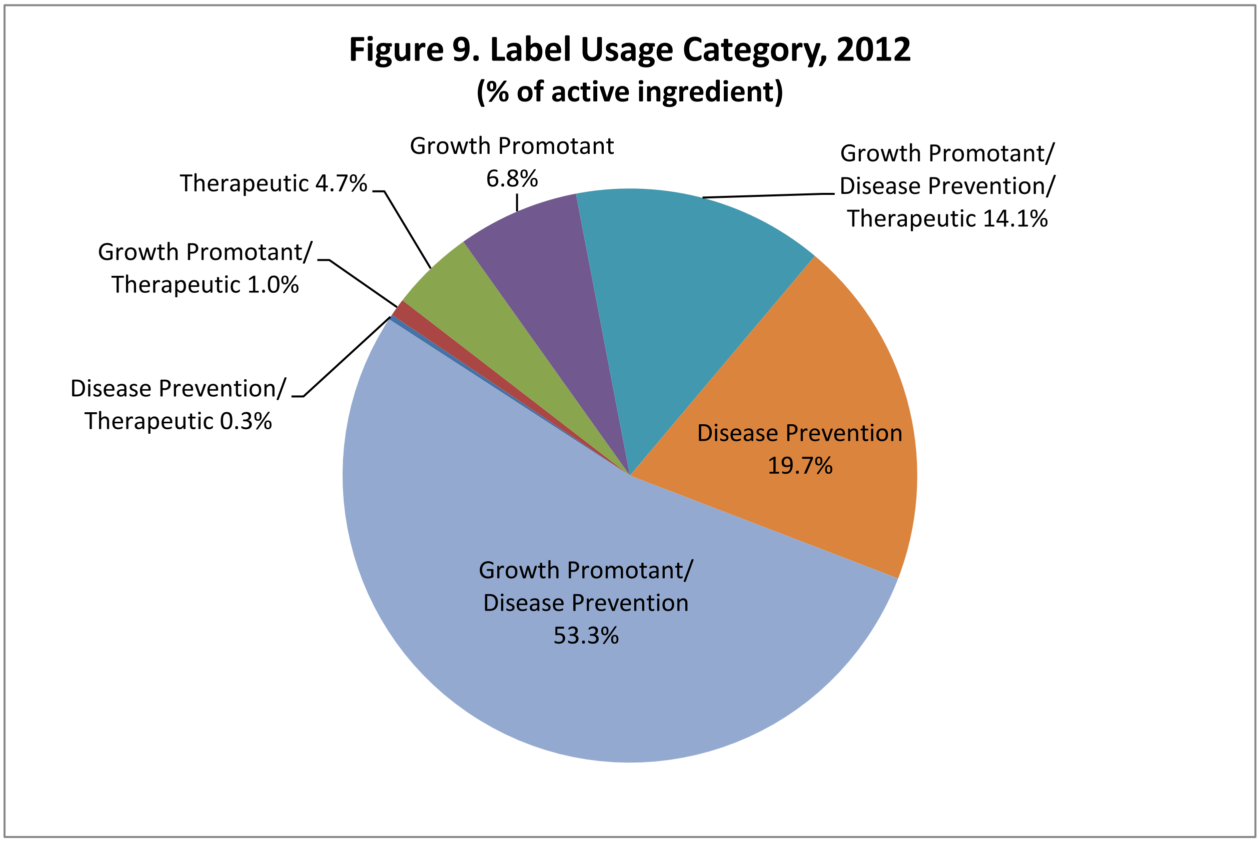
Figure 8 shows, for 2012, the method of administration for OTC antibiotic purchases based on the product labels.



In 2012, the vast majority of the active antibiotic ingredients are administered via feed. Slightly more than 5% of the active ingredients are in preparations for addition to water. Less than 1% of the active ingredients are administered via non-feed and non-water methods. Methods of administration included in the other category (and the respective percentage of active ingredient) are: injectable (0.28%), oral tablet (0.17%), palatable suspension (0.012%), intrauterine (0.008%), topical (0.004%), and intramammary (0.0001%).

Figure 8 is substantially representative of the method of administration for years 2004 to 2011. Over those years, feed administration ranges from 96.1% to 98.1% of total use. Water administration between 2004 and 2011 ranges from 1.2% to 3.3%. Other methods of administration range from 0.3% to 1.1% during this time period.

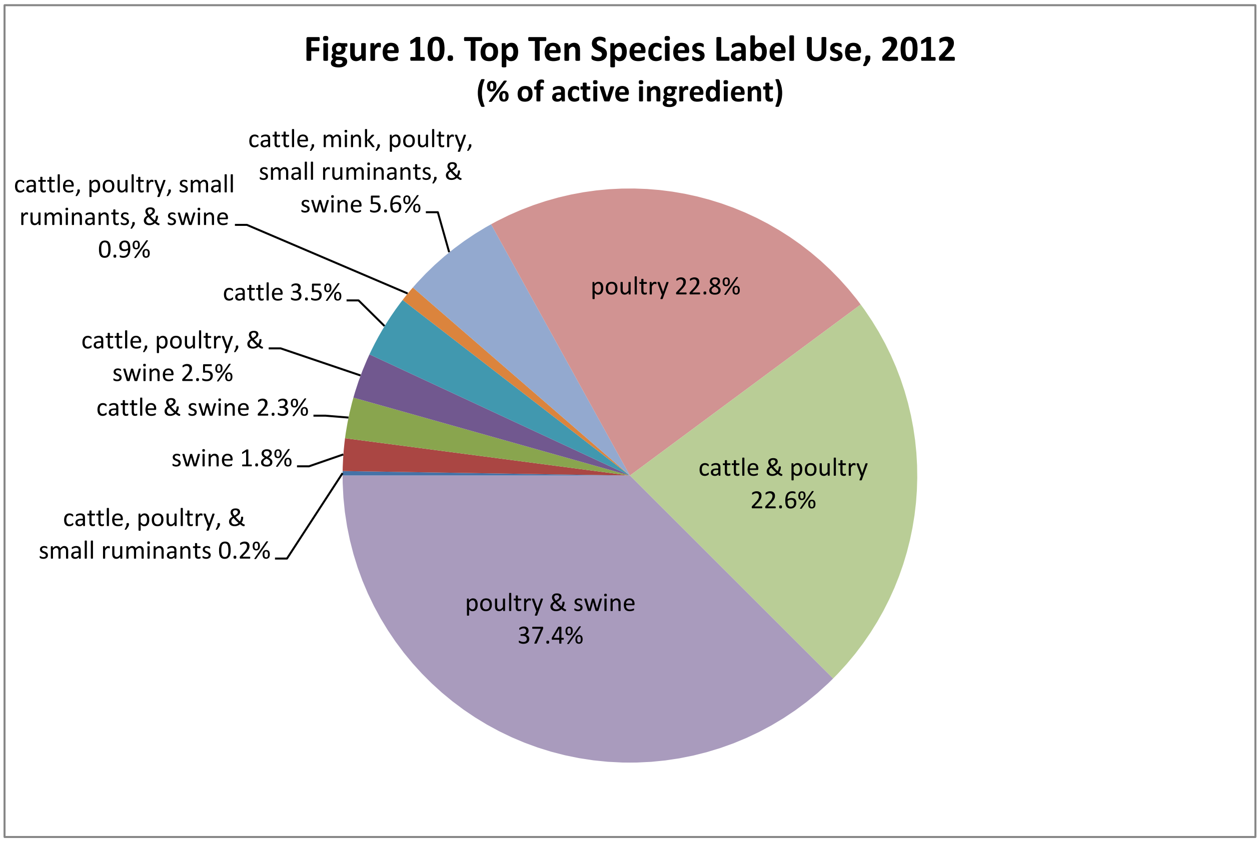
Chart 9 summarizes for 2012, the usage categories for OTC antibiotic purchases based on the product labels.



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 53.3% of the total active antibiotic ingredients used in 2012. Thirty-one percent of the 2012 antibiotic active ingredients are labelled for a single usage: 19.7% disease prevention; 6.8% growth promotion and 4.7% therapeutic. The three label usage category combinations: Growth Promotant/Disease Prevention/Therapeutic; Disease Prevention; Growth Promotant/Disease Prevention account for 87% of the total 2012 antibiotic usage. The usage categorization results for previous years are substantially similar to those for 2012.

For products with more than one label usage, it is not possible to parse the usage into the different individual categories. Due to 69% 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.

Figure 10 summarizes, for 2012, the top ten combinations of species based on the product labels.



Twenty-eight percent of AMU in 2012 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 22.6% of active antibiotic ingredients purchased in 2012. And products labelled for use solely in poultry account for 22.8% of the active ingredients. Figure 10 shows the ten label species combinations with the greatest use. The remaining 14 species labels, in total, account for less than 1% of the total active ingredient. Products labelled for: poultry; cattle & poultry; and poultry & swine account for 83% of the total active ingredients. These 2012 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 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[12]. 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 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 to 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 is penicillin G. 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[11]. The remaining 20% of human use is approximately equally split between the remaining 2 penicillin subclasses and penicillin-β-lactamase inhibitor combinations. Judicious antibiotic use requires targeting antibiotics for the infection being treated. So extended spectrum penicillins should only 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[13] 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 to human medicine.

Judicious use

The data indicate from 2002 to 2012 total AMU measured on a biomass basis increased 16%. This increase is overestimated due to missing data in 2002, and the 11 year increase is likely closer to 11%. Although the increase is small and difficult to interpret, preferably usage would remain constant if not decrease over time. Total usage 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 increase in total use is associated with slight increases in the use of category IIII and IV products which are the least important to human medicine. OTC use of category I products is negligible and total use of category II products did not have a discernible trend over the 11 years. Category I and II products are of greatest importance to human medicine. Approximately half of the active ingredients used are not used in human medicine and therefore are not considered as medically important and are categorized as low importance in human medicine (category IV). Average annual usage of category III products was approximately 40% of total usage, and use of category II products (including Penicillin G) products averaged 9% of total use from 2002 to 2012. This pattern of diminishing use of products as their importance to human medicine increases in consistent with judicious use of OTC antibiotics.

Prescriptions and prescription use only policy as sources of AMU data

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).

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.

References

1) http://www.antimicrobialcanada.com/
2) http://www.agf.gov.bc.ca/ahc/fish_health/antibiotics.htm
3) http://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/index.html
4) http://www.inspection.gc.ca/animals/feeds/medicating-ingredients/eng/1300212600464/1320602461227
5) http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/11_9_98
6) http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/11_47_82
7) http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_96363_01
8) http://www.hc-sc.gc.ca/dhp-mps/vet/antimicrob/amr_ram_hum-med_intro-eng.php
9) http://web.oie.int/downld/Antimicrobials/OIE_list_antimicrobials.pdf
10) Morrison, D.B., Saksida, S., 2013. Trends in antimicrobial use in Marine Harvest Canada farmed salmon production in British Columbia (2003-2011). Can. Vet. J. 54, 1160-1163.
11) Communicable Disease Prevention and Control Services, BC Centre for Disease Control. (2012) *BC Annual Summary of Antibiotic Utilization 2010* . Retrieved from http://www.bccdc.ca/NR/rdonlyres/194B4D3B-373E-4D10-8851-C73AAFE0A80F/0/Fullantibioticconsumptionreport16Aug2012_FINAL.pdf
12) Jensen, V.F., Jacobsen, E., Bager, F., 2004. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. Prev. Vet. Med. 64, 201-215.
13) Prescott, J. F. Beta-lactam Antibiotics: Penam Penicillins (2000). In J.F. Prescott, J.D. Bagger & R.D. Walker. (Eds) *Antimicrobial Therapy in Veterinary Medicine* (pp. 118). Ames, Iowa: Blackwell Publishing.