

Conference Report

Antimicrobial Stewardship in Canadian Agriculture and Veterinary Medicine: How is Canada doing and what still needs to be done?

John F. Prescott, Jean Szkotnicki, J. T. McClure, Richard J. Reid-Smith, David F. Léger

Department of Pathobiology (Prescott) and Population Medicine (Reid-Smith),

University of Guelph, Guelph, Ontario N1G 2W1; Canadian Animal Health Institute, 160

Research Lane, Suite 102, Guelph, Ontario N1G 5B2 (Szkotnicki); Department of Health

management, University of Prince Edward Island, Charlottetown, Prince Edward Island

C1A 4P3 (McClure); Laboratory for Foodborne Zoonoses, Public Health Agency of

Canada, 160 Research Lane, Suite 103, Guelph, Ontario N1G 5B2 (Léger, Reid-Smith)

The background

The 225 delegates attending the conference came from every province of Canada and from a variety of backgrounds, including agriculture, veterinary medicine, medicine, public health, the pharmaceutical and animal health industry, regulatory agencies, provincial Ministries of Agriculture, and journalism. Held October 30th to November 2nd, 2011 in Toronto, the conference was a follow-up to earlier conferences held in 1999 and 2005 (1,2), but expanded its scope from a focus on the human health effects of the use of antimicrobials (antibiotics and their derivatives) in food animals to a more nuanced understanding of antimicrobial resistance in all animals in which they are used. The conference was designed largely to promote the concept of antimicrobial stewardship, to discuss the many facets of stewardship, and to identify the factors that stand in the way of

good stewardship of antimicrobials in animals in Canada. It was organized to address good stewardship by different themes (Figure 1).

Opening addresses

Incoming CVMA President, **Jim Fairles** opened the conference, noting that the CVMA had been active in addressing antimicrobial resistance, most recently by promoting clinical practice guideline development for companion animals. **Duane Landals** (World Veterinary Association, and Alberta Veterinary Medical Association) brought greetings from the World Veterinary Association, which had discussed antimicrobial stewardship as a major item at its recent conference in South Africa.

The conference was entranced by the theme of “Striving for Gold- Winning with Integrity” set by keynote speaker **Beckie Scott**, Canadian Olympic Gold medal winner in cross-country skiing. She described how the Canadian cross-country ski team had moved in international competitions from consistently placing bottom in the field to the breakthrough mindset that they could achieve a medal through a combination of belief, teamwork, and continuous improvement, while maintaining integrity in the sport. Beckie’s presentation set the inspirational and optimistic tone that marked the conference. **Don Low** (Mount Sinai Hospital, Toronto, and Ontario Agency for Health Protection and Promotion) described the continuing and rising threat of antimicrobial resistance in medicine, notably particularly the recent emergence and spread of NDM-1, the carbapenemase and multidrug resistant strain of *Escherichia. coli* (and spreading to *Klebsiella* spp.) that is causing so much concern globally. He noted that this was brought to Canada from India by medical tourists, and could even be isolated in the water in New

Delhi. For the conference organizers, **John Prescott** (University of Guelph) discussed the concept of antimicrobial stewardship as a multifaceted approach to optimizing antimicrobial use while reducing resistance. He noted that, perhaps analogous to how we might address climate change, multiple small, cumulative, actions were required to address a problem of such multidimensional complexity. He urged the conference to identify the factors standing in the way of stewardship and the actions required to control resistance. He noted that bacteria can easily change to antimicrobial resistance, and that the real problem in addressing the issue may be ourselves, since we are so resistant to change.

Session 2: Antimicrobial resistance in animals and people in Canada: How big is the problem?

Stephen Page (Advanced Veterinary Therapeutics), a consulting Australian veterinary pharmacologist and passionate advocate of antimicrobial stewardship, gave a broad-ranging address discussing “From prudent use to stewardship in veterinary medicine”. He noted the large number of clinical practice guidelines now available, but questioned their effectiveness. Stewardship refers to taking personal responsibility for something one does not own, and careful and responsible management of something entrusted to our care. He discussed the “tragedy of the commons” when people do not manage a critical resource in a stewardship manner. The theme of accepting responsibility was one that ran throughout the conference. Dr. Page described the “perfect storm” as resistant bacteria had emerged over the last three decades while antimicrobial drug discovery had declined to negligible levels. He suggested possibilities for global collaborations in the area of stewardship, such as development of an auditing process for

Good Antimicrobial Practice in Canada (“CanGAP”). A stewardship model would take us from a largely passive to an active approach to controlling resistance. His description of the effective antimicrobial treatment of an elephant with tuberculosis infected from humans also inspired a conference theme, that of identifying the various “elephants in the room” preventing good antimicrobial stewardship in animals in Canada.

Rebecca Irwin (Public Health Agency of Canada) described the value and successes of the Canadian Integrated Program of Resistance Surveillance (3) over the last decade. The surveillance data suggests that extra-label use of Category 1 antimicrobials had likely led to problematic resistance in *Salmonella* and *E. coli* in retail chicken meat in some provinces, and to hard-to-treat human infections. Obtaining antimicrobial use data has been difficult but remains important in interpreting resistance data. **Patrick Boerlin** (University of Guelph) discussed emerging resistance issues in companion animals and horses, describing them as “probably getting worse”. He noted particularly CTX-M-14 and CTX-M-15 beta-lactamases in *E. coli* from dogs as well as the recent marked rise in methicillin-resistant and multi-resistant *Staphylococcus pseudintermedius* (MRSP) in dogs, and the expansion of their specific clones in Europe and in North America.

Richard Reid-Smith (Public Health Agency of Canada) said that, although we know considerably more than we did in 2005, we do not know enough about antimicrobial drug use in animals in Canada. It is generally agreed that use drives resistance. 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. He noted that in the more advanced European veterinary antimicrobial use monitoring systems (e.g., Denmark, Norway, Sweden) data collection

is facilitated by requiring prescriptions for all antimicrobial drug use. Without a system of effective use monitoring, resistance data from CIPARS and other sources in Canada are more difficult to interpret, and it is almost impossible to determine whether interventions, including practice guidelines, have an effect. More work is needed to collect use data effectively, although it is still unclear precisely how it (in what units) should be reported. Standardization of reporting internationally would allow Canada to benchmark itself against other countries.

David White (Center for Veterinary Medicine, US Food and Drugs Administration) described attempts in the United States to understand the links between animal use of antimicrobials and resistance in human pathogens, including the value of National Antimicrobial Resistance Monitoring System (NARMS) (4) resistance surveillance and of Guidance 152 document for antimicrobial drug approval. He noted the need to understand better the drivers of resistance in animal pathogens, citing the possible unexpected role of disinfectant rinsing of chicken carcasses in abattoirs in selecting resistant bacteria. **Ed Topp** (Agriculture and Agri-Food Canada), continued the theme of need for better understanding of the drivers of resistance, in particular suggesting that we investigate the effect on resistance of sewage and waste water facilities, of spreading of human sewage sludge and animal manure as fertilizer on fields, and of effluents of antimicrobial manufacturing facilities.

Session 3: Stewardship of antimicrobial drugs in animals and people in Canada:

How well are we doing?

From Agriculture's perspective, **John Campbell** (Western College of Veterinary Medicine) described developing a comprehensive understanding of antimicrobial use in livestock and controlling resistance as "Mission Impossible", because of its complexity and of the issues involved. Using a "report-card" approach, he succinctly reviewed progress on the main recommendations of the 2002 Report of Health Canada's Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance in Humans (5). For the recommendations on prescription only and stopping the direct importation of antimicrobial active pharmaceutical ingredients and of antimicrobials under "own use importation" provisions, he gave Canada grades of "F". For its development of an extra-label drug use policy he gave an "B-", a "B" for development of a national resistance and use surveillance system, and an "Incomplete" for changes in use of growth promoters. Although hard to measure, attitudes to antimicrobial use were described as changing, as farm food safety and quality assurance programs added antimicrobial use to their documentation, as veterinary curricula focused more on resistance, and as regulators added resistance as part of drug approval processes. Dr. Campbell concluded that the overall grade for agriculture is likely always to be "Incomplete", since the struggle to control resistance and improve stewardship will never be finished; this perspective was not to discourage moving forward but to emphasize the seriousness and complexity of the issues.

From the Companion Animals perspective, **Scott Weese** (University of Guelph) suggested that we do not really know how we were doing. He described antimicrobial use in companion animals as having a "Wild West" feel to it. We lack organized surveillance of use and resistance in companion animals, there is no communication between

diagnostic laboratories, no regulatory interest in antimicrobial use in companion animals, and limited research funding. Multidrug resistant pathogens are being identified in companion animals, but there appears to be little understanding among practitioners of what constituted “prudent use” or good stewardship. About two-thirds of Canadian households own a pet, and pets reflect what is going on in people. Methicillin resistance in *Staphylococcus pseudintermedius* has become a “huge problem” in companion animals in the last five years, and has “exploded internationally”. Compared to methicillin-resistant *S. aureus* (MRSA), MRSP are often highly resistant to other antimicrobials in addition to the beta-lactams, and have caused some apparently untreatable infections following minor surgery. There are fewer resistance concerns in horses, although MRSA is a challenge. Dr. Weese reported that equine veterinarians are now globally well recognized to be the most likely of any veterinary practitioner group to be colonized with MRSA (through interaction with horses). He went on to suggest that veterinarians should be cognizant of the potential for legal action by staff members if they develop an MRSA infection and if occupational exposure to MRSA was shown to be a contributing factor. Dr. Weese supported further development and implementation of practice guidelines for improved antimicrobial use, and an enhanced focus on infection control in veterinary settings.

Jim Hutchinson (Vancouver Island Health Authority) emphasized that most resistance in human pathogens is driven by antimicrobial use in people, but that use of antimicrobials in animals is part of the story. Many in the medical world disproportionately blame agriculture, which is one of the “elephants in the room” serving to distract from concepts of good antimicrobial stewardship. He suggested that

understanding and controlling resistance is not as complicated as some people think, and emphasized that the reason people now live so long is largely because of antimicrobials. Overall, he suggested that we are not doing very well in antimicrobial stewardship in medicine in Canada, but that there are some improvements. These include increased interest by politicians, improvements in measurement of use and resistance, more active hospital programs for stewardship, and rejuvenations of relevant professional societies. Internationally there is considerable activity in development of the concept of stewardship. An antimicrobial stewardship program is soon to be a requirement for hospital accreditation. Dr. Hutchinson indicated that the problem of endemic *Clostridium difficile* infections in hospitals is driving improved antimicrobial oversight. He emphasized the importance of focusing on measuring and then reducing antimicrobial use, not just focusing on measuring resistance. His final advice was that “Stewardship is about structure” and to “just worry about being the best, not about anything else”.

Session 4: Are Canadian regulations hindering good antimicrobial stewardship in Canada? Should we change?

Manisha Mehrotra (Veterinary Drug Directorate, Health Canada) gave an overview of national regulation of animal drug sale in Canada. While indicating that the Food and Drugs Acts and Regulations gave Health Canada no authority for the practice of veterinary medicine or pharmacy, including the compounding of drugs, no authority over the use of approved drugs, and no authority over extra-label use of drugs, she emphasized that Health Canada is working with stakeholders on these issue, including policy development. She discussed Health Canada’s categorization of antimicrobials into categories based on assessment of importance for use in human medicine, as well as

Health Canada's approach to antimicrobial resistance risk management (prescription status, individual versus group animal use, warning statements about extra-label drug use status). There are current federal-provincial discussions about antimicrobial use in animals in Canada, a re-evaluation of the potential for approval of Category I drugs, and starts to re-evaluate the growth promotion status of Category II and III drugs, and to re-assess whether all antimicrobial use in animals should be available only by prescription. Dr. Mehrotra said that keeping antimicrobial resistance under control will require continued collaboration with key stakeholders in the agri-food sector.

David Léger (Public Health Agency of Canada) discussed the complexity of provincial regulation of sale and distribution of antimicrobial drugs in Canada. Approval of manufacturing and drug sale is covered by the Federal Food and Drugs Act, the Feeds Act and the Health of Animals Act. Regulation of actual end use in Canada is regulated at the provincial level. In addition, many of the different provincial Acts that cover antimicrobial use (Veterinary Acts, Drugs and Pharmacy Acts, Livestock Medicines Acts) are focused on antimicrobial residue avoidance. Most provinces allow over-the-counter (OTC) sales of some antimicrobials, whereas Québec requires prescription of all antimicrobials for animals. A refocus of the provincial regulations from residue avoidance to also address resistance management will better align them with current concerns.

Ashwani Tiwari (Canadian Food Inspection Agency) noted that CFIA is involved in antimicrobial stewardship through monitoring (collection of abattoir samples for CIPARS, activities of the Feeds Division, and the Flock Sheet program in broiler production) and prevention (approval of vaccines, recognition of On-Farm Food Safety

Programs). Use of antimicrobials in animal feeds involves CFIA enforcing the Compendium of Medicating Ingredients Brochures, or ensuring veterinary prescription of any in-feed drug with an unrestricted DIN. As with the monitoring by CFIA of the confidential “flock sheets” that accompany broiler chickens to the abattoir, the focus the animal feed activities is on avoiding antimicrobial residues.

Addressing “What needs to change?” from the point-of-view of the Canadian veterinary pharmaceutical industry, **Jean Szkotnicki** (Canadian Animal Health Institute) urged an end to the “own use importation” and “active pharmaceutical ingredients” loopholes in the federal regulations, since there is no Canadian safety risk assessment involved in these products. Risk assessment should be equal across the board. The OUI and API exemptions under federal regulation are unique to Canada. She estimated that the total value of OUIs and APIs usage was more than one-third of that of the value of licensed product. Ms. Szkotnicki said that Canada needs a restricted import permit program to ensure timely availability of veterinary drugs, and to support and enable new product innovation in animal health management. She urged modernization of the Food and Drugs Act, which was 57 years old (almost as old as antimicrobials), development of a “decision tree cascade” like that in the United Kingdom, national support for the Canadian Global Food Animal Residue Avoidance Databank (CgFARAD) (6), and a robust, science-based, timing and enabling regulatory environment.

The conference was delighted by a robust but short panel discussion between the Session 4 speakers, together with **Sylvie Dansereau** (Ministère d’Agriculture, Pêcheries et Alimentation du Québec) and **Duane Landals**. Asked what it would take to change the regulations, Duane Landals suggested that “a disaster” might generate the political will to

change. He noted also the high sense of responsibility of farmers to produce a quality product. Manisha Mehrotra stated that Health Canada was moving towards phasing out growth promoters and making antimicrobials veterinary prescription only, and she again noted that Health Canada has no authority over drug use including extra-label drug use. Duane Landals thought that the current system of provincial regulation of drug use generally worked well, although there are numerous possible issues relating to it. Dre. Dansereau described the historical development of the different system of drug distribution in Québec, which requires prescriptions for every type of antimicrobial use in animals, including on-farm feed manufacturing. Dre. Dansereau said that the system, different from the rest of Canada, has been well accepted by farmers in Québec, relating in part to the provincial veterinary support for farmers. In the future Québec would like better antimicrobial use data.

Session 5: International aspects of stewardship: Where does Canada fit in?

Christina Greko (National Veterinary Institute, Sweden), who said that “use of an antimicrobial anywhere at any time can increase resistance anywhere else”, discussed work by the European Medicines Agency to obtain antimicrobial use data in animals. For harmonized reporting, sales were reported in “mg/population correction unit”, which was mg/live weight of all farm animals independent of species. This technical unit gives a reasonable estimate that allowed comparison between countries. It has revealed remarkable differences between European countries in farm animal use, and is now being used for benchmarking. Dr. Greko urged Canada to obtain use data, and to benchmark itself internationally; in her opinion, use data is more direct and valuable than resistance data.

In a masterly discussion of lessons learned from Europe and the United States, **Scott McEwen** (University of Guelph; Chair of the 2002 Health Canada Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance in Humans [5]), suggested that it takes “crises” to make change, citing the examples of multidrug resistant *Salmonella* in the United Kingdom that led to the 1967 Swann Report, of vancomycin resistance in *Enterococcus* that led to the banning of growth promoters in Europe, and of the emergence of food animal MRSA and ESBL in *E. coli* in The Netherlands that was leading to change in that country. He asked why Canada does not ban growth promoters, since experience in Europe suggested that a ban has had little impact on growth performance of swine. He suggested that concern about the subsequent slight increase in therapeutic use of antimicrobials is a distraction from the larger issue. He considers that 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. He noted the differences in extra-label drug use policy between the United States and Canada, using the example of the extra-label restrictions on fluoroquinolone use in poultry before it was eventually banned. He also recognized how difficult it is to revoke drug approvals. An expert on risk assessment, Dr. McEwen promoted the value of risk assessment, saying that we need to assess the risks before managing them but also that we cannot delay action until all risks have been assessed. Finally, he thought that those who favour a voluntary stewardship approach to some aspects of antimicrobial use over a regulatory approach have to be able to measure the impact of such an approach, and require robust antimicrobial use data to do so.

In the final talk on international aspects of stewardship, **Manisha Mehrotra** discussed Canada's recent pivotal role in developing the globally significant Codex Alimentarius's Guidelines for assessment of the risk of antimicrobial resistance in food on human health (7).

Summarizing Sessions 1-5

In summarizing the first five sessions, **Stephen Page** asked “what is the single most important step for Canada?” He noted the sparse nature of use data in Canada, suggesting that after 15 years of interest one would have thought this would now be available. When available, there needed to be common units of measurement so that Canada could benchmark itself against developing international standards. He noted that some stewardship initiatives had occurred, for example in guideline development and in the initiatives around ceftiofur resistance in *Salmonella* in chickens. He was clear that the OUI and API loopholes should be closed. He could see solutions through initiatives such as Quebec's requirement for prescription for all antimicrobial use in animals, through use of electronic medical records, through changing attitudes to and interest and skills relating to antimicrobial use, through the use of CgFARAD, and through Jim Hutchinson's infectionnet blog (8). He again promoted the concept of CanGAP as a national initiative. He said that “Canada knew what it should be doing” and “why can't Canada be the best”? From an Australian perspective, Canada was on the cusp of converting 12 years of development into an action plan.

Session 6: When science meets the real world; Does theory match reality in Canada?

Scott Brown (Pfizer Animal Health) gave a delightful overview of optimal antimicrobial use in a perfect world, noting that we do not live in a perfect world where resistance is concerned, and discussing dilemmas associated with optimization of antimicrobial treatment. Dosages optimized for efficacy may be too low for suppression of resistance. The best approach was to “hit the pathogen as hard as you can, as quickly as you can, and leave no survivors” but this did not take into account the effect of antimicrobials on commensals rather than the target organism. **Trish Dowling** (Western College of Veterinary Medicine) discussed how and why practitioners choose antimicrobials, and showed a neat web-based system for calculating dosage. There was sometimes a conflict between using older antimicrobial drugs (“lower fire power”) and the client convenience of formulations of some newer drugs. She gave numerous examples of poor choice of antimicrobials. **J. T. McClure** (Atlantic Veterinary College) discussed the CVMA’s development of national general and food animal practice specific prudent use guidelines. This took considerable effort from those involved. He thought that the disease specific recommendations are not a large departure from current practice but that there had been a failure to focus on user education following the development of these guidelines. There had been no attempt to measure the impact of the guidelines. **Jim Hutchinson** discussed prudent use guidelines in medical practice in Canada, noting that there are numerous hospital, local, provincial, national and international examples but that guideline development is a hard process. One difficulty of practice is that so much diagnosis was empirical. For him, a major question is not “which antimicrobial” but “if antimicrobial”. There are no guidelines for assessing population use and no good tools for measuring adherence to guidelines. Finally, **Marie Archambault** (Faculté de Médecine

Vétérinaire, Université de Montréal) reviewed the value of the veterinary educational programs around stewardship. She saw a need for national competencies to be established, which could also be used for continuing education programs.

Session 7: Stewardship of antimicrobials in animals in Canada: How can we improve?

The conference split into 9 Concurrent Sessions (aquaculture, beef cattle, companion animals, equine, sheep and goats, poultry, swine, and veal and the young dairy calf. These sessions spent the rest of the day following Session 6 discussing how we can improve antimicrobial use in these different groups. The companion animal session was largely devoted to practice guideline development, and joined forces with the equine group. Each session was asked to report responses back to the conference on 3 questions: 1. What are the impediments to reducing antimicrobial use? 2. What “stewardship issues” need to be addressed in the next 5 years? 3. What is the most important stewardship issue that needs to be addressed nationally. Details of the presentations made by national and international speakers in each of the Sessions are available from www.antimicrobialcanada.com.

Session 8: Conference summary: What is needed to improve antimicrobial stewardship in animals in Canada in the next 5 years?

Report back from the Concurrent Sessions

Table 1 summarizes the common themes identified between the food-animal Concurrent Sessions of the Conference. Supplementary Table 1, available on

www.antimicrobialcanada.com, summarizes the individual themes from the different Concurrent Sessions.

The view from selected conference participants

Table 2 summarizes the common themes identified by selected conference participants, and Supplementary Table 2, available on www.antimicrobialcanada.com, summarizes the major points made by these participants.

In summarizing the conference, **John Prescott** noted the theme running through the conference that Canada could be “the best in the world”. The way that Canadian cross-country ski team had achieved Gold, through a combination of belief, teamwork, and continuous improvement through measurement and analysis, is equally applicable to improving antimicrobial stewardship. We have to accept that stewardship is everyone’s responsibility, and to move as a country from a passive to an active approach. He saw CIPARS as “Canada’s early success story”, and suggested it was the “end of the beginning” in the fight to control resistance. We need to focus on getting animal use data, and on benchmarking ourselves against other countries. He saw the regulation of antimicrobial use and distribution as “Canada’s black hole” in stewardship, and said we need to address the OUI and API provisions, that essentially make antimicrobial use in animals unregulated in Canada. We also need to be able to ban extra-label use of antimicrobials in animals if this was shown to adversely affect human health. He said that we should not wait for a disaster to make change; continuous improvement is the way. The common themes identified by the conference as needing improvement (Tables 1,2) are essentially those identified as major recommendations in 2002 by the Health

Canada Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance in Humans. Advisory Committee report (5). We need to generate the desire for excellence and the leadership that will show how Canada can win the “Gold” for antimicrobial stewardship.

Next steps

Following the conference, the conference organizing committee agreed to members willing to serve would form an ad hoc Committee on Antimicrobial Stewardship in Canadian Agriculture and Veterinary Medicine, with the task of assisting in implementing the conclusions of the conference (Table 1, 2), and advocating for improved antimicrobial stewardship practices in animals in Canada.

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8. INFECTIONNET: For People Who Manage Infections. <http://infectionnet.org/>

Last accessed December 23, 2011.

Table 1. Common Themes from Concurrent Sessions on What Needs to be done to Effect Antimicrobial Stewardship in Food Animal Production.

1. Need for sustained uniform monitoring of antimicrobial use and resistance.
2. Regulatory issues relative to: Importation and use of non-approved product (OUI and API); MUMS product availability; extra-label drug use; availability of alternative products; and prescription only status.
3. Need for prudent use and clinical use guidelines.
4. Communications among industry players to develop a culture around awareness of antimicrobial resistance issues.
5. Need for leadership and ownership of antimicrobial resistance within the industry.

Table 2. What is needed in the next 5 years: Conference Conclusions.

1. Sustained, uniform antimicrobial use and resistance surveillance data.
2. Resolution of Regulatory Issues – OUI, API, Prescription only, Minor use-minor species issues (MUMS), extra-label drug use, use of the Cascade approach.
3. Education on the importance of antimicrobial resistance in the veterinary student curriculum.
4. Education on Stewardship and the responsibilities it entails.
5. Sustained funding for CgFARAD.
6. Infection control strategies.
7. Harmonized provincial strategies.
8. Enabling veterinary drug product regulation.
9. National leadership and oversight of antimicrobial resistance.

