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Issue Identification Paper

WORK IN PROGRESS:

Antimicrobial Resistance: Developing a Common Understanding

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Canada

Antimicrobial Resistance:
Developing A Common Understanding

This paper has two purposes: to serve as a background document on the subject of antimicrobial resistance[1] (AMR); and secondly, to begin the process of documenting key issues related to both the assessment of the risk and the development of risk management strategies and policies.
This issue paper will be updated and refined as more information becomes available.

I. BACKGROUND

1) The term "antimicrobials" or "antimicrobial agents" simply refers to all types of natural, semi-synthetic or synthetic substances which are capable of killing or inhibiting the growth of microorganisms[2]. These agents include antibiotics, antivirals, antifungals, probiotics[3], disinfectants, sanitisers, food or feed preservatives, antimicrobial pesticides or biocides and wood preservatives, among others (Appendix I).

2) There are two broad categories of antimicrobial agents: the "-cidal" agents kill microorganisms while the "static" agents arrest the growth of some microorganisms.

3) Antimicrobial agents are widely used in human and veterinary medicine and in plant agriculture for the treatment of microbial infections and are also used sub-therapeutically in agri-food and aquaculture industries. Sub-therapeutic[4] uses of antimicrobial agents in animal husbandry practices have been shown to be important in preventing bacterial infections and in growth promotion or increasing feed efficiency. The use of antimicrobial agents in plant agriculture is largely limited to the treatment of bacterial diseases of plants.

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[1]The condition in which a specific antimicrobial drug become ineffective in killing or inhibiting the growth of a targeted microorganism.

[2]For the purposes of this paper microorganisms are understood to include bacteria, yeast, protozoa, algae, and viruses.

[3]Live microbial supplements that contain a variety of beneficial microbial species and which are administered to promote the growth of beneficial flora in the gastrointestinal tract of humans or animals (e.g. Bifidobacteria and Lactobacilli). They affect the host animal by improving its intestinal microbial balance.

[4]All uses of antimicrobials for disease prevention, or prophylaxis, as well as growth promotion or performance enhancement purpose

4) AMR stops or reduces the effectiveness of antimicrobial agents and may adversely impact treatment of human and animal illness.[5]

5) Resistance may occur intrinsically[6] as the result of inherent cellular components[7] of microorganisms; by genetic selection resulting from exposure to an antimicrobial agent, or through the horizontal transfer of resistance genes[8]. Time plays an important role in determining the likelihood of resistance since the probability that a population of organisms will develop resistance to a given antimicrobial agent increases with length of exposure to that agent. Because of selective pressure, resistant strains of the microorganism will survive and reproduce, transferring their resistance to future generations and to other pathogens and commensals.

6) Microbial cross resistance develops when microbes exposed to one drug develop resistance to other antimicrobials of the same family[9].

7) Antimicrobial resistance is an important issue because the growth and proliferation of undesirable microorganisms may soon outpace our ability to control and mitigate their effect on our health and on the health of our environment.

8) Development and spread of AMR represents a serious threat with potential public health implications. Dissemination of resistance traits could narrow the line of defense against bacterial infections to only a few antimicrobial agents and could increase health care costs. It is estimated that resistant bacterial infections increase health care costs by $4 billion per year in the United States[10].

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[5]Canadian Committee on Antibiotic Resistance. 2002. Antimicrobial resistance: a deadly burden no country can afford to ignore. Report prepared by David Birnbaum for the Canadian Committee on Antibiotic Resistance; Alliance for the Prudent Use of Antibiotics. 2002. The need to improve antimicrobial use in agriculture: ecological and human health consequences. A report of the facts about antibiotics in animals and the impact on resistance (FAAIR) Project.

[6]The ability of bacterial species to thrive in the presence of antimicrobial agents due to inherent characteristics of the organisms. It is essentially the naturally-occurring resistance of a bacterium to antimicrobial agents.

[7]These include structural and genotypic features of bacterial species, which enable them to withstand antimicrobial agents. In Gram-negative bacteria, these features include the relatively low permeability characteristic of the outer membrane and the constitutive expression of drug efflux proteins in some species.

[8]Walsh C. 200. Molecular mechanisms that confer antibacterial drug resistance. Nature 406: 775-781

[9]An example can be found in the beta-lactams group of antibiotics – organisms that are resistant to penicillins are also often resistant to other beta-lactams.

[10]Antimicrobial resistance: an ecological perspective. 1999. Report on the American Academy of Microbiology colloquium. July 16-18, 1999. San Juan, Puerto Rico.

9) In Canada, recent estimates have shown that drug resistant infections add Can $14 - 26 million more in direct hospitalization costs to the annual price of health care. However, if AMR rises to endemic levels resulting in the prescription of more potent and expensive newer drugs for all treatments both in and out of hospitals, drug costs could escalate to at least Can$1.8 billion[11]. The emergence of AMR clearly threatens our ability to fight human and animal infections.

10) Development of resistance is associated with the use of antimicrobial agents in human medicine, veterinary medicine, animal husbandry, plant agriculture, aquaculture, and with environmental contamination with antimicrobial agents or with AROs[12] and consumer products.

11) The impact of using antimicrobial agents in plant agriculture to the overall development of AMR is still a subject of international discussion.

12) The following types of AMR are believed to be most relevant for assessment of human health impacts in the Canadian situation:

- Those associated with the use of antimicrobials in human medicine
- Those associated with the use of antimicrobials in veterinary medicine and livestock production

13) Other forms of AMR, which will be discussed in this paper, include those associated with:

- Antimicrobial use in non-food animals
- Antimicrobial use in the aquaculture industry
- Bactericides/disinfectants/antiseptics use in consumer products
- Environmental contamination with antimicrobial agents or AROs
- Antimicrobial use in plant agriculture

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[11]Canadian Committee on Antibiotic Resistance. 2002. Antimicrobial resistance: a deadly burden no country can afford to ignore. Report prepared by David Birnbaum for the Canadian Committee on Antibiotic Resistance.

[12]Antimicrobial-resistant organisms.

- The global movement of drug-resistant organisms

AMR associated with the use of antimicrobials in human medicine

14) Overprescription: Some health care professionals may be using a "shot-gun" approach to therapy, inappropriately prescribing antimicrobial agents to treat viral infections or to treat conditions that typically clear up by themselves (UTIs, ear infections). Health care professionals may also apply 'empirical therapy', prescribing broad spectrum drugs that affect a variety of organisms rather than waiting for test results and targeting a particular organism with the most effective narrow-spectrum drug available.

15) Prophylactic use of antimicrobial agents (including inappropriate and/or intermittent dosage, consumption patterns and timing) can lead to the development of resistance by creating an environment in which selective pressure favours the proliferation of resistant organisms.

16) Unnecessary use of over-the-counter (OTC) antimicrobials, such as topical creams, or over-consumption of available antimicrobials may contribute to the development of resistance.

AMR associated with antimicrobial use in veterinary medicine and livestock production

17) The emergence of AMR among foodborne pathogens has attracted increased attention in recent years mainly because of its implications on public health and food safety.

18) Because international data are based only on estimates, the true volume of antimicrobial use in the agri-food sector is not known. Estimates of the amount of antimicrobials used are subject to confusion[13]. In the United States, one estimate is that 50% of the 50 million pounds (22.7 million kilograms) of all antimicrobials prescribed annually are for humans and 50% for use in animals, agriculture and

[13]American Academy of Microbiology. 2002. The role of antibiotics in agriculture. A report based on a colloquium sponsored by the American Academy of Microbiology held November 2-4, 2001, in Santa Fe, New Mexico. This report pointed out the difference between the estimates reported by the Union of Concerned Scientists (see footnote 15) and those of the Animal Health Institute, which estimated a total of 17.8 million pounds (8.1 million kg) of antibiotics used for all purposes (therapeutic and non-therapeutic) in the United States, based on a survey of member companies.

aquaculture[14]. A more recent report[15] estimated that US livestock producers use approximately 24.6 million pounds (11.2 million kilograms) of antimicrobials for non-therapeutic purposes primarily to promote the growth of cattle, hogs, and poultry. Clinical uses are estimated at about 10% of total antimicrobial use[16]. The contribution of the aquaculture sector is not expected to be a significant percentage of the non-human use of antimicrobials.

19) The use of antimicrobial drugs for purposes of prophylaxis or growth promotion in food-producing animals exerts selective pressure and appears to have created large reservoirs of transferable AMR traits in these ecosystems[17].

20) These resistance traits developed in bacteria found in animals may sometimes be transmitted to human pathogens. Direct links have been made between veterinary antimicrobials use and development of resistance to different antimicrobials in humans[18].

21) There is increasing evidence that resistant bacteria are being transferred from farm animals to humans possibly through food, water or direct/indirect contact[19].

22) Therapeutic and/or sub-therapeutic use of antimicrobials (including inappropriate and/or intermittent dosage, consumption patterns and timing) can lead to the development of resistance by creating an environment in which selective pressure favours the proliferation of resistant organisms. For instance, the use of antimicrobial agents for growth promotion may alter the gut flora by eliminating certain antimicrobial sensitive bacterial species, which in turn allows antimicrobial

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[14]Levy SB. 1997. Antibiotic resistance: an ecological imbalance. In: Antibiotic resistance – origins, evolution, selection, and spread. Ciba Foundation Symposium 207. Chichester, England. John Wiley, pp 1-14.

15 Union of concerned scientists 2001. Hogging it: estimates of antimicrobial abuse in livestock. available online at http://www.ucsusa.hog/food/hogging_exec.html (accessed September 20, 2002)

[16]Estimates of total antibiotic production and uses in livestock were obtained from ASM News 67(3) 128-129

[17]Witte, W. 2000. Selective pressure by antibiotic use in livestock. Int. J. Antimicrob. Agents 16: S19-S24.

[18]The Seventh Report of the Select Committee on Science and Technology (UK, 1998) states that "the first conclusive evidence of a veterinary antibiotic (apramycin) giving rise to a human antibiotic (gentamicin) came about in the mid-1970s. The trend continues among new antimicrobial agents.

[19]Wall PG, Morgan D, Lamden K, Ryan M, Griffin M, Threlfall EJ, Ward LR, Rowe B. A case control study of infection with an epidemic strain of multiresistant *Salmonella typhimurium* DT104 in England and Wales. Communicable Disease Report 1994; 4 (review no. 11): R130-R135.

resistant or non-resistant pathogens to colonize[20] and proliferate.

23) Variable consumption rate at the animal level when administering antimicrobials to animals through feed or water contributes to AMR through selective pressure.

24) Probiotics and other microorganisms incorporated in animal feed (e.g. silage inoculants), some of which may contain resistance genes[21] or may produce antimicrobials, are often administered in blanket treatments to large groups of animals.

25) "Shot-gun" approaches to therapy: veterinarians may prescribe several drugs or broad spectrum antimicrobials that affect a variety of organisms rather than waiting for test results and targeting a particular organism with the most effective drug available. However, there is a question of availability or feasibility of waiting for susceptibility test results.

26) Illegal entry, promotion and sale of active pharmaceutical ingredients (API) for use in the agricultural industry and in veterinary medicine as well as excessive use of OTC drugs or off-label drugs may lead to increased presence of resistant microorganisms in animals.

AMR associated with antimicrobial use in non-food animals

27) The impact of antimicrobial use in non-food animals such as companion animals (pets) on the development of resistance is not known. However, there is ample opportunity for exchange of resistance genes between bacteria in companion animals and those in humans[22].

28) Recent evidence showed that methicillin-resistant *Staphylococcus aureus* infections in companion animals may originate from humans[23].

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[20]Bacterial colonization involves the ability to adhere, to invade and to resist immune defences of host cells.

[21]DNA molecules which encode protein or enzyme factors that are responsible or contribute to the ability of bacterial species to thrive in the presence of antimicrobial agents.

[22]Sternberg S. 1999. Antimicrobial resistance in bacteria from pets and horses. Acta Vet. Scand. Suppl. 92: 37-50. *Staphylococcus aureus* is an example of the type of bacteria that can be easily transferred from pets to humans and vice versa.

[23]Oughton M, Dick H, Willey BM, McGeer A, Low DE. 2001. Methicillin-resistant *Staphylococus aureus* (MRSA) as a cause of infections in domestic animals: evidence for a new humanotic disease? Canadian Bacterial Diseases

AMR associated with antimicrobial use in aquaculture industry

29) Antimicrobial agents are used for the control of bacterial diseases in the aquaculture industry. In British Columbia, medicated feed comprised 2% of total feed consumed in the salmon aquaculture industry in 1999 and less than 1 % in 2001. 97% of administered drugs are to young, non-market fish, including those in the freshwater hatchery stage.[24]

30) Increased use of vaccination has decreased the need for and use of antimicrobials in the Canadian aquaculture industry. As a result, there is very little prophylactic use of antimicrobials in the aquaculture sector in the province of British Columbia which accounts for the largest salmon production in Canada. Precise data on antimicrobial use are lacking for the rest of Canada's aquaculture industry but for marine salmon aquaculture, the BC data may be considered to be representative.

31) Antimicrobial agents that are used in aquaculture typically remain in the open environment and may flow out of production facilities into open waterways or sewage systems, where they may also interact with other environmental contaminants[25].

AMR associated with bactericide/disinfectant/antiseptic use in consumer products

32) The claim "antimicrobial" is not well-defined in consumer products regulation. Companies have found that consumers respond well to products claiming to be 'antimicrobial', 'antibacterial' etc. This culture of surface cleanliness leads to the frequent use of antimicrobial agents in the community context, exposing microbes to increased levels of antimicrobial agents and the subsequent development of resistance.

33) There is increasing concern that the use of bactericides, disinfectants and antiseptics in the home, community and health care facilities (in cleaning supplies,

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Surveillance Network. April 2001 Newsletter.

[24] These data were obtained from the British Columbia Ministry of Agriculture, Fisheries and Food via the Salmon Health Consortium and Fisheries and Oceans Canada.

[25] Benbrook, CM. 2002. Antibiotic drug use in U.S. aquaculture. Institute for Agriculture and Trade Policy (IATP). Northwest Science and Environmental Policy Center. Sandpoint, Idaho. 20 pp.

personal hygiene products etc) and the incorporation of these agents in common household products[26] increases selective pressure on bacteria to develop resistance towards these agents.

34) AMR concern related to the use of bactericides, disinfectants and antiseptics is associated with their potential to induce the expression of AMR genes, which encode multidrug efflux pumps[27] or their regulators. This mechanism almost always cause resistance to a wide variety of antimicrobial agents, especially in *E. coli*, *Salmonella*, *Pseudomonas* spp. and other bacterial species[28].

AMR associated with environmental contamination with antimicrobial agents or AROs

35) Deliberate release into the environment of genetically modified organisms (GMOs) containing AMR markers of clinical and veterinary importance may pose a risk of gene transfer from the GMOs and their food products to the gut microorganisms or to other microorganisms in the environment.

36) Inappropriate disposal of antimicrobial agents through dumping and flushing may promote the increase of AMR of pathogens and commensals in the natural environment.

37) Industrial application of chemicals (e.g. heavy metals) and antimicrobial agents in caulking, fabrics, construction/building materials, paint, etc. may contaminate air, soil, and water, contributing to the development of AMR in organisms present in the environment.

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[26]Examples of consumer products containing antimicrobial agents include: underwear (e.g. triclosan), hand and laundry soaps/detergents, household cleaners (phenols), windshield washer fluid, cutting boards (chlorine), cough syrup (pine oil), toothpaste, baby clothes, bed linens, pillows, toys, cribs, high chairs, paint, wood preservatives, facial tissue, and germicides.

[26]Broad substrate-specific systems that are used to actively pump out antimicrobial agents from bacteria cells and rendering the antimicrobial agents ineffective.

[28]Randall LP, Woodward MJ. 2001. Multiple antibiotic resistance (Mar) locus in *Salmonella enterica* serovar Typhimurium DT104. Appl. Environ. Microbiol. 67: 1190-1197; Levy SB. 1998. The challenge of antibiotic resistance. Scientific American March pp. 46-53; Moken MC, McMurry LM, Levy SB. 1997. Selection of multiple-antibiotic resistant (Mar) mutants of *Escherichia coli* by using the disinfectant pine oil: roles of the *mar* and *acrAB* loci. Antimicrob. Agents Chemother. 41: 2770-2772. Moken *et al*. 1997 reported that *E. coli* mutants selected for resistance to the disinfectant pine oil or to a household product containing pine oil also showed resistance to a wide variety of antibiotics, including tetracycline, ampicillin, chloramphenicol, and nalidixic acid

38) Industrial and private use of antimicrobials and run-off from antimicrobial sprays used for food and non-food plants may contribute to AMR in bacteria and the spread of AROs.

39) Sludge and raw and treated sewage contain AMR organisms from human and animal sources, and antimicrobial residues from metabolized or inappropriately discarded antimicrobial agents may contribute to AMR.

40) Wildlife vectors- e.g. mice, birds, insects etc. feed on treated crops and spread antimicrobial agents or resistant organisms.

AMR associated with the use of antimicrobials in plant agriculture

41) It is estimated that less than 0.5 % of total antimicrobial use in the United States is used in plant agriculture for the treatment of bacterial diseases[29]. Most of the antimicrobials, consisting mainly of streptomycin and oxytetracycline, are used in controlling bacterial diseases of tree fruits. Approximately 25, 000 pounds (11, 339 kilograms) and 13,700 pounds (6,214 kilograms) active ingredient of streptomycin and oxytetracycline respectively are used annually in the United States[30].

42) Resistance to antimicrobial agents, especially streptomycin, has been found in several plant pathogenic bacteria but resistance has not been reported against oxytetracycline in plant agriculture[31].

43) The use of antimicrobial agents, such as sterilants, disinfectants, copper and other heavy metals to kill bacteria on plants may also contribute to the development of AMR[32].

44) It is generally agreed that the magnitude of antimicrobial use on plants is small

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[29]McManus P. 2000. Antibiotic use and microbial resistance in plant agriculture. ASM News 66(8): 448-449

[30] National Agricultural Statistics Service. 1996. Agricultural chemical usage, 1995 Fruits Summary. No. 96172. U.S. Department of Agriculture.

[31]McManus P. 2000. Antibiotic use and microbial resistance in plant agriculture. ASM News, 66(8): 448-449.

[32]Antimicrobial resistance: an ecological perspective. Report on the American Academy of Microbiology colloquium. July 16-18, 1999. San Juan, Puerto Rico.

compared to the volume of use in humans and in animal husbandry[33].

AMR associated with global movement of drug-resistant organisms

45) International movement of products, animals and people has been identified as a factor in the development of AMR. In recognition of this as a global problem, international organizations such as WHO, have been advocating for harmonized strategies to address the issue of AMR[34].

[33]McManus PS, Stockwell VO, Sundin GW, Jones AL. 2002. Antibiotic use in plant agriculture. Ann.. Rev. Phytopathol. 40: 443-465.

[34]WHO. 2002. Global strategy for containment of antimicrobial resistance. Available online: http://www.who.int/emc/amr_interventions.htm

II. ISSUE IDENTIFICATION
Assessing the Risks

A. Lack of Knowledge about AMR

46) There are significant gaps in the knowledge about AMR in Canada. This affects the ability to assess the risk and predict the future impacts of resistance on public health. Lack of research and surveillance data on antimicrobial use and AMR seriously affects the evaluation of the health risks associated with the emergence and spread of antimicrobial-resistance organisms.

47) ***Current Research:***

- Several research projects on AMR are being conducted at the international level
- Health Canada is also engaged in or collaborating on a number of research projects with Canadian organizations and experts to assess the association between antimicrobial use and AMR and to evaluate the genetic and microbiological aspects of resistance and its effect on human health (see Appendix II)

48) ***Sub-Issues****:*

- Basic research is needed on almost every area including but not limited to:
  - the association between all aspects of antimicrobial use and development of resistance in humans
  - transfer of antimicrobial-resistant organisms from animals (food-producing and pets) to humans and vice versa
  - molecular and cellular mechanisms of resistance development
  - resistance and links to virulence[35]
  - development of rapid diagnostic tests
  - new product development (new antimicrobial agents, therapeutic

[35]Helms M, Vastrup P, Gerner-Smidt P, Mølbak K. 2002. Excess mortality associated with antimicrobial drug-resistant *Salmonella typhimurium.* Emerg. Infect. Dis. 8: 490-495.

alternatives and vaccines)

- ❑ other research priorities will emerge from further consideration and assessment of the key issues

B. Risk[36] Associated with AMR

49) The emergence of drug resistance has complicated the treatment of infections caused by bacteria, viruses, fungi and protozoa.

50) In Canada as well as in other countries, patients are increasingly infected with antimicrobial-resistant organisms, including bacteria, viruses, fungi and parasites. Examples of clinically important antimicrobial-resistant bacteria include, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multi-drug resistant *Streptococcus pneumoniae*, multi-drug resistant *Salmonella*, and antibiotic-resistant *Neisseria gonorrhoea*, among several others[37] (Appendix III).

51) Bacterial resistance to several antimicrobial agents represents the greatest threat to infectious diseases therapy.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

52) MRSA is an increasingly common cause of disease in Canada. The first outbreak was reported in 1981. Occasional outbreaks have been reported in hospitals across Canada. MRSA has also been implicated as a cause of infections in several domestic animals (canine, bovine and equine populations)[38].

53) The incidence rate of MRSA in Canada increased from 0.46 cases per 1000

[36]The probability that a particular adverse event occurs during a stated period of time. As a probability in the sense of statistical theory, risk obeys all the formal laws of combining probabilities. Explicitly or implicitly, it must always relate to the risk of a specific event or set of events and where appropriate must refer to an exposure to a hazard specified in terms of its amount or intensity, time of starting or duration. (Warner F. 1992. Risk: analysis perception and management. Report of a Royal Society Study Group. The Royal Society. London: Pp 1-12.)

[37]Conly J. 2002. Antimicrobial resistance in Canada. Can. Med. Assn. J. .167: 885-891.

[38]Oughton M, Dick H, Willey BM, McGreer A, Low DE. 2001. Methicillin-resistant *Staphylococcus aureus* (MRSA) as a cause of infections in domestic animals: evidence for a new humanotic disease? Canadian Bacterial Surveillance Network (CBSN) Newsletter. April 2001.

hospital admissions in 1995 to 4.12 cases per 1000 admissions in 1999[39] In Ontario alone, the number of patients colonized or infected with MRSA increased from about 1400 cases in 1995 to over 9000 cases in 2000 but there is a decrease of 18% in the number of MRSA cases in Ontario between 2000 and 2001[40].

54) At the international level, more than 95 % of patients with *S. aureus* infections worldwide do not respond to first line antimicrobial agents. Given the fact that *S. aureus* is the most common cause of hospital-acquired infections, the development of MRSA has serious public health implications. Although infections caused by MRSA can be treated with another antimicrobial agent, vancomycin, it should be noted that resistance to vancomycin is also emerging. One of the greatest public health risks is the transfer of vancomycin resistance to *Staphylococcus aureus*, and especially to MRSA given the fact that the vancomycin resistance trait is transferable from *Enterococcus* species.

Vancomycin-resistant Enterococci (VRE)

55) Enterococci are numerous in and very commonly colonize the intestinal tract of humans and animals. As a result of this, the human carrier population is high. Enterococcal species are intrinsically resistant to a wide variety of antibiotics. Human health outcomes are unclear but the transfer of resistance (transposon/plasmid-mediated *van* genes) to other more pathogenic organisms represents a serious health concern.

56) The development of resistance to vancomycin and outbreaks of vancomycin-resistant enterococcal (VRE) infections have been reported. Although there has been a decrease in the number of vancomycin-resistant Enterococci (VRE) cases in Canada since 1998, the number of cases of VRE has gone up from less than 100 in 1995 to more than 400 cases in the year 2000 (Canadian Bacterial Diseases Network).

57) The threat of infection with VRE is especially serious among patients who are already immuno-compromised.

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[39]Simor AE, Ofner-Agostini M, Bryce E, Green K, McGeer A, Mulvey M, Paton S, and the Canadian Nosocomial Infection Surveillance Program, Health Canada. 2001. The evolution of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: 5 years of national surveillance. Can. Med. Assoc. J. 165(1): 21-26.

[40]Canadian Bacterial Surveillance Network. 2002. MRSA and VRE - the Ontario experience. CBSN Newsletter. Issue 1, May 2002.

Multidrug-resistant *Streptococcus pneumoniae*

58) *Streptococcus pneumoniae* is responsible for 5,000 cases of bloodstream infections, 700,000 cases of middle ear infection, and 125,000 cases of pneumonia leading to hospitalization each year in Canada. There is evidence of increasing resistance of *S. pneumoniae* to fluoroquinolones[41]. Surveillance studies have also indicated increasing emergence of multiple antibiotic- resistant *S. pneumoniae*[42].

Multidrug-resistant *Salmonella*

59) *Salmonella* is well known as a leading cause of foodborne illness.

60) Various *Salmonella* serovars are commonly isolated from animals and humans. The *Salmonella* serovars isolated from animals have varying degrees of resistance to antimicrobial agents.

61) The incidence of resistant *S. typhimurium* appears to be rising and the number of drugs it successfully resists is also increasing. More than one third of *S. typhimurium* cases involve a multidrug resistant (MDR) strain of the bacteria.

62) *S. typhimurium* remains very persistent in the environment and is often transmitted from animals to humans through the food chain. Manure from infected cattle and swine can spread contamination through food crops and through the water supply. Environmental exposure is thus an important issue.

63) *S. typhimurium* can be separated into a number of phage types. *S. typhimurium* DT104 is very often multi-resistant to antimicrobials, is frequently isolated from cattle and pigs and is a common cause of food-borne salmonellosis in humans.

64) Development of illness due to *S. typhimurium* DT104 has been linked to antimicrobial use in animals[43].

Antibiotic-resistant *Neisseria gonorrhoeae*

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[41]Low DE. 2001. Fluoroquinolone resistance in *Streptococcus pneumoniae.* CBSN Newsletter April 2001.

[42]Data provided by the Canadian Bacterial Surveillance Network (CBSN).

[43]Glynn MK, Reddy S, Fiorentino T *et al*. 1998. Antimicrobial agent use increases infections with resistant bacteria: a FoodNet case-control study of sporadic, multi-resistant *S. typhimurium* infections, 1996-1997. In: Program and abstracts of 36th Annual Meeting of the Infectious Disease Society of America, 12-15 November 1998, Denver, Colorado. Alexandria, Virginia: Infectious Diseases Society of America. 1998: 84, Abstract 52.

65) In Canada, the incidence of *N. gonorrhoeae* infection has dropped from 134.7/100,000 population (35,287 cases) in 1986 to 20.2/100,000 (6,222 cases) in 2000. This dramatic decrease in the incidence of *N. gonorrhoeae* infections is partly due to improved diagnostic methods, enhanced education programs, enhanced surveillance and contact tracing and the availability of single dose antimicrobial therapies for treatment.

66) The current recommended single dose therapy for youth and adults with gonorrhea is either cefixime 400 mg orally, ceftriaxone 125 mg i.m., ciprofloxacin 500 mg orally or ofloxacin 400 mg orally. These therapies are more expensive (ranging between $5 and $8 per treatment) than the previous treatment using penicillin or tetracycline (costing approximately $1 per treatment).

67) However, there is an increasing trend of quinolone resistance in *N. gonorrhoeae* in different parts of the world especially in the Far East. The number of ciprofloxacin resistant strains isolated in Canada, mainly imported from overseas, has increased from 1994 to 1999. In 1999, the number of reported cases of ciprofloxacin resistance increased by 170% from that of 1997. Since antimicrobial therapy is an important intervention of this treatable disease, the National Laboratory for Sexually Transmitted Diseases (NLSTD) has been monitoring the susceptibility of the *N. gonorrhoeae* strains to ensure efficacy of therapy used.

68) **Existing Measures to Control AMR**

- Infection control measures and guidelines to prevent transmission (Health Canada's infection control guidelines for occupational health in health care, steering committee on infection control, guidelines for Canadian health care facilities, guidelines on vancomycin use, guidelines for testing and reporting of antimicrobial susceptibility)
- National surveillance system (Canadian Nosocomial Infection Surveillance Program; the Nosocomial Infections and Molecular Typing section of Health Canada's Bureau of Microbiology in Winnipeg; Canadian Tuberculosis Laboratory Surveillance System; Canadian Bacterial Surveillance Network; National Laboratory Surveillance Network on *N. gonorrhoeae* susceptibility; Canadian Hospital Epidemiology Committee etc)
- *Salmonella typhimurium* DT104 policy development process

- ❑ Phage typing and antibiotic resistance typing[44]
- ❑ Research
- ❑ Education programs

69) **Sub-Issues:**

- ❑ Risk factors for developing illness versus education and treatment costs
- ❑ Epidemiologic links
- ❑ Development of molecular methods for the surveillance of antibiotic resistance genes
- ❑ Inadequacy of existing measures

[44]Phage typing and antibiotic resistance typing (R-typing) are being performed at the National Microbiology Laboratory (NML) in Winnipeg and at the Office International des Epizooties (OIE) *Salmonella* Reference Laboratory in Guelph.

III. ISSUE IDENTIFICATION:

DEVELOPING RISK MANAGEMENT STRATEGIES/POLICIES

A broad range of health-related issues need to be taken into consideration in developing effective risk management strategies and policies on AMR.

The issues identified below are based on the current understanding of AMR. Risk assessments which are in progress may shed light on other key issues.

Some of these issues fall within the purview of Health Canada, others are the responsibility of other partners.

70) **Health System**

- Capacity to anticipate, prevent and respond in a timely manner to the threat of antimicrobial-resistant pathogens
- capacity to prevent the emergence of microorganisms resistant to available antimicrobial drugs
- capacity to control outbreaks caused by antimicrobial-resistant organisms in humans
- capacity for diagnosis/treatment/follow-up of infections caused by antimicrobial-resistant organisms
- capacity to treat patients in the absence of effective antimicrobial drugs
- capacity for education of physicians, nurses, and other health care providers
- capacity for patient and family education regarding AMR of disease-causing bacteria
- effective communication of risks to those most affected/involved and to the general public
- capacity for public involvement in the risk management and policy decision-making processes

71) **Agricultural System**

- capacity for education of veterinarians, livestock producers/farmers, pharmacists
- capacity for diagnosis and treatment of animal infections caused by antimicrobial-resistant organisms
- capacity to control outbreaks of animal diseases caused by antimicrobial-

resistant organisms
- ❑ impact on animal welfare
- ❑ potential costs and benefits to farmers, livestock producers, and pharmaceutical industries

72) **Ethical**

- ❑ public trust that action will be taken to address the issue
- ❑ prevention of harm
- ❑ public's right to know
- ❑ antimicrobial/antibacterial product labeling

73) **Accountability**

- ❑ liability of health care providers
- ❑ liability of human and animal health pharmaceutical manufacturers
- ❑ liability of farmers (livestock producers)
- ❑ liability of Health Canada as a public health and regulatory agency
- ❑ health care workers and institutions have fiduciary and juridical responsibilities to control the emergence of antimicrobial-resistant organisms
- ❑ information sharing, ownership or stewardship roles of information holders
- ❑ clarity of roles and responsibilities in the decision-making process
- ❑ public understanding of the roles and responsibilities in decision-making

74) **Physical Environment**

- ❑ disposal of antimicrobial agents (technological changes and the re-introduction of organisms)
- ❑ inappropriate disposal of antimicrobial agents, such as flushing unused drugs down the toilet
- ❑ environmental impacts (on animals, plants, soils, water, air) of antimicrobial disposal in the environment
- ❑ environmental impact of the dumping of faeces/carcasses of animals infected with antimicrobial-resistant organisms
- ❑ release of antimicrobial agents through the application of manure or biosolids (human waste) as fertilizer in agriculture
- ❑ release of antimicrobial agents from human waste through discharge of effluents from sewage treatment plants
- ❑ waste water treatment facilities may not kill or remove AROs so they

enter the water to be taken in at the downstream water intake pipes and may not be killed there either

75) **Social Environment**

- potential impacts on families and communities
- impacts on certain sub-populations
- impacts on various social and health settings such as day care and health care facilities
- mistrust of government in the policies/strategies for controlling the emergence and spread of AMR
- potential impact on treatment of patients infected with antibiotic-resistant organisms

76) **Public Perception**

- public perception of AMR
- media's role in shaping public perception
- fear of emerging 'super-bug' diseases
- fear of prolonged incapacitation due to infections by antibiotic-resistant organisms
- mistrust of government in protecting health and in the systems that have been established to reduce and manage health risks

77) **Lifestyle and Personal Health Practices**

- impact on use of products derived from antibiotic-treated animals
- potential impact on care of companion animals
- potential impact on use of personal hygiene products (cosmetics, hand antiseptics, etc.)

78) **Health Economics**

- prioritizing health issues/balancing competing health needs and limited resources and factoring in the uncertainties of theoretical risk versus other better understood risks
- potential economic impact of not putting sufficient measures in place and the long term costs associated with the emergence and spread of AMR
- potential employment and income impacts
- costs versus benefits and impacts of the treatment or prevention options and other comparative analysis and options

- costs of effective antimicrobial drugs (i.e. AMR may lead to use of more expensive antimicrobial agents)
- potential antimicrobial drug shortage situation
- alternative drugs to deal with drug shortages
- lack of incentives for drug manufacturers to look for alternatives (i.e. research on alternative therapies)

79) **Other Considerations**

- measures to reduce risk of exposure to AMR may increase risks for other sub-populations
- clarification of respective implications/links to other health issues
- the importance of consistency across jurisdictions in Canada in policies and practices
- the importance of international collaboration in reducing the risk to Canadians posed by AMR
- animal health and welfare
- impacts of mitigating actions as well as approaches to precluding AMR (e.g. impact of actions taken to withdraw drugs)
- potential economic impact on farmers and industries (human and animal health pharmaceutical manufacturers)
- potential costs and benefits related to the manufacture of antimicrobial products (OTC and prescription drugs, household disinfectants, antiseptics and cosmetics)
- potential costs and benefits to the consumers
- potential impact on exports, imports and trade relationships with other countries
- perception of risk may lead to stigmatization of products, technologies and places
- political issues
- Canada's obligations under international trade agreements

APPENDIX I

List of antimicrobial/antibacterial/anti-infective agents contributing to the development of AMR

- antibiotics
- antivirals
- antifungals
- probiotics
- slimicides
- hard surface disinfectants and sanitizers
- wood preservatives (heavy duty stain, anti-sapstain, joinery and remedial)
- material preservatives (fuel additives, preservatives of metal working fluids, anti-fouling paint)
- swimming pool bactericides
- fungicides for plant disease control
- crop bactericides

APPENDIX II

Canadian Research and Surveillance Projects relating to AMR and Use in Food Production

Multi-species/General Resistance Projects

Surveillance of antimicrobial resistance in aquaculture & agri-food sectors. Health Canada (Deckert, A., Irwin, R.) - New project

Antimicrobial resistance testing in support of a National Integrated Surveillance System for antimicrobial resistance in agri-food and aquaculture. (Deckert, A., Muckle, A., Michel, P., Poppe, C., Irwin, R., Mann, E.) - New project

Epidemiology & evolution of Enterobacteriaceae infections in humans & domestic animals. Wellcome Trust International Partnership Research Award in Veterinary Epidemiology. University of Guelph (McEwen, S.), Health Canada (Johnson, R., Poppe, C.) - Ongoing

National integrated surveillance of priority foodborne pathogens - AMR *Salmonella* contamination in meat sampled under HACCP. Health Canada (Michel, P., Champagne, M., Muckle, A., Deckert, A., Irwin, R., Mann, E., Gour, L., *et al.*) - Ongoing

Information infra-structure supporting the integration of food, animal, environment & human surveillance data. Health Canada (Mann, E., Pollari, F.), University of Guelph (McEwen, B., Odumeru, J.), OMAFRA (Johnson, P.) - Ongoing

Program to monitor antimicrobial resistance in bacteria isolated from animals and food in Québec. MAPAQ (Nadeau, M., Côte, G., Bergeron, H., Lamontagne, G., Higgins, R.) - Ongoing

Antimicrobial resistance of *Salmonella* and *Campylobacter* isolates from hog, beef and chicken carcass samples from provincially inspected abbatoirs in Ontario. University of Guelph (Odumeru, J., McEwen, B.), OMAFRA (McNab, B.), Health Canada (Poppe, C., Irwin, R.) - Ongoing

Antimicrobial resistance among food isolates of *Campylobacter* spp. identified during outbreak investigations in Ontario. Health Canada (Farber, J.M., Medeiros, D., Sanders, G., Austin, J., Graham, C., Sattar, J., Hockin, J.), Region of Ottawa-Carleton Health Department, Ontario Ministry of Health - Ongoing

Development of Alberta integrated antimicrobial resistance surveillance program. Food Safety Division, Alberta Agriculture Food and Rural Development (Rajic, A., Manninen, K. et al.), Health Canada (Deckert, A.) - Proposal submitted

Multi-provincial *Salmonella typhimurium* case control study. Health Canada. (Doré, K.), Alberta Health and Wellness, Northern Alberta and Southern Alberta Provincial Laboratories of Public Health, British Columbia Centre for Disease Control, Ontario Ministry of Health and Long-Term Care, Saskatchewan Provincial

Laboratory, and LCDC - Ongoing

Use Projects (including the association between use and resistance)

Surveillance of antimicrobial use in agri-food and aquaculture sectors. Health Canada (Reid-Smith, R., Irwin, R.), University of Guelph (McEwen, S. *et al.*) - Ongoing

Research in antimicrobial use & resistance in agri-food, aquaculture and veterinary medicine. Health Canada (Reid-Smith, R.) - New Project

Surveillance of antimicrobial use by B.C. feed mills. BCMAFF (Wetzstein, M.), Health Canada (Irwin, R., Reid-Smith, R.), Centre for Coastal Health (Sifton, E.) - Ongoing

Molecular Resistance Projects

Factors affecting transfer of genes encoding multiple antibiotic resistance to *Salmonella typhimurium* DT 104. ILSI funded project. Health Canada (Poppe, C., Muckle, A., Ziebell, K.), University of Guelph (McEwen, S., Prescott, J.) OMAFRA (Alves, D.) - Ongoing

Epidemiological typing of *Campylobacter* clinical, food and environment isolates used pulsed-field gel electrophoresis. Health Canada (Farber, J.M.) - Ongoing

Genetic aspects of antimicrobial resistance and virulence of *Salmonella* isolated from animals and humans. Health Canada (Poppe, C.) - Ongoing

Beef and Dairy Resistance Projects

Antimicrobial sensitivity of HACCP isolates from federally inspected slaughter plants in Alberta, Saskatchewan and Ontario. Van Donkersgoed, J., Alberta Agriculture Food and Rural Development (Manninen, K.), University of Guelph (McEwen, S.), VIDO (Potter, A.), Health Canada (Irwin, R.) - Ongoing

Use Projects (including the association between use and resistance)

Antimicrobial use in the Ontario beef industry. OCA & OMAFRA funded. University of Guelph (Bair, C., McEwen, S., Martin W., Griffiths, M.), Health Canada (Irwin, R., Reid-Smith, R.) - Ongoing.

Antimicrobial resistance in selected bacteria of beef cattle and associated with on-farm antimicrobial use. University of Guelph (McEwen, S., Archambault, M., McEwen, B.,), Health Canada (Reid-Smith, R., Poppe, C.) OMAFRA (Alves, D., McNab, B.) - New project.

Pork Resistance Projects

The use of virginiamycin and tylocin as growth promoters in pigs and the occurrence of streptogramin and macrolide resistant enterococci in pigs and humans. Health Canada (Poppe, C.), University of Guelph (McEwen, S., Akwar, H.) - Ongoing

Salmonella spp. in finishing pigs in Alberta: bacteriological and serological prevalence, serotype distribution, antimicrobial resistance profiles and risk factors. Food Safety Division, Alberta Agriculture Food and Rural Development (Rajic, A., Keenliside, J., Mc Fall, M., Wu, J., Manninen, K.), University of Guelph (McEwen, S.), Health Canada (Deckert, A.) - Ongoing

National integrated surveillance pilot project of priority foodborne pathogens - AMR resistant Salmonella in pigs at slaughter in Quebec. Health Canada (Champagne, M., Michel, P., Irwin, R., Deckert, A.), University of Montreal (Quessy, S.) - Ongoing

Use Projects (including the association between use and resistance)

Use of antimicrobials in 90 large swine operations in Alberta. Food Safety Division, Alberta Agriculture Food and Rural Development (Rajic, A., Keenliside, J., Manninen, K.), University of Guelph (McEwen, S.), Health Canada (Deckert, A., Reid-Smith, R.) - Ongoing.

Poultry Resistance Projects

Campylobacter infection in employees at a poultry plant in Ontario. Health Canada (Buck, P., Sockett, P., Rodgers, F., Woodward, D., Griffi, C.), Perth District Health Unit (Tamblyn, S.) - Potential Project, proposal accepted.

Campylobacter jejuni and *Campylobacter coli* in humans and retail chicken products in a defined geographical area in Ontario. Health Canada (Valdivieso-G.A., Deckert, A., Reid-Smith, R., Irwin, R.), CIDPC (Doré, K., Buck, P.) - New project.

Determination of the prevalence of *Campylobacter jejuni* in broiler chickens at slaughter. Alberta Agriculture Food and Rural Development (Vanderkop, M., McFall, M., Sorensen, O.) - Ongoing

Environment Resistance Projects

Microbial diversity and antibiotic resistance in surface and ground water from the Oldman River basin. University of Lethbridge / Alberta Agricultural Research Institute (Thomas, J., Buryns, J.), Health Canada (Michel, P.) Proposal submitted.

Environmental impact of manure handling practices and relationship to use of antimicrobials in livestock and poultry. AAFC, Research Branch (Topp, E.), University of Guelph (McEwen, S.), ESWE, Germany (Ternes, T.) - Ongoing

Aquaculture Resistance Projects

Prevalence of antimicrobial resistance and drug residues in B.C. aquaculture and wild salmon and in related shellfish. Health Canada (Jia, X., Stephen, C., D'Aoust, J-Y., Irwin, R.), B.C. aquaculture and wild salmon industries, Fisheries and Oceans Canada, B.C. Ministry of Agriculture and Food, Canadian Food Inspection Agency.- Ongoing

Companion Animal Resistance Projects

Patterns over time of antimicrobial drug resistance in bacteria from companion animals. University of Guelph (Prescott, J., Hanna, B., Drost, K.), Health Canada (Reid-Smith, R.) - Analysis & manuscript in preparation.

Use Projects (including the association between use and resistance)

Self-reported factors affecting antimicrobial decision making in companion animal practitioners. Health Canada (Reid-Smith, R.), University of Guelph (Bonnett, B., Strutt, C., Rinkardt, N.), Queen's University (Ford, D., Zoutmann, R.) - Ongoing

Use of "top-shelf" antimicrobials in veterinary teaching, referral and emergency hospitals. Health Canada (Reid-Smith, R.), University of Guelph (Prescott, J., Hanna, B.) - Ongoing

Risk Assessment

Risk assessment of human health impact of antimicrobial use and resistance in agri-food. University of Guelph (Bair, C., McEwen, S., Martin, W.), Health Canada (Irwin, R., Reid-Smith, R.) - Ongoing

Alternatives

Research on probiotics. Health Canada, Bureau of Microbial Hazards (Kalmokoff, M.), Therapeutics Products Programme (Hefford, M., Seere, T.)

Human Resistance Projects

Baseline study on the incidence, etiology and burden of illness due to infectious gastroenteritis in Canada - NSAGI. Health Canada (Doré, K.) - Ongoing

National enteric disease GIS initiative; spatial distribution of *Salmonella typhimurium* DT104. Health Canada (Michel, P., Ravel, A.), Ontario Ministry of Health and Long-Term Care (Middleton, D.) - Ongoing

Programme on Surveillance and Control of Antimicrobial Resistance in *Salmonella*, *Shigella*, and *Vibrio cholera* in the Americas. Health Canada, LCDC collaborative project with PAHO (Rodgers, F., Woodward, D.) - Ongoing

Situation analysis of public health surveillance systems for capture of information on antimicrobial resistant enteric pathogens in Canada. Health Canada (Doré, K.) - Ongoing

New strategies for overcoming antimicrobial resistance with natural health products. University of Ottawa (Dillon, J., Arnason, J.T., Krantis, A., Durst, T.), Health Canada (Foster, B.)- Ongoing

A strategy for examining the development of host- and anti-microbial resistance. Health Canada (Foster, B.),

University of Ottawa (Dillon, J., Arnason, J.T., Krantis, A.), Plant Bioactives Research Institute, Utah, USA (Lawson, L.)-Ongoing

Completed Projects

Antimicrobial resistance among bacterial isolates from food producing animals in Ontario. University of Guelph (McEwen, B., Archambault, M., Smart, N., McEwen, S.) OMAFRA (McNab, B., Alves, D.) Health Canada (Poppe, C., Valdivieso-G, A.) - Completed

The magnitude and distribution of drug resistance among *Salmonella* isolated from animals, foods of animal origin, and humans. Health Canada (Poppe, C.). - Completed

Over-the-counter (OTC) sales of antibiotics in Ontario. OMAFRA (McBride, G., Sills, A.), Health Canada (Reid-Smith, R., Irwin, R.) - Data collection completed

National sales of antimicrobial drugs through veterinary purchasing companies for 1997 and 1998. Centre for Coastal Health (Sifton, E., Stephen, C.), Health Canada (Reid-Smith, R., Irwin, R.) - Data collection completed

Prevalence of resistance among *E. coli* isolated from bulls before and after treatment for bovine respiratory disease. University of Guelph (McEwen, S., Martin, W.), Health Canada (Poppe, C.) - Completed.

Associations among therapeutic and in-feed antimicrobial use and resistance in fecal commensals and pathogens of swine. NPPC funded study. University of Guelph (McEwen, S.), Health Canada (Poppe, C.) - Completed

Prevalence of *Salmonella* spp. and thermophilic *Campylobacter* spp. in Alberta slaughter hogs. Food Safety Division, Alberta Agriculture Food and Rural Development (Sorensen, O., McFall, M., Manninen, K.) - Completed

Temporal changes in the microbial resistance pattern of *E. coli* isolated from pigs in Ontario. University of Guelph (McEwen, S., Popa, M.), Health Canada (Poppe, C.) - Completed

The prevalence of drug resistance among *Campylobacter* spp. isolated from chickens, turkeys, poultry meat and meat products, and from humans. Health Canada (Valdivieso-G, A., Michel, P., Irwin, R., Poppe, C.), Ontario Ministry of Health (Ciebin, B.) - Completed

A descriptive study of *Salmonella typhimurium* and *Salmonella typhimurium* DT104 infections reported in Ontario. Health Canada (Ford, M., Michel, P., Doré, K., Majowicz, S., Aramini, J., Ahmed, R., Rodgers, F., Wilson, J.), Ontario Ministry of Health and Long-Term Care (Middleton, D., Deeks, S., Cieben, B.), University of Guelph (McEwen, S.) - Completed

Prudent use of antibiotics in the Ontario beef industry. University of Guelph (Powell, W., McEwen, S.), Health Canada (Irwin, R.) - Completed

Antimicrobial resistance in *Campylobacter jejuni* and *Campylobacter coli* isolated from humans and poultry products in Ontario. Health Canada (Valdivieso-G, A., Michel, P., Irwin, R., Poppe, C.), Ontario Ministry of Health (Ciebin, B.), University of Guelph (McEwen, S.) - Completed

Surveys of provincial/territorial, hospital and federal stakeholders regarding current ARO surveillance and research activities and issues related to the collection and use of surveillance data. Health Canada (Doré, K., Habinski, S, Poirier, R., Reid-Smith, R.) - Completed

Occurrence of multi-resistant *Staphylococcus aureus* in Alberta bulk milk. Alberta Agriculture Food and Rural Development (Sorensen, O., McFall, M., Manninen, K.) - Completed

APPENDIX III

Relevant Antimicrobial-Resistant Organisms With Potential Impacts on Canadian Public Health Care System

- methicillin-resistant *Staphylococcus aureus* (MRSA)
- vancomycin-resistant *Staphylococcus aureus* (VRSE)
- vancomycin-resistant Enterococci (VRE)
- fluoroquinolone-resistant *Salmonella typhimurium*
- multidrug-resistant *Neisseria gonorrhoeae*
- multidrug-resistant tuberculosis (MDR-TB)
- multidrug-resistant *Streptococcus pneumoniae*
- multidrug-resistant *Campylobacter*
- penicillin-resistant *Streptococcus pneumoniae* (PRSP)
- fluoroquinolone-resistant *Streptococcus pneumoniae*
- fluconazole-resistant *Candida*
- amantadine-resistant influenza virus
- drug-resistant hepatitis B virus
- drug-resistant HIV strains

APPENDIX IV

Federal and Provincial Regulations Concerning Antimicrobial Agents*

Jurisdiction	**Legislation**
Federal	· Food and Drugs Act and Regulations · Controlled Drug and Substance Act · Feeds Act and Regulations
Alberta	· Alberta Livestock Disease Act · Veterinary Profession Act
British Columbia	· Pharmacists Act
Manitoba	· Pharmaceutical Act
Newfoundland and Labrador	· Current legislation under review
New Brunswick	· An Act Respecting the New Brunswick Veterinary Medical Association
Nova Scotia	· Veterinary Medical Act · Pharmacy Act
Ontario	· Livestock Medicines Act
Prince Edward Island	· Veterinary Medical Act · Pharmacy Act
Quebec	· Veterinary Surgeons Act · Pharmacy Act and the · Animal Health Protection Act

*Adapted from the report of Health Canada's Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health (Available online: http://www.hc-sc.gc.ca/vetdrugs-medsvet/amr/e_policy_dev.html)

APPENDIX V

LIST OF MEMBERS

Interdepartmental AMR Science Committee

(October 2002)

Rebecca Irwin (chair)	Laboratory for Foodborne Zoonoses, PPHB, HC
Lai King Ng (co-chair)	Winnipeg Laboratory, PPHB, HC
Lateef Adewoye (secretariat)	Veterinary Drugs Directorate, HPFB, HC
Denis Allard	Canadian Food Inspection Agency
Joe Banoub	Fisheries and Oceans Canada
Robert Charlebois	Canadian Food Inspection Agency
Shiv Chopra	Veterinary Drugs Directorate, HC
Kathryn Doré	CIDPC, PPHB, HC
Brenda Linke	Pest Management Regulatory Agency, HC
Manisha Mehrotra	Veterinary Drugs Directorate, HC
Michael Mulvey	Winnipeg Laboratory, PPHB, HC
Shirley Paton	CIDPC, PPHB, HC
Pat Pentney	Canadian Food Inspection Agency
Cornelius Poppe	Laboratory for Foodborne Zoonoses, PPHB, HC
Will Robertson	Healthy Environments and Consumer Safety, HC
William Yan	Food Directorate, HPFB, HC
Vern Seligy	Healthy Environments and Consumer Safety, HC
Gilles Olivier	Fisheries and Oceans Canada

Interdepartmental AMR Policy Committee

(October 2002)

Diane Kirkpatrick (chair)	Veterinary Drugs Directorate, HC
Lateef Adewoye (secretariat)	Veterinary Drugs Directorate, HC
David Blakey	Healthy Environments and Consumer Safety, HC
Marie-Josee Bolduc	Health Products and Food Branch, HC
Francine Brunet	Pest Management Regulatory Agency, HC
Tim Carey	Fisheries & Oceans Canada
Vasu Dev Sharma	Veterinary Drugs Directorate, HC
Joseph Given	Office of Regulatory and International Affairs, HC
Rebecca Irwin	Laboratory for Foodborne Zoonoses, PPHB, HC
Jean Kamanzi	Canadian Food Inspection Agency
Tiiu Kauri	Healthy Environments and Consumer Safety, HC
Marie S Lemaire	Natural Health Products Directorate, HC
Linda Morrison	Canadian Food Inspection Agency
Kim Ostapyk	Office of Regulatory and International Affairs
Shirley Paton	CIDPC, PPHB, HC
Raman Srivastava	Policy and Strategic Planning Directorate, HC
Iola Price	Fisheries & Oceans Canada
Mary Raphael	Therapeutic Products Directorate, HC
Annie Savoie	Canadian Food Inspection Agency

_____	Environment Canada
Bill Slater	Health Products and Food Branch, HC
Lynne Underhill	Canadian Food Inspection Agency
William Yan	Food Directorate, HC

GLOSSARY OF TERMS

Active Pharmaceutical Ingredients (APIs): Bulk, pharmaceutically active substances which are used in the formulation of drugs in dosage form.

Antibiotics: Natural or synthetic substances used to treat infections caused by bacteria

Antimicrobial agent: Natural, semi-synthetic or synthetic substances that are capable of killing or inhibiting the growth of microorganisms.

Antimicrobial resistance marker: Specific DNA sequences used to select for desired traits in organisms. Antimicrobial resistance genes are generally used as markers in genetic engineering studies.

Antimicrobial resistance: The condition in which a specific antimicrobial drug becomes ineffective in killing or inhibiting the growth of a targeted microrganism

Antimocrobial-resistant organisms: Microorganisms that are able to gow in the presence of anitmicrobial agents.

Commensal bacteria: The normal microflora living on the external and internal surfaces of humans or animals are referred to as commensal bacteria.

Cross resistance: Microbes exposed to one drug develops resistance to other antimicrobials of the same family. For example, resistance to gentamicin may be associated with resistance to neomycin.

Empirical theory: The practice of adminsitering an antimicrobial agent to treat animal infections prior to obtaining laboratory information on the diagnosis.

Efflux pumps (multidrug efflux pumps): Broad substrate-specific systems that are used to actively pump out antimicrobial agents from bacteria cells and rendering the antimicrobial agents ineffective. Efflux pumps contribute to acquired resistance to antimicrobial agents because of their broad substrates specificity and their expression in important pathogens, as well as their cooperation with other resistance mechanisms.

Foodborne pathogens: Bacterial pathogens that can be transmitted from animals to humans through the food chain. Examples include *Salmonella* spp. and *Campylobacter* spp., among others.

Gene regulator: Cellular factors which control the expression of genes including antimicrobial resistance genes.

Growth promotants: Antimicrobial agents that are used in animal husbandry practices for production

enhancement.

Horizontal gene transfer: Movement of genetic material between bacterial species.

Inherent cellular components: Structural and genotypic features of bacterial species, which enable them to withstand antimicrobial agents. In Gram-negative bacteria, these features include the relatively low permeability characteristic of the outer membrane and the constitutive expression of drug efflux proteins in some species.

Intrinsic resistance: The ability of bacterial species to thrive in the presence of antimicrobial agents due to inherent characteristics of the organisms. It is essentially the naturally occurring resistance of a bacterium to antimicrobial agents.

Livestock: Animals produced or kept primarily for farm, ranch, or market purposes

Metaphylactic uses: Uses of antimicrobial agents for disease treatment and prevention involving mass medication of animals with therapeutic levels of drugs when some animals are clinically diseased while others may be subclinically affected or at high risk.

Nosocomial: Hospital-acquired

Over-use of antimicrobials: Extensive use of antimicrobial agents especially when not needed.

Pathogenic bacteria: Bacterial species capable of causing diseases in animals or humans.

Probiotics: Products containing viable, defined microorganisms in sufficient numbers that alter the microflora by implantation or colonization in a compartment of the host (animals or humans) and exert beneficial health effects in the host (e.g. Bifidobacteria, Lactobacilli, Saccharomyces, Aspergillus etc.).

Prophylactic uses: All uses of antimicrobial agents for disease prevention.

Rapid diagnostic test: Methodology for quick and accurate diagnosis of infections caused by antimicrobial-resistant organisms.

Resistance gene: DNA molecules which encode proteins or enzymes that are responsible for or contribute to the ability of bacterial species to thrive in the presence of antimicrobial agents.

Resistant trait: Genotypic or phenotypic characteristics of bacterial species which enable them to thrive in the presence of antimicrobial agents.

Serovar: The variety of a bacterial species characterised by its antigenic properties.

Silage inoculants: Live microorganisms that aid in the natural fermentation of ensiled forages.

Sludge: Muddy deposit or precipitated solid matter produced by water and sewage treatment processes.

Sub-therapeutic uses: All uses of antimicrobials for disease prevention, or prophylaxis, as well as growth promotion or performance enhancement purpose.

Transposons: Mobile genetic elements which are capable of moving from one part of the chromosome to another. They are sometimes referred to as jumping genes.

Virulence: The ability of bacterial pathogens to invade host cells and cause infections.

ABBREVIATIONS

AMR	Antimicrobial resistance
API	Active pharmaceutical ingredient
AROs	Antimicrobial-resistant organism
CIDPC	Centre for Infectious Disease Prevention and Control
GMO	Genetically modified organism (usually in the sense of transgenic)
LCDC	Laboratory Centres for Disease Control
MRSA	Methicillin-resistant *Staphylococcus aureus*
NLSTD	National Laboratory for Sexually Transmitted Diseases
VDD	Veterinary Drugs Directorate
VRE	Vancomycin-resistant enterococci
VRSA	Vancomycin-resistant *Staphylococcus aureus*

REFERENCES

Aarestrup FM, Seyfarth AM, Emborg H-D, Pedersen K, Hendriksen RS, Bager F. 2001. Effect of abolishment of the use of antimicrobial agents for growth promotion on occurrence of antimicrobial resistance in fecal enterococci from food animals in Denmark. Antimicrob. Agents Chemother. 45: 2054-2059.

Alliance for the Prudent Use of Antibiotics. 2002. The need to improve antimicrobial use in agriculture: ecological and human health consequences. A report of the facts about antibiotics in animals and the impact on resistance (FAAIR) project.

American Academy of Microbiology. 2002. The role of antibiotics in agriculture. A report based on a colloquim sponsored by the American Academy of Microbiology held November 2-4, 2001, in Santa Fe, New Mexico.

American Academy of Microbiology. 1999. Antimicrobial Resistance: an ecological perspective. Report on a colloquium held July 16-18, 1999 in San Juan, Puerto Rico.

Bailar JC, Travers K. 2002. Review of assessments of the human health risk associated with the use of antimicrobial agents in agriculture. Clin. Infect. Dis. 34 (Suppl 3): S135-S144.

Bast DJ, Low DE, Duncan CL, Kilburn L, Mandell LA, Davidson RJ, de Azavedo JC. 2000. Fluoroquinolone resistance in clinical isolates of *Streptococcus pneumoniae*: contributions of Type II Topoisomerase mutations and efflux to levels of resistance. Antimicrob. Agents Chemother. 44: 3049-3054.

Benbrook CM. 2002. Antibiotic drug use in U.S. aquaculture. IATP Report. Northwest Science and Environmental Policy Center, Sandpoint, Idaho. 20 pp.

Björkman J, Hughes D, Andersson DI. 1998. Virulence of antibiotic-resistant *Salmonella typhimurium*. Proc. Nat. Acad. Sci. USA. 95: 3949-3953

Canadian Bacterial Surveillance Network. 2002. MRSA and VRE — the Ontario experience. CBSN Newsletter Issue 1, May 2002.

Canadian Committee on Antibiotic Resistance. Surveillance CCAR 2001: 1. Available Online: http://www.ccar-ccra.org/surveillance-e.htm.

Canadian Committee on Antibiotic Resistance. 2002. Antimicrobial Resistance: a deadly burden no country can afford to ignore. Report prepared by David Birnbaum for the Canadian Committee on

Antibiotic Resistance

Chiu C-H, Wu T-S, Su L-H, Chu C, Chia J-H, Kuo A-J, Chien S, Lin T-Y. 2002. The emergence in Taiwan of fluoroquinolone resistance in *Salmonella enterica* serotype choleraesuis. N. Engl. J. Med. 346: 413-419.

Conly J. 2002. Antimicrobial resistance in Canada. Can. Med. Ass. J. 167: 885-891.

Davidson R, Cavalcanti R, Brunton JL, Bast DJ, de Azavedo JC, Kibsey P, Fleming C, Low DE. 2002. Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. N. Engl. J. Med. 346: 747-750.

Gaudreau C, Gilbert H. 1998. Antimicrobial resistance of clinical strains of *Campylobacter jejuni* subsp. *jejuni* isolated from 1985-1997 in Quebec, Canada. Antimicrob. Agents Chemother. 42: 2106-2108.

Gorbach SL. 2001. Antimicrobial use in animal feed — time to stop. N. Engl. J. Med. 345: 1202-1203.

Health Canada. 1999. *Salmonella typhimurium* definitive Type 104 isolates in British Columbia, 1997-1998. CCDR Vol. 25-15, 1 August 1999. Available online: http://www.hc-sc.gc.ca/hpb/lcdc/publicat/ccdr/99vol25/dr2515ea.html

Health Canada. 2000. Restaurant-associated outbreak of *Salmonella typhimurium* phage Type 1 gastroenteritis - Edmonton, 1999. CCDR Vol. 26-04, 15 February 2000. Available online: http://www.hc-sc.gc.ca/hpb/lcdc/publicat/ccdr/00vol26/dr2604ea.html

Health Canada. 2002. Report of the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health. Available online: http://www.hc-sc.gc.ca/vetdrugs-medsvet/amr/e_policy_dev.html

Health Canada. 2001. *Neisseria meningitidis* with decreased susceptibility to penicillin in Ontario, Canada 1997-2000. Population and Public Health Branch. CCDR. Vol. 27-09, 1 May 2001. Available online: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/ccdr-rmtc/01vol27/dr2709ea.html

Health Canada. 2001. Identification of the first vancomycin-resistant *Enterococcus faecalis* harbouring vanE in Canada. Population and Public Health Branch. CCDR. Vol. 27-12, 15 June 2001. Available online: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/ccdr-rmtc/01vol27/dr2712ea.html

Health Canada. 2001. Multidrug-resistant tuberculosis. Population and Public Health Branch CCDR. Vol. 27-19, 1 October 2001. Available online: http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/ccdr-rmtc/01vol27/dr2719eb.html

Health Canada. 2001. Tuberculosis: drug resistance in Canada, 2001. Reported susceptibility results of the Canadian Tuberculosis Laboratory Surveillance System. Available online: http://www.hc-sc.gc.ca/ pphb-dgspsp/publicat /tbdrc01/index.html

Healthcare Ontario. 2001. Antibiotic resistance: emerging risks and the partnership solution. Annual Report of Chief Medical Officer of Health for Ontario 2001.

Helms M, Vastrup P, Gerner-Smidt P, Mølbak K. 2002. Excess mortality associated with antimicrobial drug-resistant *Salmonella typhimurium*. Emerg. Infect. Dis. 8: 490-495.

Hilbert F, del Portillo FG, Groisman EA. 1999. A periplasmic d-alanyl-d-alanine dipeptidase in the gram-negative bacterium *Salmonella enterica*. J. Bacteriol. 181: 2158-2165.

Joint Expert Advisory Committee on Antimicrobial Resistance. 1999. Report on the use of antibiotics in food producing animals: antibiotic-resistant bacteria in animals and humans. Commonwealth of Australia. Available online: http://www.health.gov.au/pubs/jetacar.htm

Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, Buxton HT. 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance. Environ. Sci. Technol. 36: 1202-1211.

Levine WC, Buehler JW, Bean NH, Tauxe RV. 1991. Epidemiology of nontyphoidal *Salmonella* bacteremia during the human immunodeficiency virus epidemic. J. Infect. Dis. 164: 81-87

Levy SB. 1998. The challenges of antibiotic resistance. Scientific American. March. pp. 46-53.

Levy SB. 2001. Antibacterial household products: cause for concern. Emerg. Infect. Dis. 7(3): 512-515.

Low DE. 2001. Fluoroquinolone resistance in *Streptococcus pneumoniae*. CBSN Newsletter April 2001.

McGeer AJ. 1998. Agricultural antibiotics and resistance in human pathogens: villain or scapegoat? Can. Med. Assoc. J. 159: 1119-1120.

McManus P. 2000. Antibiotic use and microbial resistance in plant agriculture. ASM News, 66(8): 448 - 449.

McManus PS, Stockwell VO, Sundin GW, Jones AL. 2002. Antibiotic use in plant agriculture. Ann. Rev. Phytopathol. 40: 443-465.

Mizan S, Lee MD, Harmon BG, Tkalcic S, Maurer JJ. 2002. Acquisition of antibiotic resistance plasmids by enterohemorrhagic *Escherichia coli* 0157:H7 within rumen fluid. J. Food Protect. 65: 1038-1040.

Moken MC, McMurry LM, Levy SB. 1997. Selection of multiple-antibiotic resistant (Mar) mutants of *Escherichia coli* by using the disinfectant pine oil: roles of the *mar* and *acrAB* loci. Antimicrob. Agents and Chemother. 41: 2770-2772

Office International des Épizooties (OIE). 2001. Antimicrobial resistance: report prepared by the OIE Ad Hoc Group of Experts on Antimicrobial Resistance.

Oughton M, Dick H, Willey BM, McGeer A, Low DE. 2001. Methicillin-resistant *Staphylococcus aureus* (MRSA) as a cause of infections in domestic animals: evidence for a new humanotic disease? Canadian Bacterial Surveillance Network. April 2001 Newsletter.

Piddock LJV. 2002. Fluoroquinolone resistance in *Salmonella* serovars isolated from humans and food animals. FEMS Microbiol. Rev. 26: 3-16.

Poppe C., Ayroud M, Ollis G, Chirino-Trejo, M, Smart N, Quessy S, Michel P. 2001. Trends in antimicrobial resistance of *Salmonella* isolated from animals, foods of animal origin, and the environment of animal production in Canada, 1994-1997. Microbial Drug Resist. 7: 197-211.

Poppe C, Smart N, Khakhria R, Johnson W, Spika J, Prescott J. 1998. *Salmonella typhimurium* DT104: a virulent and drug-resistant pathogen. Can. Vet. J. 39:559-565.

Randall LP, Woodward MJ. 2001. Multiple antibiotic resistance (Mar) locus in *Salmonella enterica* serovar *typhimurium* DT104. Appl. Environ. Microbiol. 67: 1190-1197.

Rice LB. 2001. Emergence of vancomycin-resistant Enterococci. Emerg. Infect. Dis. 7(2): 183-187.

Sack DA, Lyke C, McLaughlin C, Suwanvanichkij V. 2001. Antimicrobial resistance in shigellosis, cholera and campylobacteriosis. World Health Organization. WHO/CDS/CSR/DRS/2001.8. pp 1-51.

Schroeder CM, Zhao C, DebRoy C, Torcolini J, Zhao S, White DG, Wagner DD, McDermont PF, Walker RD, Meng J. 2002. Antimicrobial resistance of *Escherichia coli* 0157 isolated from humans, cattle, swine, and food. Appl. Environ. Microbiol. 68: 576-581.

Select Committee on Science and Technology. 1998. Resistance to antibiotics and other antimicrobial agents. Seventh Report. 17 March.

Silver S, Phung LT. 1996. Bacterial heavy metal resistance: new surprises. Ann. Rev. Microbiol. 50:

753-789.

Simor AE, Ofner-Agostini M, Bryce E, Green K, McGeer A, Mulvey M, Paton S, and the Canadian Nosocomial Infection Surveillance Program, Health Canada. 2001. The evolution of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: 5 years of national surveillance. Can. Med. Assoc. J. 165(1):21-26.

Smith DL. 2002. Animal antibiotic use has an early but important impact on the emergence of antibiotic resistance in human commensal bacteria. Proc. Nat. Acad. Sci. 99: 6434-6439.

Smith KE, Besser, JM, Hedberg, CW, Leano, FT, Bender, JB, Wicklund, JH, Johnson, BP, Moore, KA, Osterholm, MT and the Investigation Team. 1999. Quinolone-resistant *Campylobacter jejeuni* infections in Minnesota, 1992-1998. N.. Engl. J. Med. 340: 1525-1532.

Sorum H, Sunde M. 2001. Resistance to antibiotics in the normal flora of animals. Vet. Res. 32: 227-241.

Steckelberg JM, Terrell CL, Edson RS. 1988. Laboratory-acquired *Salmonella typhimurium* enteritis: association with erythema nodosum and reactive arthritis. Am. J. Med. 85: 705-707.

Sternberg S. 1999. Antimicrobial resistance in bacteria from pets and horses. Acta Vet. Scand. Suppl. 92: 37-50.

Sulavik MC, Dazer M, Miller PF. 1997. The *Salmonella typhimurium mar* locus: molecular and genetic analyses and assessment of its role in virulence. J. Bacteriol. 179: 1857-1866.

Swartz MN. 2002. Human diseases caused by foodborne pathogens of animal origin. Clin. Infect. Dis. 34: S111-S122.

Tapsall J. 2001. Antimicrobial resistance in *Neisseria gonorrhoeae*. World Health Organization. WHO/cds/csr/drs/2001.3.

The European Agency for the Evaluation of Medicinal Products. 1999. Antibiotic resistance in the European Union associated with therapeutic use of veterinary medicines. Report and qualitative risk assessment by the Committee for Veterinary Medicinal Products. July 1999.

Threlfall EJ, Rowe B, Ferguson JL, Ward LR. 1986. Characterization of plasmids conferring resistance to gentamicin and apramycin in strains of *Salmonella typhimurium* phage Type 204 c isolated in Britain. J. Hyg. Camb. 97: 419-426.

Threlfall EJ. 2002. Antimicrobial drug resistance in *Salmonella*: problems and perspectives in food- and water-borne infections. FEMS Microbiol. Rev. 742: 1-8.

Union of Concerned Scientists. 2001. Hogging it: estimates of antimicrobial abuse in livestock. Available online: http://www.ucsusa.org/food/hogging_exec.html. (Accessed September 20, 2002).

Wall PG, Morgan D, Lamden K, Ryan M, Griffin M, Threlfall EJ, Ward LR, Rowe B. 1994. A case control study of infection with an epidemic strain of multiresistant *Salmonella typhimurium* DT104 in England and Wales. Communicable Disease Report 4 (Review no. 11): R130-R135.

Walsh C. 2000. Molecular mechanisms that confer antibacterial drug resistance. Nature 406: 775-781.

Warner F. 1992. Risk: analysis, perception and management: Report of a Royal Society Study Group. The Royal Society. London: pp 1-12.

Wegener HC, Aarestrup FM, Jensen LB, Hammerum AM, Bager F. 1999. Use of antimicrobial growth promoters in food animals and *Enterococcus faecium* resistance to therapeutic antimicrobial drugs in Europe. Emerg. Infect. Dis. 5(3): 329-335.

Wenzel RP, Edmond MB. 2000. Managing antimicrobial resistance. N. Engl. J. Med. 343: 1961-1963.

Witte, W. 1998. Antibiotic use in animal husbandry and resistance development in human infections, Robert Koch Institute, Weernigerode, Germany. Alliance for the Prudent Use of Antibiotics (APUA) Newsletter, Vol.16 (3): 1, 4-6.

Witte W. 2000. Selective pressure by antibiotic use in livestock. Int. J. Antimicrob. Agents 16: S19-S24.

World Health Organization. 1997. The medical impact of the use of antimicrobials in food animals. Report of a WHO Meeting. Berlin, Germany. October 13-17, 1997.

World Health Organization. 2000. WHO global principles for the containment of antimicrobial resistance in animals intended for food. Report of a WHO Consultation. Geneva, Switzerland. June 5-9, 2000.

World Health Organization. 2001. WHO global strategy for containment of antimicrobial resistance. Available online: http://www.who.int/emc/amr_interventions.htm.