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# Health Policy Research Bulletin

## Antimicrobial Resistance: Keeping It In the Box!

The use of antimicrobial drugs, such as antibiotics, to treat infectious diseases is one of the most important milestones in the history of medicine. However, because of the widespread use of these drugs, many strains of the major classes of disease-causing bacteria are now resistant to one or more antibiotics. The growth and spread of resistant microorganisms has become a significant global health issue that has serious and potentially irreversible consequences.

Drawing on evidence from both laboratory research and surveillance monitoring, this issue of the *Health Policy Research Bulletin*:

- describes how microorganisms develop resistance through a process of natural selection and explains how and why antimicrobial resistance (AMR) has become such a complex problem
- explores how the inappropriate use of antimicrobials in human and veterinary medicine, and animal husbandry has contributed to the problem
- examines the impact of AMR on health and the health care system as treatment options become increasingly limited by the diminishing supply of safe, effective and affordable drugs
- explains why a strong evidence base is needed for developing strategies to prevent and control the spread of drug-resistant microorganisms

Finally, although many questions remain, the evidence highlights the need for comprehensive, coordinated action to avert an escalation in resistance and the potential emergence of large-scale outbreaks of drug-resistant infections.

## In this Issue



Canada

## Some Commonly-Used Terms

**Acquired resistance:** The development of antimicrobial resistance through mutation or acquisition of genetic material from other bacteria or the environment.

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

**Antimicrobials:** Natural, semi-synthetic or synthetic substances that are capable of killing or inhibiting the growth of microorganisms. These agents include antibiotics, antivirals, antifungals, disinfectants, antiseptics and sanitizers.

**Antimicrobial drug residue:** Any compound present in the edible tissue of treated animals that results from the use of an antimicrobial drug product, including the original drug, its metabolites and any substance formed in or on food as a result of the use of this antimicrobial drug.

**Antimicrobial resistance:** A condition in which a certain antimicrobial agent becomes ineffective in killing or inhibiting the growth of a targeted microorganism.

**Bacteria:** Single-celled organisms with only one chromosome capable of multiplying by cell division. Many are beneficial; others cause disease in humans, animals and plants.

**Commensal bacteria:** The normal microflora living on the external and internal surfaces of humans or animals.

**Cross resistance:** This develops when microbes exposed to one drug develop resistance to other antimicrobials of the same family.

**Enteric bacteria:** Bacteria which are associated with the intestinal tract of humans and animals, such as *Escherichia, Salmonella* and *Shigella.*

**Foodborne pathogens:** Bacterial pathogens that can be transmitted from animals to humans through the food chain.

**Intrinsic resistance:** The ability of bacterial species to thrive in the presence of antimicrobial agents due to inherent characteristics of the organisms.

**Microorganism or microbe:** Single cell organisms that are too small to be visible to the naked eye, including bacteria, fungi, viruses, protozoa and microalgae.

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

**Prophylactic uses:** Use of antimicrobials for disease prevention.

**Resistance gene:** DNA molecules that contribute to the ability of bacterial species to thrive in the presence of antimicrobial agents.

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

**Virus:** A very small microorganism, consisting primarily of genetic material wrapped in a protein, which can only multiply inside living host cells.

**Zoonoses:** Diseases transmitted between vertebrate animals to humans.

Our mission is to help the people of Canada maintain and improve their health.

*Health Canada*

## About the Health Policy Research Bulletin

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We welcome your feedback and suggestions. Please forward your comments and any address changes to bulletininfo@hc-sc.gc.ca or phone (613) 954-8549 or fax (613) 954-0813. Electronic HTML and PDF versions of the Bulletin are available at: http://www.hc-sc.gc.ca/arad-draa

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# Antimicrobial Resistance: An Escalating Policy Issue

*The following article is based on an interview with* **Diane Kirkpatrick**, *Director General, Veterinary Drugs Directorate, Health Products and Food Branch, Health Canada, conducted by Nancy Hamilton, Managing Editor of the* Health Policy Research Bulletin.

### Q *What is antimicrobial resistance and why is it an important health policy issue?*

Antimicrobials are substances like antibiotics and disinfectants, which can kill or inhibit the growth of microorganisms. However, microorganisms can become resistant to antimicrobials, and when this happens they are no longer destroyed by antimicrobial action. This is known as antimicrobial resistance (AMR). AMR develops when microorganisms are either exposed to antimicrobial agents or when resistance genes are transferred from one organism to another (see the article on page 6). We often hear about the creation of "super bugs" in the lay press — this is basically a reflection of the ability of some pathogenic microorganisms to survive in the presence of antimicrobials or, in other words, to resist treatment and propagate further.

The growth of undesirable microorganisms can outpace our ability to control and mitigate their effects on human health and the health of our environment. As a result, AMR has become a significant health issue. It has narrowed our line of defence against bacterial infections and has left us with fewer effective antibiotics, thereby complicating treatment and leading to greater morbidity and mortality. AMR poses serious economic as well as health policy challenges. For example, recent estimates have shown that drug-resistant infections add $14 million to $26 million in direct hospitalization costs to the annual price of health care in Canada.

### Q *What does current evidence tell us about the human health risks of AMR?*

Although antimicrobials are used in a broad array of applications, available information suggests that the most compelling areas for assessing human health risks relate to antimicrobial use in human and veterinary medicine, and livestock production. Increasingly, patients are being infected with drug-resistant organisms, such as Methicillin-Resistant *Staphylococcus aureus*, Vancomycin-Resistant *Enterococci* and Penicillin-Resistant *Streptococcus pneumoniae*. Indeed, resistant bacterial strains have been observed for most of the major infectious diseases in the world, including malaria, tuberculosis, pneumonia and dysentery. In veterinary medicine and livestock production, there is mounting evidence that drug-resistant bacteria are being transferred from animals to humans, possibly through, food that comes from animals, water, or direct or indirect contact (e.g., soil).

While many questions remain unanswered, current evidence underscores the need for intervention to preclude an escalation of resistance and its adverse health consequences. Given the potentially serious and irreversible consequences of AMR if it is left unchecked, authorities are using the Precautionary Principle/Approach to guide risk management decisions (see the article on page 25).

### *What kinds of strategic policies do we need to prevent AMR and control its spread?*

We need to begin by recognizing that private decisions by individuals about the use of antimicrobials — for example, in a health care or agricultural setting — will have an impact on AMR from a general public perspective. Consequently, to prevent the development of AMR and control its spread, action must be taken within a comprehensive public policy that considers the health benefits and risks of antimicrobial use and the impact of interventions on society.

In human medicine, we need to address issues relating to the essential and non-essential uses of antimicrobial drugs, as well as the how, why and when of prescribing these drugs. In veterinary medicine and animal production, we need to look at how antimicrobials are used to promote growth and prevent disease, in addition to their therapeutic uses. We must also examine the impacts on human health of using the same antimicrobials in animals as we do in human medicine. Strategic policies relating to prudent and judicious use of antimicrobials are needed and their development and application will depend on research, surveillance, education, and infection prevention and control efforts.

### *How is research informing policy in the area of AMR?*

Research is of paramount importance in understanding how AMR develops and spreads. Both scientific research and surveillance monitoring are essential to determine the health benefits and risks of antimicrobial use and to assess the impacts of AMR. The resulting information is vital for the development of appropriate risk management strategies and informed policy decisions. To that end, the federal government's interdepartmental AMR Policy and Science Committees are coordinating research and policy-related AMR activities. These committees have prepared an issue identification paper entitled "Antimicrobial Resistance: Developing a Common Understanding" (see "Who's Doing What?" on page 28). This paper summarizes the "knowns and unknowns" relating to AMR and documents key issues for risk assessment and policy development.

### *What stage is Canada at in the AMR policy development process and what is Health Canada's role?*

Notwithstanding the fact that AMR is a much-debated subject in Canada and internationally, steps have been taken to address the issue. Health Canada is spearheading a number of policy development activities that are consistent with the department's overall Decision-Making Framework. AMR surveillance and tracking systems are being established to generate the data and evidence required to conduct comprehensive risk assessments (see the article on page 20). Guidelines have been drafted for evaluating the microbiological safety of veterinary antimicrobials, taking into account potential AMR implications. While we are pursuing this work from a Canadian perspective, we are also benefiting from linkages being forged with experts both nationally and internationally.

The interdepartmental AMR Policy and Science Committees are addressing a number of key priorities, including the prudent and judicious use of antimicrobials, as well as the type of host factors and environmental conditions that contribute to the development and spread of resistance in bacteria. This work is being assisted by the June 2002 Report from the Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health, as well as the work of the Canadian Committee on Antibiotic Resistance (CCAR). As Health Canada's Deputy Minister Ian Green stated in his keynote speech at the 2002 CCAR national AMR policy conference:

*"The challenge for all of us is to determine a unified and effective way to prevent the development and control the spread of AMR."*

# Did You Know?

*Did You Know? is a regular column of the* Health Policy Research Bulletin *that explores commonly-held misconceptions about health data and information.*

## AMR: Debunking the *Myths*

**Kathy Dobbin**, *Veterinary Drugs Directorate, Health Products and Food Branch, Health Canada*

Myth

***All germs are bad.***

Fact

There are good germs and bad germs. Most of the hundreds of different classes of bacteria are actually good. If you take antibiotics or use antibacterial household products, you will also kill the good germs.

Good germs live on the skin, in the mouth and in the intestines where they help with food digestion and protect against the diseases caused by other bacteria and viruses. Over three trillion bacterial cells — which make up the gut flora — live in the gastrointestinal system. The good bacteria that live on skin are not easily removed by scrubbing.

Bad germs, which can be either viruses or bacteria, cause disease. However, unlike good germs, bad germs usually survive less than 24 hours and are easily removed by scrubbing with regular soap and water.

Myth

***People who rarely take antibiotics don't need to worry about antimicrobial resistance (AMR).***

Fact

Bacteria are antibiotic resistant when they cannot be killed by an antibiotic. It is the bacteria that are resistant, not the individual. Even very healthy people who have *never* taken an antibiotic can become infected with antibiotic-resistant bacteria.

**Did you know . . .** even though antibiotics kill most bacteria, some will survive? It is these survivors that have developed resistance. Antibiotics will not kill resistant germs and, even worse, resistance can be transferred from one bacteria to another.

Myth

***Antibacterial household products are necessary to get rid of household and pet germs.***

Fact

These special cleansing products are not required to eliminate household and pet germs. Furthermore, they can kill good bacteria, which decreases our protection against bad germs. Even bathroom germs can be removed effectively by cleaning with soap and water or household bleach, which don't contain antibacterial agents. They will do just as good a job and won't contribute to AMR.

Myth

***There is no need to worry about AMR because there are so many different kinds of antibiotics.***

Fact

There are various classes of antibiotics and different classes are effective against different illnesses. However, a number of germs are resistant to multiple antibiotics, which means that the number of antibiotics available to treat your particular illness may be limited — and therefore quite costly!

***Look** for more myth busters throughout this issue of the Health Policy Research Bulletin!*

# Antimicrobial Resistance


**Manisha Mehrotra**, *Veterinary Drugs Directorate, Health Products and Food Branch;* **Judy Dougherty**, *Health Care Acquired Infections Division, Population and Public Health Branch; and* **Cornelius Poppe**, *Laboratory for Foodborne Zoonoses, Population and Public Health Branch (Guelph), Health Canada.* *The authors would like to acknowledge the commentary provided by the Canadian Committee on Antibiotic Resistance (CCAR).*

*Antimicrobial resistance (AMR) is a natural process in which microorganisms develop and express resistance to antimicrobial substances. Antimicrobials are widely considered to be one of the most important discoveries in the history of medicine.[1] However, their widespread use has led to increasing treatment problems for a number of common infectious diseases, because some strains of the offending bacteria have become resistant to nearly all known antimicrobial agents. In this article, the authors introduce the term "antimicrobial resistance" and explain how and why bacteria develop resistance to antimicrobial agents.*

## What Are Antimicrobials and Why Are They Used?

Antimicrobials are substances that have the capacity to kill or inhibit the growth of microorganisms. Microorganisms are single cell organisms such as bacteria, fungi and viruses that live virtually everywhere — in soil, air and water, and in the human body. Of the more than 500 different species of bacteria that live in our bodies, some have the potential to cause disease (pathogens), but most are beneficial (commensals) and help with functions such as digesting food and forming barriers against pathogens to prevent infection.

Although antimicrobials can be prepared synthetically, they are also produced naturally as metabolic products of certain bacteria and fungi. For example, some soil bacteria and fungi have the capacity to secrete metabolic products that can inhibit the growth of other soil microbes. This type of antimicrobial action serves to reduce competition and confers an ecological advantage on the microorganisms secreting these antimicrobial substances. It is this unique ability that makes antimicrobial agents (both natural and synthetic) indispensable in controlling the infectious diseases caused by a variety of pathogenic microorganisms.

Over the years, antimicrobials have been used in various ways — most importantly, in human and veterinary medicine to treat infectious disease and in animal husbandry to promote growth and prevent disease in food-producing animals. The use of antimicrobial drugs in human medicine has resulted in spectacular gains in human health and life expectancy.

## Why Do Bacteria Develop Resistance?

Unfortunately, microorganisms can and do develop resistance to antimicrobials. When this occurs, the antimicrobial agent is no longer effective in killing or inhibiting the growth of resistant microorganisms. Since the development of resistance is best studied in bacteria, antimicrobial resistance (AMR) is often defined as the capacity of bacteria to survive exposure to a defined concentration of an antimicrobial

substance. Although resistant bacteria are adept at surviving the effects of antimicrobial agents, they vary in their degree of susceptibility as each antimicrobial agent can act on a spectrum of bacteria. There are two main classes of antimicrobials — "-cidal," which kill the target microorganism and "-static," which can inhibit their growth.

## Resistance — A Natural Process

Resistance is a natural phenomenon that occurs when bacteria that produce antimicrobials act to protect themselves from those same antimicrobials. It has been shown that bacterial resistance was present before antimicrobials were used in human medicine and that this "intrinsic" resistance reflects the evolutionary adaptation of bacteria to natural toxins in their environment. Intrinsic resistance can occur for one of several reasons — the normal antimicrobial target is not present in the bacterial cell, is not susceptible to the antimicrobial, or cannot be reached by the antimicrobial. Intrinsic resistance can also be due to the presence of natural degrading enzymes.

There are two ways a bacterial population can artificially acquire resistance when exposed to an antimicrobial. The first involves a change or mutation in the bacterium's genes,[2] while the second occurs when the bacteria acquires resistance genes present in other bacteria,[3,4] also known as "extrinsic" resistance. Resistance genes can be transferred directly from members of their own species or from an unrelated species. In both cases, the ability to resist an antimicrobial gives bacteria a considerable advantage; they are able to multiply and expand their unique niches by colonizing surfaces and attaching to receptors previously occupied by often harmless or beneficial bacteria that are destroyed by exposure to the antimicrobial.

For a bacterial population to develop resistance, two conditions must be met: the antimicrobial compound must be in prolonged contact with the bacterial population; and the compound must be at a concentration that allows the bacteria to survive (generally referred to as a sub-inhibitory concentration). Resistant bacteria will then be favoured (selected) and multiply at the expense of non-resistant bacteria.[5]

## How Do Humans Contribute to AMR?

Although AMR is a natural process, it has been exacerbated by the abuse, overuse and misuse of antimicrobials. As resistance develops in response to selection pressure exerted by an antimicrobial compound, the use of an antimicrobial for any purpose has the potential to contribute to bacterial resistance. Today, most disease-causing bacteria are resistant to at least some antimicrobials and, in many instances, to a large number of drugs.

Antimicrobials have been used for various purposes, including the treatment of human illness, animal husbandry, aquaculture and agriculture. Their use in common household cleaning products is also becoming widespread and has the potential to compound the problem of AMR. As shown in Table 1, antimicrobial use has become standard practice in many areas. Unfortunately, inappropriate use has also become widespread.

As described in the article on page 10 ("AMR: A Global Human Health Problem"), the overuse and misuse of antimicrobials, such as antibiotics, by doctors, other health personnel and patients is contributing to the increasing severity of AMR in human medicine. The use of an antimicrobial for any infection, in any dose and over any time period, causes a "selective pressure" on microbial populations. Under optimal treatment conditions, the majority of infecting microbes will be killed and the body's immune system will deal with the remainder. However, if a few resistant mutants remain in the population because the treatment is insufficient or the patient is immuno-compromised, the mutants can multiply and cause even more harm. Resistant

**Myth**

*My prescription says to take an antibiotic four times a day. If I only manage to take a couple of pills a day, that should be okay.*

**Fact**

**The interval between doses has been developed to ensure a constant and adequate blood concentration for fighting bacterial infection. Not following instructions may lead to treatment failure and the development of AMR. Proper use of antibiotics is important not only for you and your family, but for your pets as well.**

Table 1: **Factors Contributing to AMR**

## In Human Medicine

- Overuse and misuse of antibiotics, for example:
  - prescribing broad-spectrum antibiotics before receiving a laboratory report of the bacterium's susceptibility
  - prescribing antibiotics for viral infections
  - stopping an antibiotic treatment regime after the symptoms are alleviated but before the treatment is completed
  - organization/daycare policies requiring a doctor's prescription before returning from an illness
- Increased risk of transmission, for example:
  - spread of drug-resistant pathogens in fertile environments such as hospitals, via patient call bells, telephones, etc.
  - lapses in infection control (related to increased workload and limited resources), the most common being health care workers' lack of compliance with hand hygiene recommendations[6,7]
- Increased risk factors for developing infections and thereby resistance, for example:
  - a growing population of immuno-compromised patients
  - increased use of invasive devices and procedures (e.g., central venous catheters, dialysis)
- Emergence of new drug-resistant strains of old infectious diseases (e.g., tuberculosis and malaria)
- Increased trade and travel, resulting in the widespread global transmission of resistant microbes

## In Agricultural and Veterinary Practices

- Use of antibiotics in intense animal husbandry:
  - prophylactic mass treatment against infectious diseases
  - low doses in feed for growth promotion
- Use of growth promoters belonging to the same groups of antibiotics used in human medicine
- Direct transmission of drug-resistant pathogens from:
  - contaminated food (e.g., raw or insufficiently heated milk and milk products, undercooked meat)
  - contaminated water
  - animals to owners and farm workers
- Possible spread of non-metabolized antimicrobials through effluents from animals into the environment
- Use of antimicrobials in plant agriculture (e.g., spray on fruit trees)

## In Consumer Products

- Use of "antibacterial" cleaners and other products containing compounds that are similar to or affect resistance to broad-spectrum antimicrobial drugs[8]

bacteria can then be readily spread from person-to-person in fertile environments such as hospitals and other health care institutions.

The widespread use of antimicrobials outside of human medicine is also a serious concern. As reported in the article on page 16 ("Antimicrobial Use and Resistance in Animals"), approximately half of all antimicrobials produced are used for disease control and growth promotion in food-producing animals destined for human consumption. Practices such as these, which foster the selection of antimicrobial-resistant pathogens in animals, contribute to the potential risk of transmission to humans.

## A Multifaceted Problem

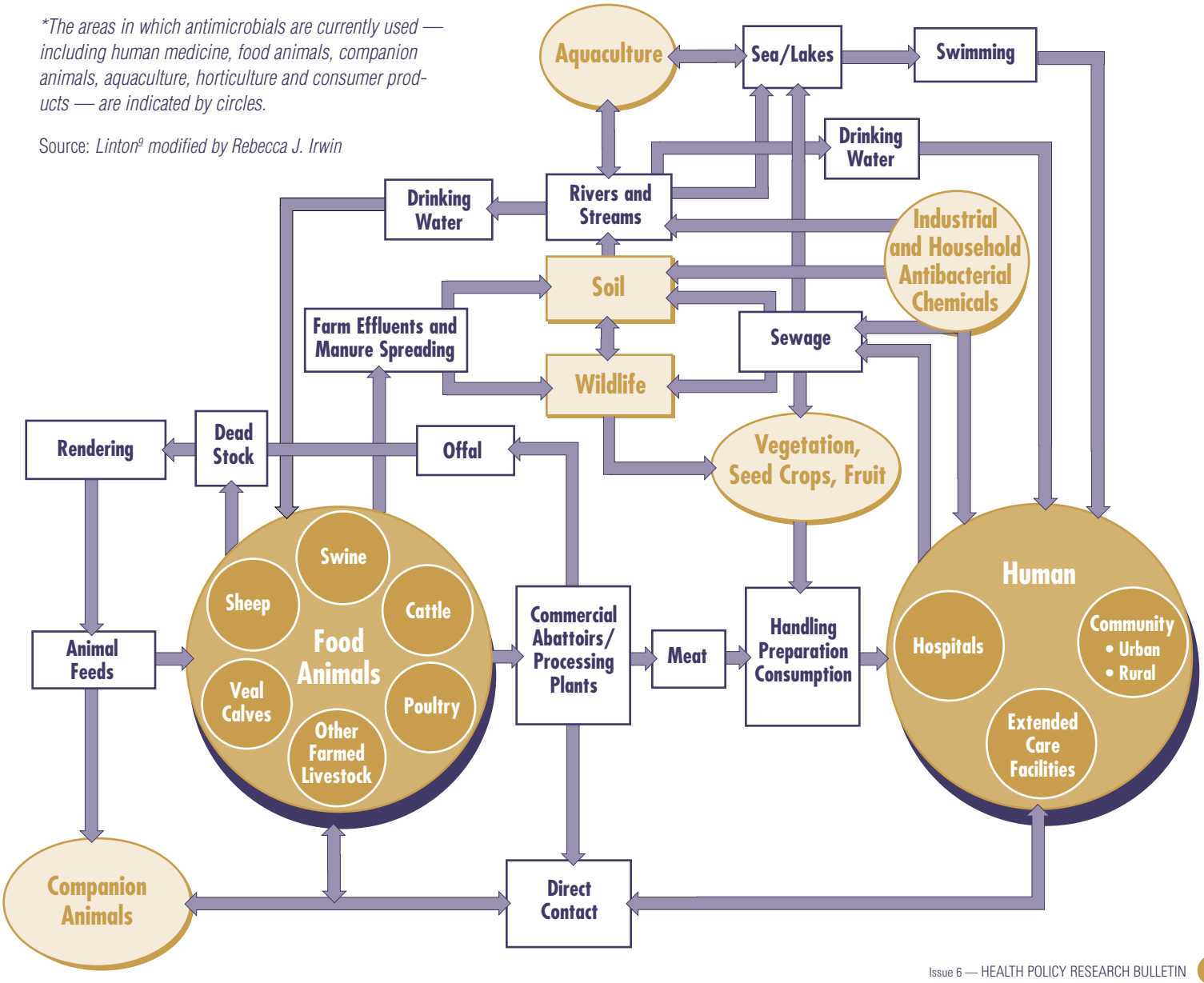
AMR is a complex and multifactorial problem, both in terms of its origins and its impacts. Because bacteria can move freely throughout the environment, the development and spread of resistance easily crosses geographic and other boundaries. As Figure 1 shows, there are many potential pathways by which resistant organisms may be introduced or mobilized between populations of humans, animals, fish, water sources and plants.[9] AMR and its complexities are discussed further in the articles that follow.

*Please note: Full references are available in the electronic version of this issue of the Bulletin: http://www.hc-sc.gc.ca/arad-draa*

Figure 1: **Epidemiology of Antimicrobial Resistance***

**The areas in which antimicrobials are currently used — including human medicine, food animals, companion animals, aquaculture, horticulture and consumer products — are indicated by circles.*

Source: *Linton[9] modified by Rebecca J. Irwin*



# AMR: A Global Human Health Problem

**Judy Dougherty**, *Centre for Infectious Disease Prevention and Control, Population and Public Health Branch;* **Cornelius Poppe**, *Laboratory for Foodborne Zoonoses, Population and Public Health Branch (Guelph); and* **Manisha Mehrotra**, *Veterinary Drugs Directorate, Health Products and Food Branch, Health Canada*

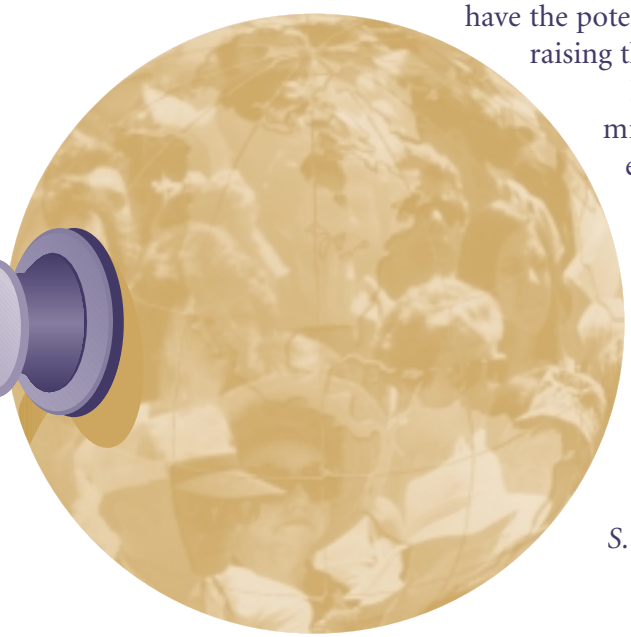
*Antimicrobial resistance (AMR) has become a significant global health problem that crosses many jurisdictional boundaries. This article examines the magnitude of the problem, the impacts of AMR on human health and the resulting burden on the health care system.*

## Introduction

The impact of AMR on human health is enormous. Reports from around the world[1-3] document the increased risk of death, extended and more complex illnesses, lengthened hospital stays, and increased surveillance and infection control costs associated with AMR. When treatment fails or the response to treatment is slow, the patient remains infective for a longer time, leaving more opportunities for the resistant strain to spread.

## A Rapidly Growing Problem

In the past, medicine and science were able to stay ahead of the natural phenomenon of resistance through the discovery of potent new antimicrobials. Today, when a resistant strain emerges, a new "wonder drug" is not necessarily available. Most alarming of all is the advent of microbes that have "accumulated" resistance genes to virtually all currently available drugs. These so-called "super bugs" have the potential to cause untreatable infections, raising the spectre of a post-antibiotic era.



For a growing number of resistant microorganisms, there is either no effective therapy or only one or two antibiotics that are difficult to administer, expensive and have increasingly toxic side effects. The treatment history for infections caused by *Staphylococcus aureus* (see box), a natural part of the skin's bacterial flora, illustrates how rapidly treatment options can diminish.[4]

The incidence of Methicillin-Resistant *S. aureus* (MRSA), as a proportion of

## A History of Diminishing Options

*Staphylococcus aureus* (*S. aureus*) strains showing resistance to penicillin were discovered six decades ago, shortly after penicillin became widely available. Since then, resistance has kept pace with medical science.

- 1960: Discovery of semisynthetic penicillins, such as methicillin, followed rapidly by a report of MRSA in 1961.
- First confined to acute care hospital settings, MRSA is later reported in long-term care facilities and, more recently, in communities around the world.[5]
- 1996: The first strain of *S. aureus* with reduced susceptibility to vancomycin (the treatment of choice for serious MRSA infections) is reported in Japan; subsequent reports appear in the United States and Europe.[6] As of 2003, no cases of *S. aureus* with intermediate or complete resistance to vancomycin have yet been identified in Canada.
- Mid-2002: Reports of clinical infections caused by *S. aureus* that are fully resistant to vancomycin are published in the United States.[7]
- 2001: Introduction of linezolid, the first of a new class of totally synthetic antimicrobials;[8] within a year, reports of resistance emerge.

*S. aureus* isolates, increased from 1 percent in 1995 to 8 percent in 2000.[9] According to data from the recent Canadian Nosocomial Infection Surveillance Program (CNISP), this rate dropped off slightly in 2001 and in the first part of 2002 (see Figure 1).

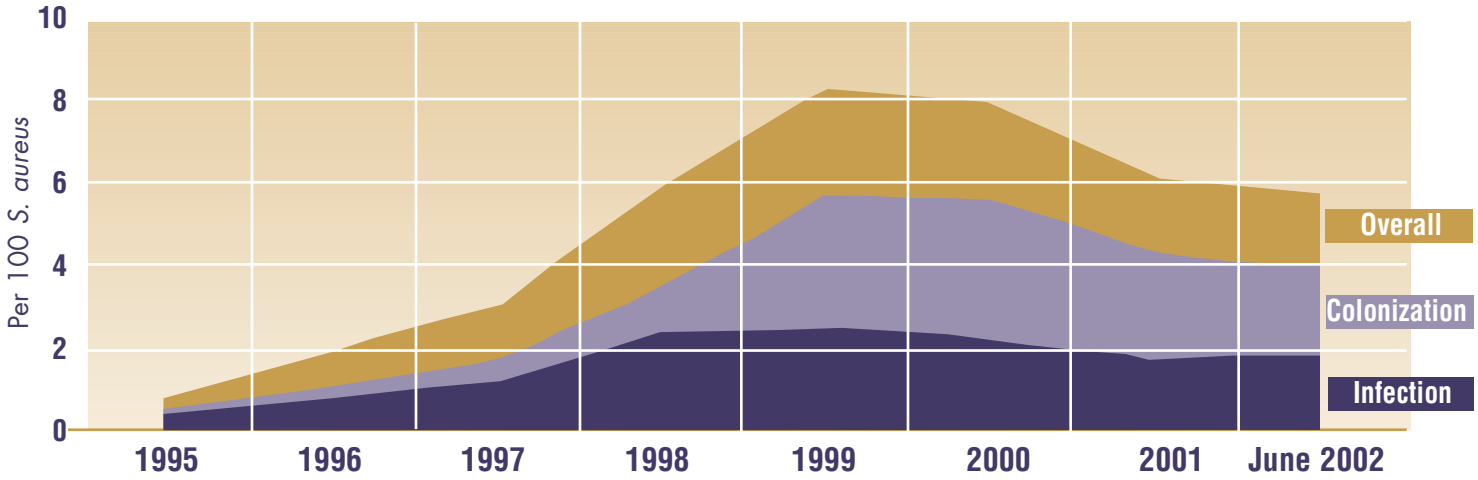
Canadian rates for MRSA and Vancomycin-Resistant *Enterococcus* (VRE) are lower than those in many other countries, a phenomenon that may be due to differences in antimicrobial consumption. Once a critical threshold of antibiotic consumption is reached, resistance grows more rapidly than it decays.[10] This pattern underscores the need for diligent surveillance of antimicrobial use and resistance, as well as early intervention once resistance is detected.

In Canada, there was a significant decline in human antimicrobial prescriptions between 1995 and 2000.[11,12] It is conceivable that Canadians have not yet reached the critical threshold needed to produce a sharp rise in resistance. Although the slight decrease in resistance to *S. aureus* may be due to a reduction in antimicrobial prescriptions, this does not mean that efforts to promote appropriate antimicrobial use should be relaxed — an absence of evidence does not necessarily mean an evidence of absence.

## Impacts on Human Health

Many pathogens other than MRSA and VRE have also become resistant to a range of antimicrobials and may cause serious illness in humans (see Table 1). Each year, *Streptococcus pneumoniae* causes an estimated

Figure 1: **MRSA Rate per 100 *S. aureus*, 1995–June 2002**[13]




*Source: CNISP 2002 MRSA Summary, used with permission.*

**Note: S. aureus denominators may include repeats.*

Table 1: **Resistant Organisms in Canada**

| Resistant Organism | Prevalence | Incidence | Trend | Data Source |
|---|---|---|---|---|
| Methicillin-Resistant *Staphylococcus aureus* | N/A | 3.9 per 1,000 patient admissions | Possible decrease | 1 |
| Vancomycin-Resistant *Enterococcus* | N/A | 0.52 per 1,000 patient admissions | Increase | 1 |
| *Klebsiella pneumoniae*/extended-spectrum beta lactamase (ESBL) resistance | N/A | 0.8% *K. pneumo.* isolates | Not known | 2 |
| *Escherichia coli*/ESBL resistance | N/A | 0.28% *E. coli* isolates | Not known | 2 |
| *Salmonella* species | †40.4% resistance in the strains tested | N/A | Not known | 3 |
| *Shigella* species | ‡96.6% resistance in the strains tested | N/A | Not known | 3 |
| Fluoroquinolone-Resistant *Neisseria gonorrhoeae* | 2.4% | N/A | Increase | 4 |
| Penicillin-Resistant *Streptococcus pneumoniae* (PRSP) | 15.0% | N/A | Increase | 5 |
| Drug-resistant tuberculosis | 10.1% | N/A | Decrease | 6 |
| Multi-drug-resistant tuberculosis (resistance to at least isoniazid and rifampin) | 1.0% | N/A | Stable | 6 |

*Data Sources:*

*1. Canadian Nosocomial Surveillance Program, 2001-2002 data. Data are from hospitalized patients.*
*2. Canadian Nosocomial Surveillance Program, 1999-2000 data.*
*3. National Laboratory for Enteric Pathogens, NML, Winnipeg, 1999-2002 data.*
*Total number of isolates reported: † 26,487 ‡ 4,455.*
*4. National Laboratory for Microbiology, Winnipeg, 1991-2001 data.*
*5. Canadian Bacterial Surveillance Network, 1988-1998 data.*
*6. Tuberculosis, Drug Resistance in Canada, 2001.*

**Myth**

***Antibacterial soap is the only effective way to ensure clean hands and avoid colds or flu.***

**Fact**

**The most effective way to have clean hands and avoid colds or the flu is to wash with regular soap and water. Colds and the flu are caused by viruses, and antibacterials don't work on viruses! Using antibacterial soap is not only ineffective, it can lead to antimicrobial resistance.**

**Myth** *If I cook my meat well, I will not be at any risk of consuming antimicrobial resistant organisms.*

**Fact** **Cooking is not the same as sterilization. Most cooking methods will reduce the population of bacteria and will often kill food-borne pathogens, which is important. However, the remaining bacteria can still carry the genes for AMR.**

500,000 cases of pneumonia, 55,000 cases of bacteraemia and 6,000 cases of meningitis in the United States.[14] In Canada, the prevalence rates of *S. pneumoniae* strains with reduced susceptibility to penicillin rose from 2 percent in the late 1980s[15] to more than 12 percent a decade later.[16] Notably, Canada's rate remains substantially lower than that of many other countries.[9]

Although the precise financial burden associated with antimicrobial resistance is not known, it is estimated that resistance at least doubles the cost of treating a susceptible infection. It also adds between $40 million and $52 million per year to indirect and direct health care costs in Canada.[17] Some of the health care costs attributable to antimicrobial resistance are:[18]

- increased length of hospital stay
- additional investigations (e.g., laboratory and radiological)
- additional drug treatments (as affected individuals are less likely to respond to the first antibiotic used to treat the infection)
- isolation procedures

When bacteria become resistant to first choice or "first-line" drugs, treatment must be switched to second- or third-line drugs, which are often more expensive and less readily available, and have more toxic side effects. For example, the drugs needed to treat multi-drug-resistant forms of tuberculosis are over 100 times more expensive than the first-line drugs used to treat non-resistant forms of the disease.

Reduced treatment options and the increased cost of treatments pose substantial problems. Less tangible, but very disconcerting, is the impact that an antimicrobial-resistant infection has on quality of life. Family, work and social life are seriously disrupted and many people report feelings of depression, anxiety and social isolation as a result of prolonged and uncertain treatment.[17-20]

## Populations at Risk

A person's susceptibility to infection from either an antimicrobial-resistant or antimicrobial-susceptible pathogen, as well as the severity of that infection, depend on the characteristics of the pathogen (i.e., dose and virulence) and the host (i.e., immune status).[21] Populations at particular risk include the following:

### At Risk Due to Increased Vulnerability

- the very old or the very young[22]
- people who have received previous antimicrobial therapy
- people who have undergone an invasive procedure or therapy
- critical care patients (they are often exposed to antibiotic pressure and have disturbances in their normal flora and defence mechanisms)
- people with infections or diseases that compromise their immune response[23]
- patients being treated with immuno-suppressive drugs

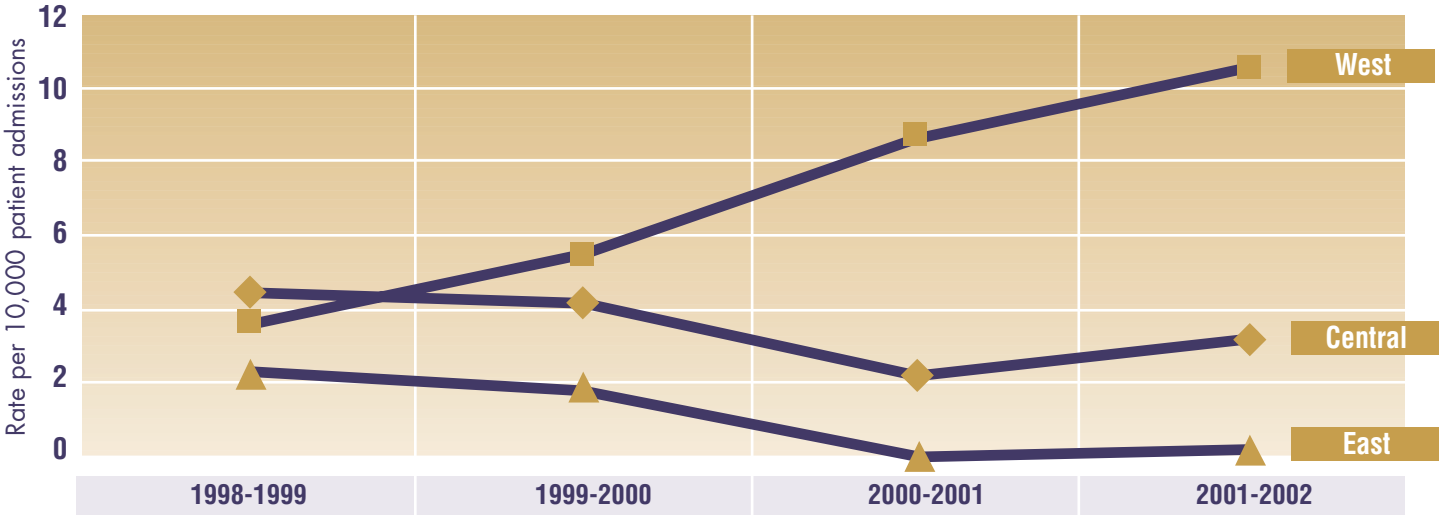
### At Risk Due to Increased Exposure

- recent hospital patients
- people being cared for by common caregivers in an institution with a history of infection with resistant organisms
- those consuming food products contaminated with drug-resistant pathogens
- people having direct contact with animals that are infected with or are shedding resistant enteric pathogens[1]

## Geographic Differences

The significant geographic variation in the rate of infection by drug-resistant pathogens underscores the importance of comprehensive surveillance systems.

Figure 2: **VRE Incidence Rates by Region, per 10,000 Patient Admissions, 1998–2002**




**West** — *Manitoba, Saskatchewan, Alberta, British Columbia* **Central** — *Québec, Ontario* ***East** — *Newfoundland and Labrador, Nova Scotia, New Brunswick*

***Note:** Data for Prince Edward Island not included.* ***Source:** CNISP 2002 Summary, used with permission.*

In large part, national and regional differences reflect the varying patterns of antimicrobial use in agricultural and veterinary practices. For example, until a few years ago, some European countries used the antibiotic avoparcin as a growth promoter in poultry and swine production. These same countries experienced high rates of VRE in their human population.[24] In human medicine, high rates of VRE are generally seen in countries known for high rates of prescribing vancomycin.[25] Correspondingly lower rates for VRE are observed in countries such as Canada, where the use of vancomycin is more judicious. At the same time, however, regional differences for VRE have been reported within Canada (see Figure 2).

There is also evidence of regional and national differences resulting from the consumption of food products contaminated with drug-resistant pathogens. Ethnic background and consumption habits can affect the rate of drug-resistant infections within the population.[26] For example, an Ontario study showed that a high percentage of dairy farmers and their families consume non-pasteurized milk and are at greater risk of becoming infected with drug-resistant pathogens in the milk.[27]

## Prevention and Control Strategies

Although a number of factors have contributed to the problem of AMR, the best documented of these is the inappropriate use of antimicrobials. This includes overuse and over-prescribing, as well as underuse as a result of lack of access, inadequate dosage, poor adherence and inferior drugs. Regardless of the reason, the end result is the same — an infection caused by a resistant microorganism cannot be treated effectively and often leads to a more serious illness or, in some cases, even death.

Prevention and control measures must include the prudent use of antimicrobials in the treatment of infectious diseases in both humans[17,28] and animals.[29] Other actions to prevent infection with, and the spread of, resistant pathogens in hospitals include routine and additional infection control precautions, with thorough

**Myth** *Children's toys should be disinfected with antibacterial soap, especially during cold season.*

**Fact** **Using antibacterial soap on children's toys is a waste of time and money. Washing them in hot, soapy water is all that is needed. Because soap does not contain antibacterials, it does not promote AMR; however, it removes the grease and dirt that attract bad germs.**

handwashing being the most effective preventive action.[30] Although screening of all patients for resistant organisms is not practical, Health Canada recommends targeted surveillance for specific organisms in high risk areas or during outbreaks.[31]

Food- and waterborne infection with drug-resistant pathogens can be prevented by ensuring that adequate quantities of potable water are available and by promoting the consumption of milk, cheese, poultry and other meats that have not been contaminated at the source, or that have been prepared from properly pasteurized products.

## National and International Scope of AMR

Resistant strains have been found in all of the major infectious diseases, including malaria, tuberculosis, pneumonia and dysentery. A growing global public health problem, AMR reflects the failure of many antimicrobial agents to treat infectious diseases effectively. Hospitals worldwide are facing unprecedented crises from the rapid emergence and spread of resistant microbes.

In some developing countries, antimicrobials can be purchased in single doses without a prescription. Because of economic hardship, patients often stop taking an antimicrobial before the bacteria have been completely eliminated. Here in Canada, antimicrobials are available; however, many people simply stop taking their drugs when they begin to feel better, before the treatment regime is finished.

In many developing countries or countries without a publically-funded health plan, the high cost of second- or third-line drugs can be prohibitive when bacteria become resistant to first-line drugs. As a result, some diseases are no longer treated in regions where resistance to first-line drugs is widespread. Although the overall number of antimicrobial prescriptions in Canada has declined over the past five years, the number of prescriptions for second- or third-line drugs has increased.[12]

The exact magnitude of the resistance problem for different pathogens and in various geographic areas is not well known. Hence, there is an urgent need to review current use patterns of antimicrobials across all sectors — in human and veterinary medicine, animal production and aquaculture, as well as in the plant protection industry. As discussed in the article on page 16 ("Antimicrobial Use and Resistance in Animals"), the world's expanding food requirements have led to the widespread use of antimicrobials as growth promoters in food-producing animals. These practices have contributed to a rise in resistant pathogens such as *Salmonella* and *Campylobacter*, which can be transmitted from animals to humans.

## The Need for Global Action

A serious global issue with potentially devastating consequences, AMR requires urgent action. The World Health Organization (WHO) has taken a leadership role in alerting the international community to the severity of the problem. In September 2001, the WHO launched the first global AMR strategy recommending interventions to slow the emergence and reduce the spread of resistance in a diverse range of settings (see "From Science to Policy" on page 25).

*Please note: Full references are available in the electronic version of this issue of the Bulletin: http://www.hc-sc.gc.ca/arad-draa*

**Myth**

***The only way to get rid of a persistent sore throat and/or cough is by taking antibiotics.***

**Fact**

**A common occurrence with colds and flu, most sore throats are caused by viruses. The only way a doctor can tell for certain if a sore throat is caused by a virus or by *Streptococcus* bacteria (strep throat) is by taking a throat swab. Similarly, most coughs are due to viruses, although they can be a symptom of pneumonia. If your doctor suspects pneumonia, an X-ray should be taken and antibiotics are usually prescribed.**

**Did you know . . .**

**colds, flu, croup, laryngitis and most cases of bronchitis (including viral bronchitis) are due to viruses and cannot be helped by antibiotics! In patients with viral bronchitis, 45 percent still have a cough after two weeks and 25 percent have a cough after three weeks. Be patient; it takes a while for your body to recover from a virus.**

# Antimicrobial Use and Resistance in Animals

**Scott McEwen**, *Professor, University of Guelph and Chair of Health Canada's Advisory Committee on Animal Issues and Impact on Resistance and Human Health*

*Human beings do not live in an isolated bubble; we share the environment with plants, animals and a host of microorganisms. As described in the article on page 8, bacteria are a fundamental part of this environment — they live in our bodies and move relatively freely throughout the ecosystem in food, water, air and soil.*

*This article examines the relationship between antimicrobials and one important element of the human environment — animals. For years, antimicrobials have been used to promote growth and to prevent and treat disease in food animals, pets and farmed fish. Yet, there is accumulating evidence that resistance among bacteria in animals can adversely affect human health.*

## How Antimicrobials Are Used in Animals

The human health impact of antimicrobial use in animals is an exceptionally controversial part of the issue of antimicrobial resistance, and one that is not well understood.[1] Because of the large volume of antimicrobials used in animal agriculture — as much as 50 percent of total antimicrobial production by weight[2] — most of the attention on non-human use has focused on this issue.

Antimicrobials are used in food animals for therapy to treat disease, control or prevent infection (prophylaxis), and promote growth and increase production. Although therapeutic treatments may be administered to individual animals, it is often easier and more cost effective to treat entire groups of animals by medicating their feed or water. Prophylactic treatments are typically used during high risk periods for disease, for example, after weaning or transport. Most controversial of all is the use of antimicrobials to enhance growth or performance. That being said, however, the distinction between these categories of use is often blurred, which has important implications for achieving prudent antimicrobial use.

Many antimicrobials are only available with a veterinary prescription; however, most provinces (except Québec) allow others to be sold over-the-counter, either at retail outlets or in feeds. While some of the drugs used in animals have no direct counterpart in human drugs, most classes of animal drugs are also used in humans. Some of these are registered for use in feed as growth promoters or prophylactics.

## Development and Spread of Resistance

As in humans, bacteria in animals can become resistant to antimicrobials through genetic mutation or when resistance genes are transferred from another organism. All antimicrobial use provides some selection pressure favouring

organisms that are resistant to the drug. Moreover, because the genes encoding resistance to multiple drugs are often linked together, the use of one antimicrobial drug may also result in resistance to a completely unrelated drug (co-selection). Although resistance can occur with any type of use, specific concerns have been raised about long-term, low-dose treatments of antimicrobial growth promoters and over-the-counter, in-feed antimicrobials used for prophylaxis.

Resistant bacteria can spread quickly among animals, herds and countries even without the aid of antimicrobial selection pressure. While antimicrobial use is an important consideration, animal management practices, bacterial adaptation, travel and international trade also contribute to the spread of resistance. Moving carrier animals among herds and from country to country contributes to the problem, as does the practice of keeping susceptible animals in close confinement. As food animal production in Canada becomes increasingly intensive, especially in poultry, swine and beef feedlot production, large numbers of susceptible animals are kept in high density areas, encouraging the spread of resistant bacteria. Resistance can then be transferred to humans through food, water or direct animal contact. As illustrated in the figure on page 9, vectors such as rodents, insects and birds also transport resistance determinants throughout the ecosystem.

## Impact on Human and Animal Health

Although many uncertainties remain, recent studies show that agricultural uses of antimicrobials have an impact on human health.[3,4] Resistance among bacteria in animals can have *direct* adverse effects on human health when resistance is transferred through zoonotic infections (from animals to humans). Although most of the recent evidence clearly linking agricultural use of antimicrobials with human health outcomes addresses zoonotic foodborne infections, the magnitude of its impact on human morbidity and mortality is uncertain.[5,6] *Indirect* effects occur when resistance genes in animal bacteria are transferred to human pathogens. There is increasing concern about the reservoir of resistance that is building in enteric commensals of animals that may be transferred to related, or even unrelated, human bacteria through the exchange of genetic material.

Resistance is also a problem in some animal pathogens and becomes an animal health concern when approved drugs lose their effectiveness and veterinarians are forced to prescribe more expensive drugs. In addition to increasing the costs of animal health care, resistance also raises human health concerns when it results in antimicrobial resistant infections in humans that require the use of newer drugs.

*Myth*

***Since vegetarians do not eat meat, they are not affected by AMR associated with food-producing animals.***

**Fact**

**Outbreaks of foodborne diseases are frequently associated with raw fruits and vegetables that are contaminated by human or animal waste. Any foodborne bacteria could be resistant to antimicrobials. Even though you may not eat food produced from animals, you may be affected by bacteria entering the ground water through the feces and urine of food-producing and other animals. This can affect drinking water and irrigation for produce. It is also common practice to spray fruit trees with antibacterial solutions.**

## Strategies to Control Resistance

The most important strategies for controlling antimicrobial resistance among animals include surveillance of antimicrobial use and resistance, effective regulation and the prudent use of antimicrobials in animals. Of particular concern are drugs also used in the treatment of human infections and antimicrobials used in low doses for long periods of time (i.e., growth promoters and prophylactics). Other key strategies include research, educational programs for veterinarians and food animal producers, and reducing the need for antimicrobials through alternative treatments and infection control.

### Improved Surveillance

Current Canadian surveillance data on antimicrobial use and resistance related to both human and animal health are fragmented, drawn from only a few regions and animal species. As discussed in the article on page 20 ("Building an Evidence Base for AMR"), a few focused studies and surveillance projects have been conducted and a number are currently under way. Improved surveillance of

resistance in foodborne bacteria in animals and humans and better monitoring of drug use are essential in identifying human health impacts and determining the effects of intervention strategies. Information about the variance in antimicrobial use and resistance is needed to identify the determinants of antimicrobial resistance and is vital for good policy making and risk-based public health practice.

Some countries (notably Denmark) have developed excellent surveillance systems[7] that have been used to determine when interventions are needed and to measure the effects of interventions on drug use, resistance, animal health and productivity, and human health. Figure 1 shows the impact of removing antimicrobial growth promoters in Denmark on the overall quantities of antimicrobials used.[7]

Figure 2 demonstrates the impact of removing one growth promoter (avoparcin, an antimicrobial related to vancomycin), on Vancomycin-Resistant *Enterococci* (VRE) in food animals.[7] A reduction in avoparcin was followed by a sharp reduction in the prevalence of VRE in poultry broilers while the prevalence of VRE was much slower to decline among swine. Analysis of VRE strains from swine showed that genes encoding resistance to both vancomycin and erythromycin (a macrolide) were closely linked. Stopping the use of tylosin, another macrolide drug, as a growth promoter in swine in 1998 and 1999 was followed by a reduction in VRE, providing strong evidence that the use of tylosin had selected for resistance to vancomycin, a completely unrelated drug.

## Sound Regulatory Policy

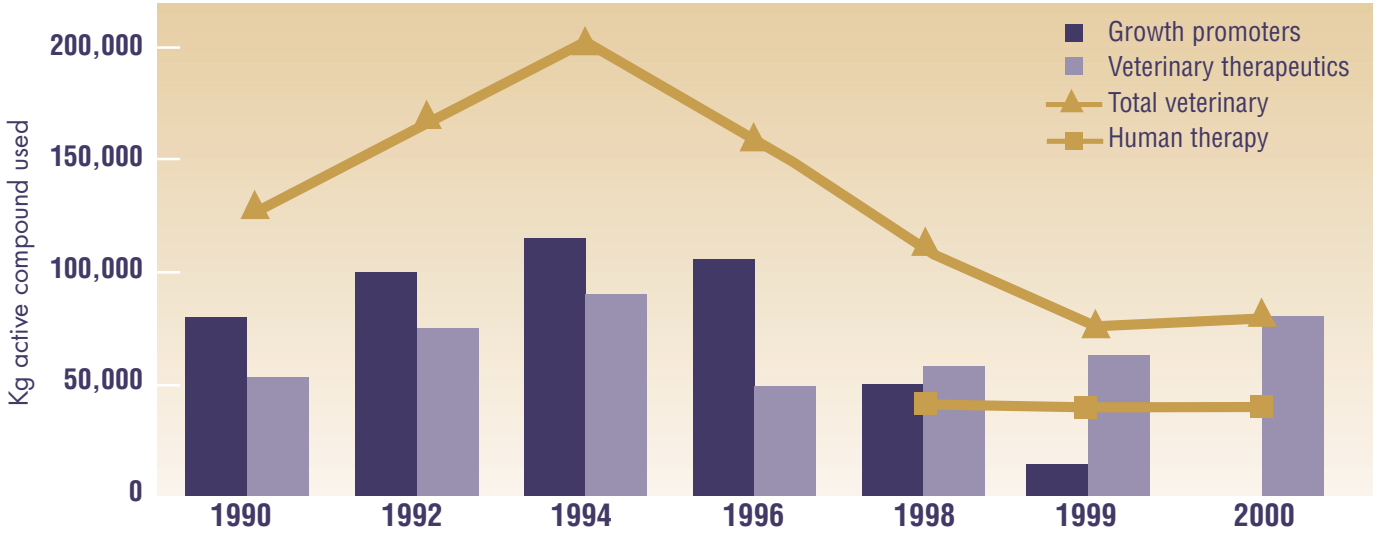
Effective regulation of veterinary drugs is essential in protecting public health. National authorities must decide which drugs may be safely used in animals and under what conditions. As discussed in the article on page 25 ("From Science to Policy"), sound regulatory policy should include a transparent decision-making framework, as well as valid methods and criteria to assess the safety of veterinary drugs with respect to antimicrobial resistance. Substantial research is needed to develop these methods and criteria.

The evolving evidence base on the risks associated with antimicrobial resistant organisms and resistance genes presents new challenges for veterinary drug regulation. Particular areas of regulatory concern include: the approval of new animal drugs, the review of currently approved drugs, the use of antimicrobials without prescription, the importation of antimicrobials by producers for their "own use," the potential for illegal direct use in animals of imported bulk pharmaceutical ingredients, and veterinary prescription for extra-label use.

## Prudent Use of Antimicrobials

Prudent use of antimicrobials (i.e., use that maximizes therapeutic effect while minimizing resistance) is essential in all aspects of animal production.

Figure 1: **Trend in Use of Antimicrobials for Growth Promotion and Therapy in Food Animals and Use for Therapy in Humans in Denmark, 1990–2000**




*Reprinted with permission.*

**Myth** *The antimicrobials used in animal feed are always necessary.*

**Fact** **In-feed antimicrobials may not be necessary to improve the health of livestock. If you are involved in livestock production, make sure you know what antimicrobials are in your feed formulation and why they are there. It is not clear from the scientific literature that all in-feed antimicrobials are efficacious in today's modern livestock-rearing facilities.**

The Canadian Veterinary Medical Association (CVMA) has issued general and specific prudent use principles that, although basically sound, do not provide sufficient incentives or address barriers to their implementation.[8] While some of these barriers are financial, such as possible losses in production efficiency and capital costs for management changes, a major problem is the lack of awareness about resistance issues among veterinarians and producers. On the positive side, many farming groups have developed food safety or quality assurance programs that are showing promise in promoting prudent antimicrobial use.

### Alternatives to Antimicrobials in Animals

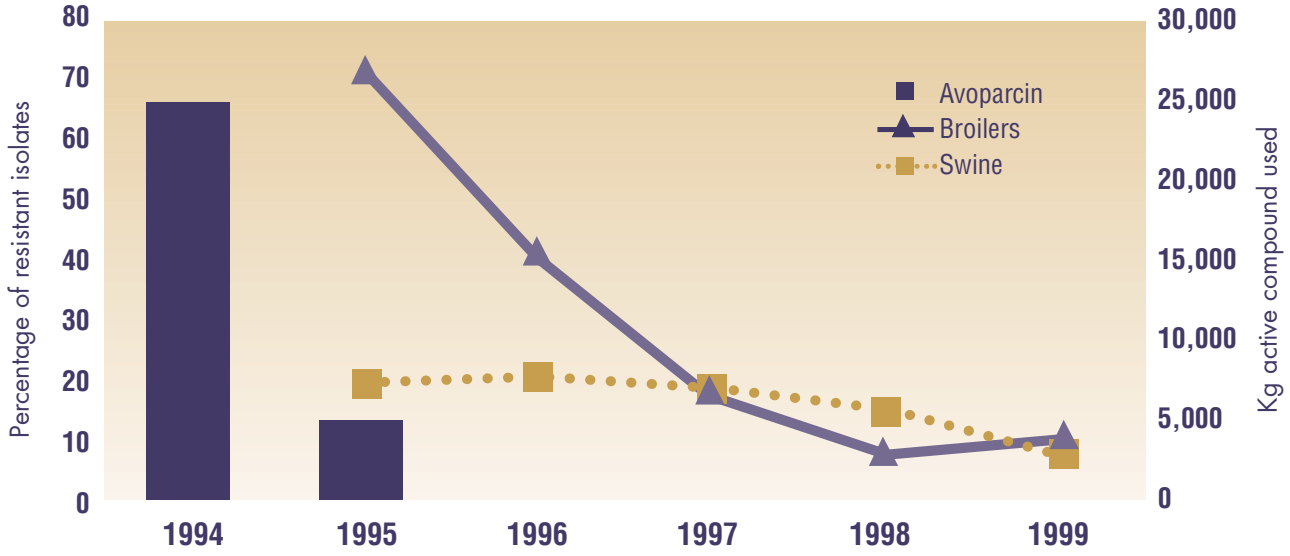
Because most farmers and veterinarians view antimicrobials as effective, efforts to reduce their use must present alternative means of efficiently and humanely raising healthy animals for food. Although various alternatives are available, many are not as effective as antimicrobials. New methods and approaches are needed, especially as alternatives to growth promoters. Improved and more widely used vaccination programs and farm management practices that reduce the likelihood and impact of infectious diseases should help reduce the need for prophylactic and therapeutic treatment.

## A Final Word

In animals, resistance occurs whenever antimicrobials are used, whether for therapy, to prevent disease or to promote growth. Resistance becomes a problem when it reduces the effectiveness of drugs used to treat infections in animals. It is also a problem when resistant bacteria spread from animals to humans, requiring more expensive drugs to treat resistant infections in humans. Sound regulatory policy encouraging the safe and prudent use of antimicrobials is required to reduce the risks of resistance, while research and surveillance are urgently needed to provide the scientific basis for policy and prudent use guidelines.

*Please note: Full references are available in the electronic version of this issue of the Bulletin: http://www.hc-sc.gc.ca/arad-draa*

Figure 2: **Trends in Occurrence of Resistance to Vancomycin Among *E. Faecium* from Broilers and Swine and the Consumption of the Growth Promoter Avoparcin in Denmark, 1994–1999**

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# BUILDING the Evidence Base for Antimicrobial Resistance

*While a substantial body of evidence is emerging on the ecology of antimicrobial resistance (AMR) and its impact on human and animal health, many questions remain unanswered. Building an effective evidence base requires laboratory and field research, surveillance of antimicrobial resistance and antimicrobial use, and integration and interpretation of the resulting data.*

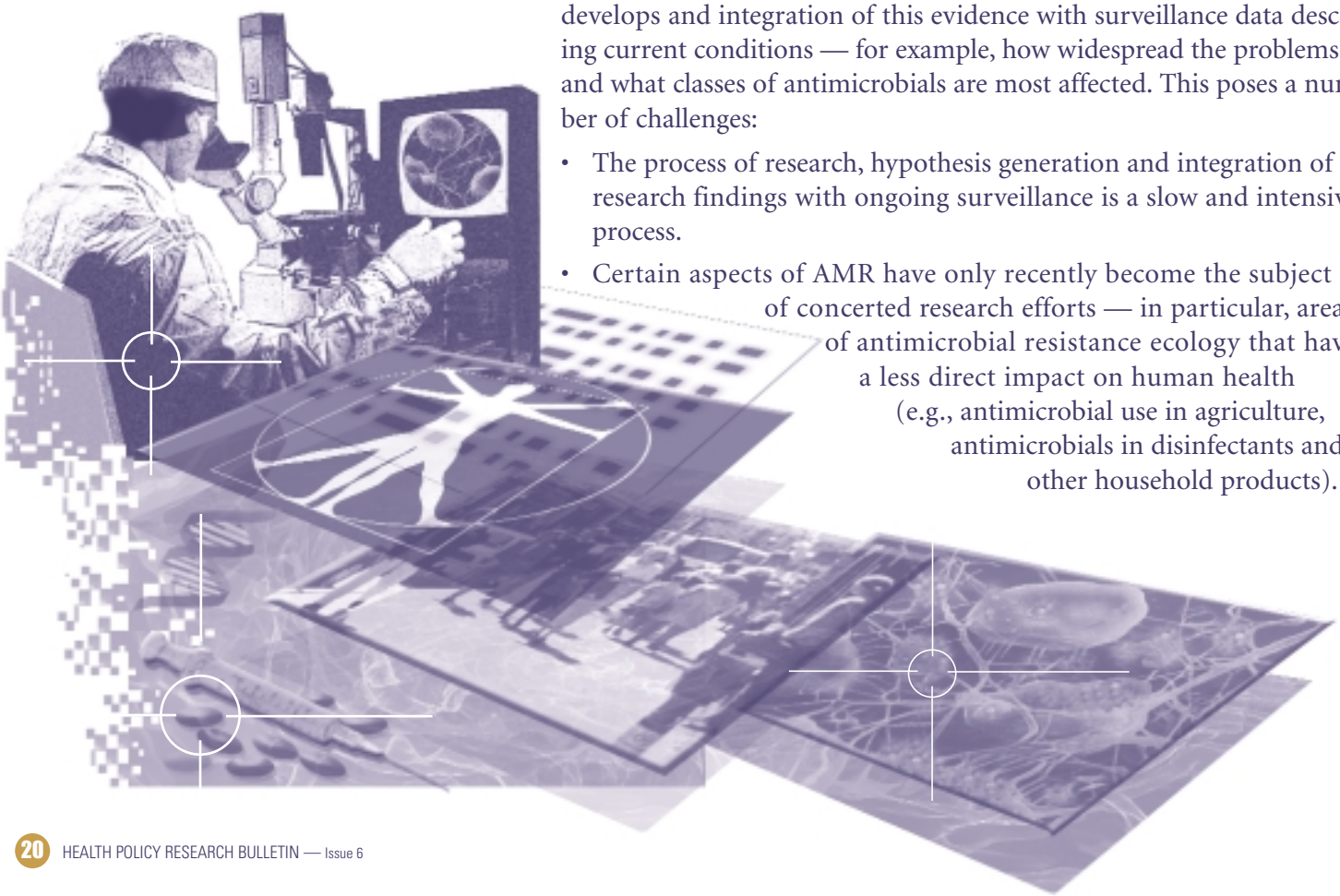
## Introduction

Antimicrobial resistance is a complex problem that includes a vast network of mechanisms and pathways through which resistant bacteria can cause or contribute to illness in humans and animals. In addition, antimicrobial drugs act primarily on the bacteria causing the disease, rather than the host. Antimicrobials also act on other normal gut and skin bacteria that are on or in the host at the time of treatment. A further complication is that antimicrobials can continue to act after they have been excreted in urine or feces — for example, on environmental bacteria.

## The Need for Research and Surveillance

Sorting out the evidence about what contributes to AMR requires a critical appraisal of the strength of research evidence on how AMR develops and integration of this evidence with surveillance data describing current conditions — for example, how widespread the problems are and what classes of antimicrobials are most affected. This poses a number of challenges:

- The process of research, hypothesis generation and integration of research findings with ongoing surveillance is a slow and intensive process.
- Certain aspects of AMR have only recently become the subject of concerted research efforts — in particular, areas of antimicrobial resistance ecology that have a less direct impact on human health (e.g., antimicrobial use in agriculture, antimicrobials in disinfectants and other household products).



- Most AMR surveillance programs have only been under way for a short time.

As a result, there are substantive gaps in the evidence concerning the origins and growth of AMR and the full impacts of antimicrobial use on human and animal health.

## What Contributes the Most to AMR?

The inclination among those who use antimicrobials — including physicians, veterinarians and food animal producers — is to de-emphasize the possible impact of their own use of antimicrobials on AMR, while "pointing the finger" at other sectors. As a consequence, most disagreements about AMR have focused on whether the "blame" for resistance should be attributed to the use and misuse of antimicrobials in animals or in humans. Given the complexity of AMR, it is unlikely that these issues will be easily resolved. Regardless of the extent to which various antimicrobial uses contribute to the overall problem, responsible antimicrobial stewardship requires the judicious use of all antimicrobials, whatever their intended purpose.

Because antimicrobial agents used in agriculture, veterinary medicine and human medicine generally belong to the same or similar class of chemical, they often exhibit similar resistance pressures. For example, without complete information, it would be difficult to know for certain if tetracycline-resistant bacteria found in a raw meat product were the result of tetracycline use on the farm where the meat originated, contamination of the farm's water supply with resistant bacteria from human sewage, or contamination by a slaughter plant worker being treated with tetracycline.

Despite this complexity, there is value in building the evidence base to better understand the interrelationships between antimicrobial use and AMR in all sectors. To be effective, policies and interventions aimed at containing AMR need to target specific aspects of the AMR ecosystem. The stronger the evidence base, the easier it will be to design and evaluate the effectiveness of these interventions.

## The Transfer of Resistance: What Does the Evidence Say?

A number of studies have examined the transfer of resistance among bacterial populations in animals and humans. Considered together, these studies indicate

The following example illustrates how antimicrobial use in one sector may contribute to AMR in another. Similarly, antimicrobial use practices in one part of the world could contribute to AMR problems in another geographic area.

*Enterococci* are enteric bacteria commonly found in both human and animal feces. Although not usually harmful, enterococci can cause disease in immunocompromised patients. *Enterococci* easily become resistant to antibiotics and are a leading cause of hospital-acquired infection.[1,2]

Isolation of Vancomycin-Resistant *Enterococci* (VRE) from healthy people in Europe is relatively common. This has largely been attributed to the widespread use of avoparcin as a growth promoter in swine and poultry production in Europe.[3,4] Although avoparcin was introduced as an antimicrobial growth promoter because it had no application in human medicine, it is a close relative of vancomycin.

There is genetic evidence that the vancomycin resistance genes were transferred from animal source VRE, which was consumed as a contaminant of foods of animal origin, to antimicrobial susceptible *Enterococci* in the human gut.[3,4] In addition, a study of human volunteers who consumed animal-source *Enterococci* showed that the bacteria remain in the human intestinal tract theoretically long enough to transfer resistance genes to resident *Enterococci*.[5] The presence of VRE in the community acts as a reservoir for VRE infections in hospitalized patients. Despite the presence of this reservoir, VRE has not become a major problem, probably because vancomycin is not often used in European hospitals.[3]

However, vancomycin *is* heavily used in American hospitals, where it is typically a last line of defence for treating enterococcal infections. When VRE was introduced into American hospitals in 1989, it became a major problem despite the fact that avoparcin had never been used in North American agriculture and VRE had not been identified in the community. Although it is not known for certain if VRE was introduced into the United States from Europe, travel between the continents and imported foods are plausible primary sources of VRE for hospital infections.[4,6]

that all antimicrobial use, whether directed at animal, human or other bacteria, contributes to the overall burden of AMR in human pathogens.[6] Since it is ethically difficult to design experimental studies demonstrating the direct transfer of resistant bacteria or resistance genes among animal and human populations, investigators generally rely on laboratory experiments, observational studies (e.g., case control studies) and surveillance data. As illustrated in the box on page 21, some interesting findings are emerging about the relationship between antimicrobial use and the development of resistance in exposed populations.

## The Role of Surveillance

Surveillance of AMR is critical in providing context for the results of laboratory and field research, and for monitoring the effectiveness of policies and other interventions. However, surveillance data must be interpreted in light of the strengths and weaknesses of the surveillance program that generated the data. These data are often acquired through **passive surveillance** techniques, such as diagnostic laboratory submissions, which have the advantage of using existing reporting mechanisms. Unfortunately, passive techniques generally record only the most severe incidents, or those occurring in known susceptible populations (e.g., infants, the elderly), which generally represent a small proportion of the true number of incidents. For example, of the estimated 1.4 million cases of non-typhoidal *Salmonella* in the United States each year, only 2.7 percent were recorded through passive surveillance.[7]

Passive surveillance systems may also be hampered by other factors such as lack of data on at-risk populations, incompatibility among the system contributors, and the lack of systematic data collection methods and comparability in laboratory methods. For these reasons, traditional passive surveillance systems do not provide a comprehensive view of the current situation but, rather, a "tip-of-the-iceberg" picture and an indication of emerging issues. **Active surveillance**, on the other hand, strives to gather data that is statistically representative of the general population. Although they require substantial resources and are more difficult to administer,[8] several active surveillance programs are currently providing critical data in the human health arena.

Surveillance data are needed to provide information on variations in AMR occurrence both geographically and over time, and on variations in antibiotic use and other suspected determinants of AMR. These data are critical for identifying correlations and, eventually, causation, as well as informing decisions on interventions and evaluating their effectiveness.

### Monitoring and Tracking Resistance

In Canada, there are several AMR surveillance programs already under way including the Canadian Nosocomial Infection Surveillance Program (CNISP), which is highlighted in "AMR: A Global Human Health Problem," on page 10; and the gonorrhea surveillance program described in "Using Real-Time Data in Decision Making" on page 31.

Efforts to assess the impact on human health of antimicrobial drug use in food animals has been hampered by the relative lack of representative data on AMR in enteric bacteria (e.g., *Salmonella, Campylobacter, E. coli*) of animal, food and human origin. Prevalence, incidence and trend data are available for several antimicrobial resistant organisms (AROs) (see Table 1 in "AMR: A Global Human Health Problem" on page 12) but the

*Myth*

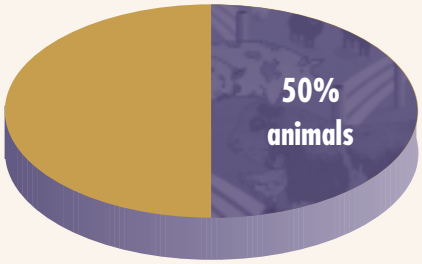
***Leftover antibiotics can be used the "next time," or given to another family member.***

**Fact**

**It is important to take all the antibiotics that are prescribed. While your symptoms may disappear, the bacteria may not all be destroyed. Surviving bacteria are those most resistant and produce a bacterial population that is more resistant to the antibiotic. Moreover, you should never give leftover antibiotics to someone else, or save them for another time. In the first place, an antibiotic that is prescribed for a specific infection may not be effective against a different one. Secondly, there may not be enough antibiotic left to effectively kill the bad bacteria the second time around. And remember — don't throw antibiotics away or flush them down a drain because they will go into a landfill or into the water table. All of these actions can contribute to AMR. Instead, return unused antibiotics to a pharmacy, where they will be disposed of properly.**

## Key Use Data

Estimates of the proportion of antimicrobials used in animals versus humans vary because of the lack of quantitative use data available (see "Antimicrobial Use and Resistance in Animals" on page 16). However, the most widely quoted estimate is that about half of all antimicrobials in the United States are used in animals.[9] In the United States, 20 percent to 50 percent of antimicrobials prescribed in the community are deemed inappropriate. For example, up to 50 percent of patients with viral rhinitis (runny nose due to a cold) are prescribed antimicrobials. In hospital settings 25 percent to 45 percent of antimicrobial use is inappropriate.[10,11] Little similar data are available for agriculture and veterinary medicine; however, even without considering whether it is appropriate to use antimicrobials as growth promoters, it seems likely that some antimicrobial use by veterinarians and farmers may be injudicious.




**The most widely quoted estimate is that about half of all antimicrobials in the United States are used in animals.[9]**

data on *Salmonella* and *Shigella* are typically incomplete due to under-reporting.[7] Until recently, Canadian surveillance data on enteric AROs of animal and human origin were restricted to passive surveillance of *Salmonella* and *Shigella*.[12,13] In most countries, data on resistance in bacteria of animal origin, enteric or otherwise, are provided by passive surveillance systems. Some countries, including Denmark and the United States, have developed more active animal-origin AMR surveillance systems.[14,15] As described in the previous article (page 16), these data have been used to document the efficacy of public policy interventions by demonstrating the magnitude of the change in resistance in important pathogenic and commensal bacteria.

### Monitoring Antimicrobial Drug Use

A number of reports[16-18] have stated that monitoring the use of antimicrobials in animals and humans is essential to control the development of AMR in bacteria affecting the health of humans and animals. As discussed in "AMR: A Global Human Health Problem" on page 10, some human use data is available in Canada.[19,20] These data provide a useful, albeit incomplete, picture of antimicrobial use in humans (see box). In contrast, publicly available data on antimicrobial use in food animals are scarce in Canada, making it difficult to determine which drugs are used, in what quantities, and for what purposes.[21] This also contributes to difficulties in understanding the relationship between antimicrobial use and the emergence and spread of resistance among animals and between human and animal populations.[18]

### Integrated Surveillance Systems

Several European countries have developed integrated surveillance systems incorporating antimicrobial use monitoring with resistance surveillance.[15,22,23] Data collection is facilitated by regulations mandating that antimicrobials be available by prescription only and

**Myth**

*The only way to clear up ear infections in children is to take antibiotics.*

**Fact**

**Because of the risk of developing AMR, prescribing antibiotics is no longer recommended for children with frequent ear infections. Up to 80 percent of children with ear infections will get better without antibiotics. Wash your hands frequently and urge your children to wash their hands regularly since most ear infections occur after a cold.**

that both animal and human prescriptions be filled at a pharmacy. Information is collected from a central database of pharmaceutical sales data, as well as from prescription databases. The report of the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP) includes data on annual antimicrobial use, along with data on human consumption, and animal, food, and human AMR. Such reporting is proving invaluable in evaluating the impact of regulatory decisions on the prevalence of resistance in human and animal populations.[15]

### CIPARS — Integrating Surveillance in Canada

Health Canada has been working with its partners to develop a nationally integrated program for the surveillance of enteric AROs. Under development for several years, the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) has launched several projects in both the human and veterinary sectors (see "Who's Doing What?" on page 28 for contact information). CIPARS is currently collecting information on antimicrobial use and AMR in enteric bacteria found in animals and humans.

Preliminary projects have also been developed to test the feasibility of a representative, methodologically-unified approach to surveillance. Modelled after initiatives such as DANMAP and the National Antimicrobial Resistance Monitoring System (NARMS) in the United States, these projects will monitor trends in the development of AMR in enteric bacteria isolated from humans and animal and food sources. Targeted research projects, including farm and retail studies, have also been launched to support these surveillance initiatives.

A pilot project of the human component of CIPARS was launched in early 2003 as a collaborative project coordinated by Health Canada and involving all provincial public health laboratories. Isolates recovered from human cases of *Salmonella* are forwarded to Health Canada for AMR testing. These data will be integrated with agri-food data and information about antimicrobial use to examine AMR along the food chain. Work continues on the development of systems for monitoring antimicrobial use in agriculture and veterinary medicine, and in the treatment of human enteric illness.

*Myth*

*Handwashing won't stop the spread of infections and colds.*

**Fact**

**Washing your hands makes a big difference! Up to 80 percent of infections are passed hand to hand. When recruits at the Health Naval Research Center in San Diego were told to wash their hands at least five times a day, the result was a 45 percent reduction in respiratory illnesses. It's especially important to wash your hands after being around someone who has a cold or the flu.**

**Did you know . . .**

**using a hot air dryer after washing your hands leaves them warm and moist — an excellent breeding ground for bad germs. Studies show that drying your hands with a towel is 42 percent more effective than just washing them (but don't share towels).**

## Moving Forward

As enhanced mechanisms for collecting AMR surveillance data and the technologies for managing it are developed, it will be more feasible to link surveillance data from various sources. For instance, the Canadian Integrated Public Health Surveillance Program (CIPHS) is a recent national initiative that encourages sharing of health data among local, provincial/territorial and federal heath authorities.[24] As well, developments in molecular genetics and new epidemiological techniques will make it easier to interpret surveillance information and integrate it with research data. As our understanding of the ecology of AMR improves, so too will our capacity to provide credible data for risk assessment and policy making.

*Please note: Full references are available in the electronic version of this issue of the Bulletin: http://www.hc-sc.gc.ca/arad-draa*

# From Science to Policy

**Lateef Adewoye, PhD**, *Veterinary Drugs Directorate, Health Products and Food Branch, Health Canada*

*Given the global nature of antimicrobial resistance (AMR), policy action is needed at a number of levels. Action must be based on evidence from both scientific research and surveillance monitoring. Although the evidence base for AMR is growing, many uncertainties remain. However, because of the potentially serious health threats posed by AMR, decisions often must be made in the absence of complete scientific evidence. This article explores current regulatory challenges related to AMR, discusses how a precautionary approach is guiding risk management decisions and examines Canada's AMR strategy within the context of international action to minimize the development and spread of antimicrobial resistance.*

## Introduction

Bacterial resistance was observed almost as soon as the first antibiotic, penicillin, was discovered 75 years ago. Yet, it is only in the last decade that the alarming increase in AMR has been seen. As discussed in previous articles, the complexity of AMR reflects the wide range of uses for antimicrobials and the varied mechanisms through which bacteria become drug resistant. In response to the seemingly ubiquitous use of antimicrobials, several national and international organizations are developing strategies to minimize the development and spread of antimicrobial-resistant organisms. The World Health Organization (WHO) is at the forefront of such efforts with its 2001 release of the first Global Strategy for Containment of Antimicrobial Resistance,[1] which is based on extensive consultations with international scientific and policy experts (see "Who's Doing What?" on page 28).

## How Are Science and Research Informing Policy?

Advances in science and technology almost always lead to new ways of thinking and create new policy challenges. Likewise, policy evolves with advances in scientific knowledge and information on risk assessments. For issues as complex as AMR, policy making requires a systematic consideration of evidence from a variety of sources. Where direct scientific evidence has been available, it has weighed heavily in the decision-making process. For example, the ban on the use of the antibiotic avoparcin in Denmark was based on direct scientific research and surveillance evidence linking avoparcin use in food animals to an increase in vancomycin-resistant bacteria in human populations.[2]

Sometimes, decisions must be made even when scientific evidence is absent or insufficient. In situations where there are serious or irreversible threats to human health, jurisdictions use the precautionary approach or principle to guide risk management decisions. In Europe, for instance, certain antimicrobial growth promotants used in livestock production were banned in 1999 because of their potential risks to human health.

### Managing Risks: The Precautionary Approach

The high probability of a severe or irreversible health impact makes a good case for taking special care. Given the incomplete evidence base for AMR and its serious and potentially irreversible health threats, regulatory bodies must use a precautionary approach in managing public health

risks. This does not mean, however, that decisions are made without considering available evidence. Rather, there can be a defensible scientific basis for decision making even though the level of evidence falls short of full scientific proof.

In a risk management approach, a critical step in assembling the evidence is identifying the **hazard** and determining the nature of the **risk**. In the case of AMR, there are three clearly distinct, but closely related hazards — the antimicrobial agents themselves, the antimicrobial resistant organisms and the antimicrobial resistance genes.[3] Because the implications of broad antimicrobial use were not initially obvious, many antimicrobials in use today were approved based on information that was required by regulatory agencies when the drugs were approved. In retrospect, it appears that over the past few decades the regulatory process focused on the hazards posed by the antimicrobial agent rather than the hazards posed by the resistant organisms and the resistance genes. Over the years, the extensive use of antimicrobials across all sectors, including overuse and inappropriate use, has exacerbated the problem. Sound risk analysis of all AMR hazards is imperative to accurately determine the extent of the problem.

Regulatory agencies face a number of risk assessment challenges in evaluating the link between antimicrobial use and the development of antimicrobial-resistant bacteria in humans: How do we assess the release of hazards, the level of human exposure and the consequences of such exposure? Are alternative antimicrobial therapies available for human infections caused by resistant bacteria? What are the anticipated risks? While the goal is to reduce the level of uncertainty in decision making, if scientific uncertainties persist, risk management measures must be put in place to protect human health.

The regulatory challenges are daunting, particularly given the number of "unknowns" about AMR. When available, scientific data must be considered in the context of a broad array of social, ethical, economic, behavioural and environmental issues. Additionally, risk management decisions must take into account the impacts on individuals and communities, human and animal health, and health economics, as well as on international trade and the global movement of people, products and animals.

## Evolving Evidence: Ongoing Regulatory Challenges

Policy makers must take into account the evolving scientific understanding of AMR when developing new policies and guidelines for infection prevention and the prudent use of antimicrobials, and when assessing the safety of antimicrobial products. Until recently, the regulatory focus was on antimicrobial drug residues, not antimicrobial resistance. As a consequence, federal regulations in animal husbandry have been in place for some time, limiting drug residues and establishing withdrawal periods for antimicrobials before animals are slaughtered. However, the growing use of antimicrobials worldwide has increased the selective pressure in many animal species so that reservoirs of resistant organisms now exist. This has led to new regulatory concerns and questions about the public health implications of AMR.

The regulatory challenges are daunting, particularly given the number of "unknowns" about AMR. When available, scientific data must be considered in the context of a broad array of social, ethical, economic, behavioural and environmental issues. Additionally, risk management decisions must take into account the impacts on individuals and communities, human and animal health, and health economics, as well as on international trade and the global movement of people, products and animals.

A recent study assessing the human and financial burden of drug-resistant infections in Canada showed that drug costs alone could escalate to at least $1.8 billion from current levels of $659 million if drug resistance were to rise to endemic levels.[4] The potential impact on health care costs, as well as the impacts on morbidity and mortality, are key public health issues that require governmental intervention. The cornerstone

of any meaningful intervention must rest on a scientific understanding of the risks and how best to minimize them.

As discussed in the article on page 20, scientific evidence is being gleaned from a number of surveillance and research activities. Surveillance systems have been the driving force for the detection of antimicrobial-resistant bacteria worldwide. Scientific research has informed our understanding of the mechanisms of bacterial resistance and the spread of resistant bacteria or resistance traits. Health Canada is spearheading a variety of research projects on AMR within the department and in collaboration with external partners. Measures are also being taken to harmonize Canada's AMR strategy with those of its trading partners. As part of this overall strategy, the policy recommendations of Health Canada's AMR Advisory Committee are being considered in risk management decisions concerning the use of antimicrobials in food-producing animals.[5]

## A Canadian Strategy for Controlling AMR

Due to the potential impacts on public health, agriculture and the environment, the federal government is developing overarching policies to address the emergence and spread of AMR. Although AMR is a multifaceted phenomenon for which scientific consensus is often lacking, there are increasing areas of scientific agreement that provide the starting points for moving forward.

Several international reports have highlighted the need for scientific evidence in making regulatory decisions or formulating intervention strategies. Health Canada places a high priority on obtaining such information, as demonstrated by the recently established Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS; see article on page 20).

The spectre of AMR pervades every segment of society. For this reason, risk management and the development of action strategies must involve all concerned groups and authorities, including industry, labour, interest groups, professional organizations, research institutions and interested individuals, as well as federal, provincial and territorial authorities. The involvement of these stakeholder groups is especially important given the unique information they can contribute to the evidence base and risk assessment models, including data on antimicrobial use by commodity groups (sales data), drug efficacy, bacterial resistance and animal health benefits.

## What is the National Action Plan on AMR?

In the interests of developing a national action plan for controlling antimicrobial resistance, Health Canada cosponsored a consensus conference with the Canadian Infectious Diseases Society in May 1997. The conference produced 27 recommendations focusing on antimicrobial use, detecting resistance, creating partnerships and evaluating the action plan.

While certain aspects of the plan have been implemented, much remains to be done. In October 2002, the Canadian Committee on Antibiotic Resistance (CCAR) organized a follow-up National Policy Conference to propel action on many of the remaining recommendations. Although the Canadian health care system has mechanisms in place to prevent the emergence and spread of drug-resistant bacteria, it is essential that members work together to build on these. A number of provinces and national organizations are engaged in several such initiatives (see "Who's Doing What?" on page 28).

## In the Midst of Uncertainties!

Notwithstanding the complexity of AMR, Canada is steadily gathering new evidence and information. Because AMR is a global issue, exchanging information with other countries is vital to developing strategies for dealing with AMR. The involvement of stakeholder groups at every stage of risk assessment and management adheres firmly to the principles of Health Canada's Decision-Making Framework,[6] ensuring that the full range of issues is captured and decisions are made in the broader context. In a world where science is in a state of flux, the readiness of regulatory agencies to invest in and use information will determine the success of risk assessment and management processes.

*Please note: Full references are available in the electronic version of this issue of the Bulletin: http://www.hc-sc.gc.ca/arad-draa*

# Who's Doing What?

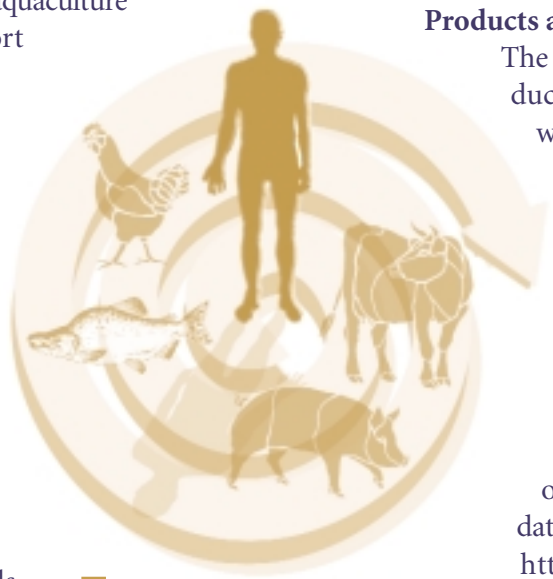
*Who's Doing What? is a regular column of the Health Policy Research Bulletin that profiles key players involved in policy research in the current theme area. Key players in the forefront of the fight against AMR include governmental and non-governmental organizations at the local, national and international levels.*

**Lateef Adewoye, PhD**, *and* **Kathy Dobbin**, *Veterinary Drugs Directorate, Health Products and Food Branch, Health Canada*

## In Canada

- **Health Canada's Advisory Committee on Animal Uses of Antimicrobials and Impact on Resistance and Human Health**
  The Advisory Committee was created in 1999 to provide advice on the development of policies, surveillance and research related to the use of antimicrobials in the agri-food and aquaculture sectors. The committee's final report was presented to Health Canada in June 2002 (available at: http://www.hc-sc.gc.ca/vetdrugs-medsvet/amr_final_response_to_ac_cp_e.html).

- **Veterinary Drugs Directorate (VDD), Health Products and Food Branch, Health Canada**
  VDD is leading the development of policies on animal uses of antimicrobial agents. In keeping with its responsibility for approving the use of antimicrobials in animals, VDD is assessing regulatory and data requirement issues related to veterinary antimicrobial products. It also chairs the interdepartmental AMR Policy Committee, which together with the interdepartmental AMR Science Committee, assesses AMR risks and develops risk management strategies and Canadian policies on human and non-human uses of antimicrobial agents (available at: http://www.hc-sc.gc.ca/vetdrugs-medsvet/index_e.html).



**The Veterinary Drugs Directorate is leading the development of policies on animal uses of antimicrobial agents. In keeping with its responsibility for approving the use of antimicrobials in animals, VDD is assessing regulatory and data requirement issues related to veterinary antimicrobial products.**

- **National Microbiology Laboratory (NML)**
  NML manages an ongoing AMR research and surveillance program for enteric pathogens, *Neisseria gonorrhoeae*, *N. meningititis*, *Mycobacterium tuberculosis*, nosocomial acquired infections and other bacterial/viral pathogens. E-mail Lai_King_Ng@hc-sc.gc.ca for more information.

- **Laboratory for Foodborne Zoonoses (LFZ), Population and Public Health Branch, Health Canada**
  LFZ coordinates the development of an integrated AMR surveillance and antimicrobial use monitoring program in the agri-food and aquaculture sectors and is active in research on AMR at the human–animal–environment interface.

- **Bureau of Chemical Safety (BCS) and Bureau of Microbial Hazards (BMH), Food Directorate, Health Products and Food Branch, Health Canada**
  The BCS and BMH have been conducting research on AMR associated with antimicrobial use in the agri-food and aquaculture sectors, and on human exposure to veterinary drug residues for risk assessment purposes.

- **Canadian Bacterial Surveillance Network (CBSN)**
  CBSN studies the prevalence, mechanisms and epidemiology of AMR and publishes resistance data for select human pathogens (see: http://microbiology.mtsinai.on.ca/research/cbsn.shtml).

- **Health Canada's Centre for Infectious Disease Prevention and Control (CIDPC)**
  The CIDPC is actively involved in AMR surveillance and collaborates with other groups to develop guidelines on infection prevention and control (see: http://www.hc-sc.gc.ca/pphb-dgspsp/centres_e.html or http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/noib-inpb/index.html).

- **Canadian Committee on Antibiotic Resistance (CCAR)**
  Created by Health Canada in 1997 following a national consensus conference on antibiotic resistance, CCAR publishes articles and undertakes a variety of AMR communications activities, including the recent National Policy Conference on Antibiotic Resistance advancing the National Action Plan on AMR (see: http://www.ccar-ccra.com/).
- **Canadian Institute for Health Research (CIHR)**
  CIHR's Institutes of Infection and Immunity, and Population and Public Health are collaborating with Health Canada and several other federal government departments to fund research projects on AMR in the food chain under the "Safe Food and Water Research Initiative" (see: http://www.cihr-irsc.gc.ca/institutes/iii/funding/2002_opportunities_e.shtml).

## In the Provinces

Several provinces are involved in activities aimed at managing AMR. These range from an AMR action plan in British Columbia to the "Do Bugs Need Drugs" (http://www.dobugsneeddrugs.org) initiative in Alberta and the EQUIRE (Étude Québécoise sur les pathogènes respiratoires) surveillance network in Québec.[1]

## On the International Front

- **World Health Organization (WHO)**
  The WHO addresses the impacts of AMR as part of its global outreach efforts and recently published a global strategy for the containment of AMR (see: http://www.who.int/emc/amr_interventions.htm).
- **VICH**
  The work of the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) is coordinated by the International Federation for Animal Health (IFAH). The AMR Working Group of the VICH recently released a guidance document entitled "Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food Producing Animals with Respect to Antimicrobial Resistance" (available at: http://www.oie.int/eng/OIE/en_oie.htm).
- **FDA/Center for Veterinary Medicine (CVM), USA**
  CVM approves the use of antimicrobials in food-producing animals in the United States, engages in risk assessment of antimicrobial use in animals and develops new AMR policies (see: http://www.fda.gov/cvm/antimicrobial/antimicrobial.html).
- **US Centers for Disease Control and Prevention (CDC)**
  The CDC is leading the campaign to prevent antibiotic resistance in health care settings and to promote appropriate antibiotic use in the community. CDC cochairs the Federal Interagency AMR Task Force, which recently developed the US Public Health Action Plan to Combat AMR (available at: http://www.cdc.gov/drugresistance/).
- **The European Agency for the Evaluation of Medicinal Products (EMEA)**
  The Committee for Veterinary Medicinal Products of the EMEA has developed guidelines for evaluating the microbiological safety of veterinary antimicrobials (available at: http://www.emea.eu.int/aboutus.htm).
- **Codex Alimentarius Commission**
  This Joint Food and Agriculture Organization (FAO)/WHO Initiative is developing food standards, guidelines and codes of practice under the Joint FAO/WHO Food Standards Programme. Codex is currently developing a code of practice to minimize and contain AMR (available at: http://www.codexalimentarius.net/).
- **Australian Government**
  The Departments of Health and Ageing, and Agriculture, Fisheries and Forestry coordinate the management of antimicrobial use in animals and

*Myth*

*My family always drinks milk straight from the cow. It's much healthier, tastes great and we never get sick.*

**Fact**

**People who eat raw milk and raw milk products (cheese) are at greater risk of foodborne illness and, therefore, infection with antimicrobial resistant organisms. Approved pasteurization processes reduce the risk of foodborne diseases associated with milk consumption.**

**Monitoring antimicrobial resistance and/or use is a priority for many national and international organizations. In addition to national systems/networks, several programs have been institutionalized worldwide.**

humans in Australia. The Commonwealth Government is developing a national antibiotic resistance management program focusing on regulatory controls, monitoring and surveillance, infection prevention, education and research (see: http://www.health.gov.au/pubs/jetacar.htm).

- **Alliance for Prudent Use of Antibiotics (APUA)**
  APUA recently published "The Need to Improve Antimicrobial Use in Agriculture: Ecological and Human Health Consequences," a report of a Scientific Advisory Panel examining antimicrobial use in animals and its impact on resistance (available at: http://www.journals.uchicago.edu/CID/journal/contents/v34nS3.html).
- **Union of Concerned Scientists (UCS)**
  A vocal advocate of limited antimicrobial use in agriculture that has recently released estimates of the quantity of antimicrobial use in livestock, the UCS is currently working with environmental and public health organizations to advocate for a reduction in antimicrobial use in food-producing animals (see: http://www.ucsusa.org/food_and_environment/antibiotic_resistance/index.cfm).

## Surveillance Programs

Monitoring antimicrobial resistance and/or use is a priority for many national and international organizations. In addition to national systems/networks, several programs have been institutionalized worldwide.

- **SENTRY Antimicrobial Surveillance Program**
  (see: http://www.ewi.med.uu.nl/enare/)
- **National Antimicrobial Resistance Monitoring System (NARMS)**
  (see: http://www.cdc.gov/narms/)
- **European Antimicrobial Resistance Surveillance System (EARSS)**
  (see: http://www.earss.rivm.nl/)
- **European Network for Antimicrobial Resistance and Epidemiology (ENARE)**
  (see: http://www.ewi.med.uu.nl/enare/)
- **WHO Global Salm-Surv**
  (see: http://www.who.int/salmsurv/en/)
- **The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)**
  (see: http://www.vetinst.dk/high_uk.asp?page_id=180)
- **The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS)**
  In the past several years, CIPARS has launched a number of AMR surveillance and antimicrobial use monitoring projects in both the human and veterinary sectors. CIPARS is a collaboration of several federal, provincial and academic partners, including Health Canada (for more information, e-mail Rebecca_Irwin@hc-sc.gc.ca or Kathryn_Dore@hc-sc.gc.ca).

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**Myth**

*After preparing raw poultry, kitchen counters, cutting boards and knives must be cleaned with an antibacterial soap to kill salmonella and other germs.*

**Fact**

**Experts say that using antibacterial soap is a waste of time and money. Not only that, but you are risking the development of AMR. A good scrubbing with hot water and soap is usually all that is required to get rid of these germs. For extra care, use a solution of water and vinegar or household bleach.**

*Using Canada's Health Data is a regular column of the Health Policy Research Bulletin highlighting methodologies for collecting, analyzing and using health data. In this issue, the example of gonorrhea is used to illustrate how a surveillance system that generates high frequency, quick response data can inform decisions about treatment protocols.*

## Using Real-Time Data in Decision Making

**Jaylyn Wong**, *Applied Research and Analysis Directorate, Information, Analysis and Connectivity Branch, Health Canada, and* **Cathy Sevigny**, *Centre for Infectious Disease Prevention and Control, Population and Public Health Branch, Health Canada*

Health Canada is responsible for many public policy decisions concerning the protocols for treating disease. Evidence, such as the data collected by surveillance systems, is an essential part of this decision-making process. To be truly effective, surveillance systems must generate data frequently enough so that up-to-date information is available when decision makers need it. Moreover, decision-making systems must be able to respond to the evidence quickly, which requires clear indicators and sound planning.

### About Gonorrhea

The second-most commonly reported sexually transmitted infection (STI) in Canada, gonorrhea is caused by the bacteria *Neisseria gonorrhoeae*. While the rate of reported cases of gonorrhea decreased from 1980 to 1997, incidence rates rose again from 1997 to 2001.[1] Untreated gonorrhea in females can have serious consequences, including pelvic inflammatory disease, which often leads to infertility or ectopic pregnancy.[2] If diagnosed early, however, gonorrheal infections can be cured with a single dose of antibiotics.

### Canadian Treatment Guidelines

The 1998 *Canadian Sexually Transmitted Disease (STD) Guidelines* assist primary health care providers in the prevention, diagnosis, treatment and follow-up of STI in Canada.[3] Prepared by the former Laboratory Centre for Disease Control (LCDC) Expert Working Group on Sexually Transmitted Diseases, the Guidelines provide information on the appropriate clinical management of various STIs, including gonorrhea. The Guidelines currently recommend ciprofloxacin and ofloxacin — both in the fluoroquinolone (FQ) class of antibiotics — as two of the treatment options for people diagnosed with gonorrhea.[4]

Although it is generally recommended that regimens for treating gonorrhea have an efficacy approaching 100 percent and not less than 95 percent, Canadian experts have identified a target of 97 percent.[1] This precautionary approach to treating gonorrhea is necessary because of the serious ramifications of untreated infections, which include ongoing transmission and the potential for increased resistance to antibiotic treatment.

Since resistance of *N. gonorrhoeae* to the FQ class of antibiotics was systematically documented in 1992,[5] it has become endemic in many parts of the world. In Hong Kong, for example, the prevalence rate of FQ-resistant gonorrhea rose from 3.3 percent in 1993 to 49 percent in 1998. In other countries, such as Korea, Cambodia and the Phillippines, prevalence rates are higher than 50 percent. Although most prevalent in East Asia, this type of resistant gonorrhea has been documented in countries around the world, including Canada.[1,6-10]

### Monitoring and Measuring Resistance

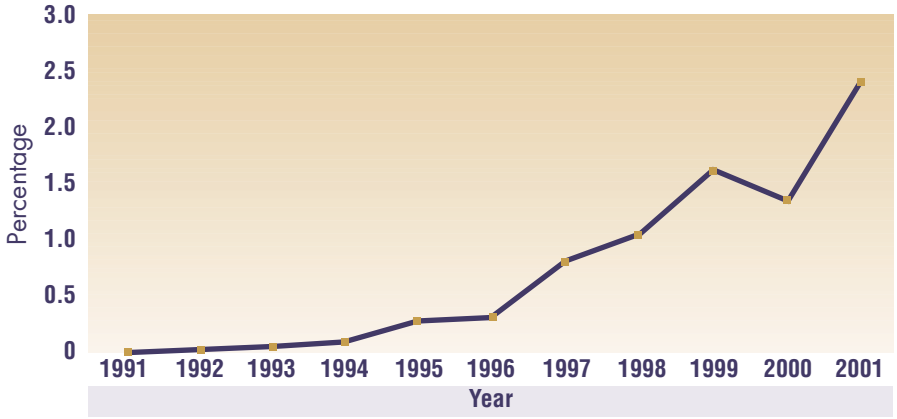
In Canada, surveillance methods are used to monitor the prevalence of resistant strains in order to provide up-to-date information about which antibiotics should be used to treat gonorrhea. Since gonorrhea is designated a "reportable" disease, physicians and/or laboratories (depending on the jurisdiction) must report all diagnosed cases to their local health departments.

Often, physicians must prescribe treatment for patients with gonorrhea while they are waiting to determine if the bacterial strain is resistant to the prescribed antibiotic. In most cases where cultures are positive for gonorrhea, isolates are sent to provincial laboratories for susceptibility testing to various antibiotics, including ciprofloxacin and ofloxacin.[11] If the isolates have a decreased susceptibility to one or more antibiotics, they are sent to the National STD Laboratory in Winnipeg for further testing.[1] The results are also given to the diagnosing physician so that an alternate treatment can be prescribed, if necessary.

Figure 1 illustrates the rising prevalence of full ciprofloxacin resistance in *N. gonorrhoeae*, which is determined on an annual basis. From 1991 to 2001, resistance increased more than 200-fold, from 0.01 percent to 2.4 percent.[12]

While early cases of FQ resistance were associated with travel in Asia, travel information is not consistently collected and reported across Canada as part of a patient's medical history. As a result, it is difficult to determine what proportion of FQ resistance in Canada can be linked to travel abroad.

Figure 1: **Percentage of *Neisseria Gonorrhoeae* Isolates Tested in Canada Resistant to Ciprofloxacin, 1991–2001**




## Public Health Concerns

When considering the example of gonorrhea, there are important public health issues related to the growing prevalence of ciprofloxacin resistance in Canada. A primary concern is the potential for increasingly limited treatment options for people infected with gonorrhea. Another is the possibility of continued transmission of resistance, which may lead to a rapid increase in FQ-resistant gonorrhea.

By identifying people with resistant strains of gonorrhea, a surveillance system generating **real-time** data can be an important tool for slowing the spread of resistance. Contacts can then be treated prophylactically with appropriate medications. This type of tracking system is essential in determining when heightened public health measures are needed to control the spread of resistant strains of gonorrhea. An emerging concern is the use of new DNA-based testing methods to detect *N. gonorrhoeae* that do not allow for susceptibility testing. Unless sentinel sites continue to use the culture testing methods for determining susceptibility, the system's ability to monitor trends in antibiotic resistant strains could be impaired.

## A Coordinated Policy Response

At 2.4 percent, the current prevalence rate of ciprofloxacin resistance is approaching the critical level of 3 percent. Health Canada is monitoring the situation closely so that it can respond quickly as new data become available. If the prevalence rate rises above the critical level of 3 percent, treatment regimes for gonorrhea involving fluoroquinolones would no longer be recommended due to the increased risk of treatment failures (less than 97 percent efficacy). In addition to other methods of informing primary care practitioners, Health Canada would likely issue a national advisory warning that ciprofloxacin and other fluoroquinolones should not be used to treat gonorrhea. This advisory would be sent to STD Directors in the provinces and territories to disseminate to local departments of health and practising physicians.

While fluoroquinolones are still appropriate for treating most cases of gonorrhea, Health Canada currently recommends that they be avoided if the patient has recently travelled to an area where FQ resistance is endemic. Similarly, as FQ resistance is known to vary among regions in Canada, the department recommends that fluoroquinolones not be used where the prevalence rate of resistance is higher than 3 percent.[1] In 2003-2004, an expert working committee will review the 1998 Canadian STD Guidelines, revising them to incorporate any new recommendations regarding treatment protocols for gonorrhea.

## Conclusion

This example has presented a surveillance system generating real-time data that are used to inform gonorrhea treatment protocols. The creation of similar real-time surveillance systems can help inform many other decision-making systems, whether they are related to antimicrobial resistance or other important health issues.

*Please note: Full references are available in the electronic version of this issue of the Bulletin: http://www.hc-sc.gc.ca/arad-draa*

# New and Noteworthy

*New and Noteworthy is a regular column of the Health Policy Research Bulletin highlighting "up and coming" policy research in the health field.*

## Health Canada's Health Policy Research Program

With the transfer of Health Canada's National Health Research and Development Program (NHRDP) to the Canadian Institutes of Health Research (CIHR) in 2001, the Health Policy Research Program (HPRP) was established to fund extramural, peer-reviewed research that contributes to the evidence base for the department's policy decisions.

HPRP is a contribution program managed by the Research Management and Dissemination Division (RMDD), Applied Research and Analysis Directorate, Information Analysis and Connectivity Branch. Its guiding principles focus on departmental policy relevance, scientific merit, appropriateness and complementarity with other federal funding programs, and fair and transparent selection processes.

HPRP supports a variety of initiatives, including: research projects (primary, secondary and synthesis research); workshops and seminars (for example, consensus workshops on policy issues); developmental contributions (including methodologies for policy research or knowledge transfer); and federal/provincial/territorial partnerships that give effect to intergovernmental agreements to fund research of national significance.

There are five key steps involved in transforming policy issues into research findings:

- **Select the Policy Issues**
  The inter-branch Policy Research Working Group (PRWG) identifies key departmental policy research themes. Once a year, RMDD solicits "context pieces" from departmental branches that describe specific policy issues corresponding with these priority themes. When a policy issue transcends a single branch, RMDD encourages the branches to collaborate on the context piece. The PRWG ranks the context pieces according to their feasibility and corporate priority.
- **Develop Requests for Proposals (RFPs) and/or Requests for Letters of Intent (RFLOIs)**
  RMDD collaborates with departmental policy contacts to develop RFPs and RFLOIs based on the top-ranked context pieces.
- **Review and Approve Proposals**
  RMDD screens letters of intent and proposals to ensure they meet eligibility requirements. Applications are then rated for scientific merit and policy content. Funding for successful applications is approved by the Minister. It generally takes approximately 8 to 12 months from the time the request is posted on the website until the project receives funding.
- **Manage Contributions**
  Funded projects, workshops and seminars are managed by HPRP staff. During the research process, branch policy contacts are available to advise researchers on the policy aspects of projects.
- **Disseminate Results**
  With the assistance of branch policy contacts, RMDD distributes research findings to appropriate decision makers and other interested parties.


To date, 15 RFPs/RFLOIs have been developed and posted on the ARAD website (see: http://www.hc-sc.gc.ca/iacb-dgiac/arad-draa/english/rmdd/funding1.html). The requests address a wide range of topics, including climate change, drug effectiveness, migration health, health risks to Canadians, integrated approaches to chronic disease prevention, health impacts of economic change, and governance and patient safety.

The 2003-2004 solicitation process for policy context pieces is now under way. During the summer and fall of 2003, top-ranked policy issues will be developed into RFPs/RFLOIs. For more information, contact: RMDDinfo@hc-sc.gc.ca

## Safe Food and Water Initiative: Microbial Contamination of Food and Water and Antimicrobial Resistance in the Food Chain

CIHR's Institute of Infection and Immunity played an instrumental role in the creation of the Canadian Research Coalition for Safe Food and Water, which is comprised of representatives from many major Canadian stakeholder groups and research funders in the field. The coalition's goal is to build a national, coordinated research agenda in the area of microbial contamination of food and water, and antimicrobial resistance in the food chain.

CIHR is currently soliciting applications to design a framework for coordinating Canadian research. The framework will combine the resources and expertise of researchers, stakeholder partners and those who use the research, such as policy makers, program administrators and public health practitioners. To assist in the process, research teams — including scientists from federal departments and academia — will be created or expanded to address specific research issues. One of the goals of the project is to help establish direct links between environmental and agricultural research, and health outcomes. More information is available at: http://www.cihr-irsc.gc.ca/index_e.shtml

## Health Canada Research Forum: From Science to Policy

The 2002 *Health Canada Research Forum: From Science to Policy* was the first national research conference organized by and for Health Canada. The Forum focused on three themes: Genomics and Health, Children's Health, and Contaminants in Food, Water and Air. A summary report of the proceedings is available at: http://www.hc-sc.gc.ca/ocs-besc/english/forum.html

Responding to the success of the 2002 Forum, the Office of the Chief Scientist is sponsoring a second departmental research conference on October 20 and 21, 2003. This year's *Health Canada Research Forum: From Science to Policy* will examine the science-to-policy continuum in the following areas:

- the health of vulnerable populations
- mental health, neuroscience and addiction
- emerging threats to public health
- health risk assessment and regulation

The Forum will provide Health Canada's policy and scientific communities with a joint venue for discussing new directions in research and examining how government-based science is being used to inform policy decisions. Registration for the event is open to all Health Canada employees, who can use the Departmental Science and Research Database (accessible through Gateway in Lotus Notes) to keep informed on all aspects of the Forum (for more information, e-mail Health_Canada_Research_Forum@hc-sc.gc.ca).

**The 2002 *Health Canada Research Forum: From Science to Policy* was the first national research conference organized by and for Health Canada. The Forum focused on three themes: Genomics and Health, Children's Health, and Contaminants in Food, Water and Air. This year's Forum will provide Health Canada's policy and scientific communities with a joint venue for discussing new directions in research and examining how government-based science is being used to inform policy decisions.**

## Women's Health Indicators Project

The Women's Health Indicators project is designed to provide baseline information to support surveillance and policy responses to women's diverse health needs. The project's goals are to:

- assist Health Canada's policy decision makers in monitoring women's health
- support appropriate and consistent data collection necessary for gender-based indicators
- provide for the transfer of knowledge to policy makers, stakeholders and the public

Reflecting the key commitments and strategic directions adopted by Health Canada's Women's Health Bureau through the department's Women's Health Strategy (1999), the project also responds to Health Canada's Gender-Based Analysis Policy (2000), which requires the integration of gender-based analysis into all departmental policies and programs. More information is available at: http://www.hc-sc.gc.ca/english/women/index.html

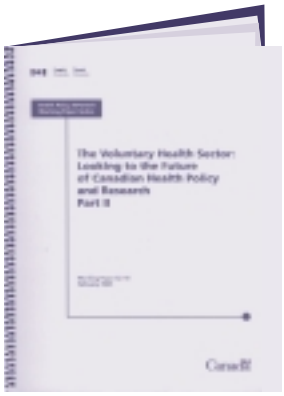
## Statistics on First Nations Health

The First Nations and Inuit Health Branch of Health Canada has released a statistical profile summarizing the health status and conditions affecting the health of First Nations living on reserve in Canada. Data from 1999 on First Nations immunization, perinatal health, mortality and communicable diseases are compared with findings for the Canadian population as a whole. The report also presents limited statistics on other factors relevant to health, such as housing conditions and water quality. The first in a series of periodic publications on health, the statistical profile is designed to improve First Nations' health by increasing the knowledge available to health professionals, researchers, community leaders and policy makers. For more information, e-mail fnihb_stats@hc-sc.gc.ca. This report is available at:http://www.hc-sc.gc.ca/fnihb/sppa/hia/publications/statistical_profile.htm

## A Tool for Gender-Based Analysis

Health Canada's Women's Health Bureau has developed a new capacity-building tool for gender-based analysis (GBA) that will be of interest both to novices and those experienced with GBA. *Exploring Concepts of Gender and Health* examines the differences between sex and gender, and discusses the integration of GBA into a decision-making framework. The tool provides case studies illustrating how GBA can be used to provide a sharper focus on the context of men's and women's lives, and how it can improve policies and programs. It also includes specific questions to consider in research development, and policy and planning. The document will be published in the summer of 2003 (watch for it at: http://www.hc-sc.gc.ca/english/women/index.html); for hard copies, please contact the Women's Health Bureau Resource Centre at (613) 946-7213.

## Health Canada's Working Paper Series



The *Health Policy Research Working Paper Series* (WPS) is produced by the Applied Research and Analysis Directorate as part of a larger policy research dissemination program designed to encourage the transfer and uptake of knowledge generated by or on behalf of Health Canada. Highlighting important research in the field, the WPS complements other departmental communications activities focusing on health policy research, including the *Health Policy Research Bulletin,* the *Policy Researcher Seminar Series* and various workshops. Five working papers were recently released:

- *New Considerations on the Empirical Analysis of Health Expenditures in Canada: 1966-1998*
- *The Voluntary Health Sector: Looking to the Future of Canadian Health Policy and Research: Part 1*
- *The Voluntary Health Sector: Looking to the Future of Canadian Health Policy and Research: Part 2*
- *Social Capital as a Determinant of Health. How Should It be Defined?*
- *Social Capital as a Determinant of Health. How Should It be Measured?*

All working papers are available at: http://www.hc-sc.gc.ca/iacb-dgiac/arad-draa/english/rmdd/wpapers/wpapers1.html

**Myth**

*Veterinarians are not needed to advise what antibiotics to use in livestock.*

**Fact**

**Veterinarians, in consultation with food animal nutritionists, are the best persons to determine whether or not an antimicrobial is needed, and which one to use. It is essential to follow the instructions of a veterinarian regarding the prudent use and safe handling of antimicrobials. It is also important to take advantage of livestock medicine courses where they are offered and to adhere to the guidelines included in commodity quality assurance programs.**

# Mark Your Calendar

| What | When | Theme |
|---|---|---|
| Global Health Economics: Bridging Research and Reforms | June 15-18, 2003<br>San Francisco, California<br>http://www.healtheconomics.org/cgi-bin/WebObjects/IheaConference | Globalism and the increased need for the development and transfer of accurate health economics research and careful policy analysis |
| Improving Outcomes Through Health Technology Assessment | June 22-25, 2003<br>Canmore, Alberta<br>http://www.istahc2003.org/ | A focus on: identifying the topics for assessment, refining assessment methods, and implementing the evidence |
| Conference on Health and Economic Policy | June 27-28, 2003<br>Munich, Germany<br>http://www.cesifo.de/ | Role of health in poverty, the effect of public policy on health, forecasting supply and demand for health, demographic outcomes in an aging population and their policy implications |
| 7th International Child and Youth Care Conference: Promise into Practice | August 20-23, 2003<br>Victoria, British Columbia<br>http://www.promiseintopractice.ca/ | Streams include: professionalism, cultural and human diversity, applied human development, relationships and communication, and developmental practice methods |
| Health Statistics Data Users Conference 2003 | September 7-9, 2003<br>Ottawa, Ontario<br>http://www.statcan.ca/english/services/workshops.htm | Data sources, data quality, analysis and dissemination |
| 5th International Conference on the Scientific Basis of Health Services | September 20-23, 2003<br>Washington, DC<br>http://www.icsbhs.org/ | Strategies for organizing health services research, using evidence to improve clinical practice, health services management, policy making and alleviating the burden of specific diseases |
| Mental Health and Addictions Conference | September 28-October 1, 2003<br>Niagara Falls, Ontario<br>http://www.ontario.cmha.ca/content/inside_cmha/conferences/making_gains.asp | Making gains: Research, recovery and renewal |
| International Conference on Health Policy Research | October 17-19, 2003<br>Chicago, Illinois<br>http://www.amstat-online.org/sections/hpss/ichpr.htm | Methodological issues in health services and outcomes research |
| 10th Canadian Conference on International Health "The Right to Health: Influencing the Global Agenda" | October 26-29, 2003<br>Ottawa, Ontario<br>http://www.csih.org/ | How research, advocacy and action can shape our future |
| First Canadian Conference on Counter-Terrorism and Public Health | October 29-November 1, 2003<br>Toronto, Ontario<br>http://www.cpha.ca/english/conf/bio-terr/bio-an_e.htm | An open forum for the delivery, exchange and discussion of information and actions related to the public health sector and bioterrorism |
| Canadian Injury Prevention Conference 2003 | November 23-25, 2003<br>Ottawa, Ontario<br>http://www.safekidscanada.com/CIPC/default.html | Designed to build on the Kananaskis 2000 national conference, the conference will focus on unintentional injury, violence and suicide prevention |

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