Antimicrobial resistance in Canada

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Abstract

Antibiotic resistance has increased rapidly during the last decade, creating a serious threat to the treatment of infectious diseases. Canada is no exception to this worldwide phenomenon. Data from the Canadian Nosocomial Infection Surveillance Program have revealed that the incidence of methicillin-resistant *Staphylococcus aureus*, as a proportion of *S. aureus* isolates, increased from 1% in 1995 to 8% by the end of 2000, and vancomycin-resistant enterococcus has been documented in all 10 provinces since the first reported outbreak in 1995. The prevalence of nonsusceptible *Streptococcus pneumoniae* in Canada in 2000 was found to be 12%. Human antimicrobial prescriptions, adjusted for differences in the population, declined 11% based on the total number of prescriptions dispensed between 1995 and 2000. There was also a 21% decrease in β-lactam prescriptions during this same period. These data suggest that systematic efforts to reduce unnecessary prescribing of antimicrobials to outpatients in Canada, beginning after a national consensus conference in 1997, may be having an impact. There is, however, still a need for continued concerted efforts on a national, provincial and regional level to quell the rising tide of antibiotic resistance.

> But I would like to sound a note of warning. . . . It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them and the same thing has occasionally happened in the body. — *Sir Alexander Fleming, 1945*[1]

> Now, at the dawn of a new millennium, humanity is faced with another crisis. Formerly curable diseases . . . are now arrayed in the increasingly impenetrable armour of antimicrobial resistance. — *Gro Harlem Brundtland, Director-General, World Health Organization (WHO), 2000*[2]

Antibiotic resistance is one of the most serious global threats to the treatment of infectious diseases.[2–8] In addition to resulting in significant increases in costs and toxicity of newer drugs, antibiotic resistance is eroding our therapeutic armamentarium. Countries and hospitals with the fewest controls on antibiotic prescribing have the greatest frequency of resistant organisms,[9,10] which suggests a causal relationship.

Microorganisms with increasing rates of resistance to commonly used antimicrobials include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), *Shigella* and *Salmonella* species resistant to multiple antibiotics, enteric gram-negative bacilli (*Klebsiella* and *Enterobacter* species) resistant to extended-spectrum β-lactams and penicillin-resistant *Streptococcus pneumoniae* (PRSP). PRSP and multidrug-resistant *Shigella* and *Salmonella* are more common in the community, whereas MRSA, VRE and β-lactam-resistant enteric gram-negative bacilli are more common in health care facilities. A 2001 article in *CMAJ*[11] demonstrated the evolution of MRSA in Canadian hospitals, with the mean proportion of isolates that were resistant increasing from about 1% to 6% between 1995 and 1999. Was this a glimpse of the future?

This review, commissioned by the Canadian Committee on Antibiotic Resistance (CCAR), a multidisciplinary group performing a collating and coordinating role for stakeholder groups across Canada, will provide the practising physician with an understanding of the origins and dynamics of antibiotic resistance and present potential solutions to this growing problem. The intent of the article is to em-

Review

Synthèse

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CMAJ 2002;167(8):885-91

phasize that the actions of each person involved in the prescribing process can make an important contribution to addressing antibiotic resistance.

Mechanisms of resistance

Antimicrobial resistance has developed predominantly in the last 50 years. The main mechanisms for survival of a threatened microbial population are genetic mutation, expression of a latent resistance gene and acquisition of genes with resistance determinants.[12,13] The 3 mechanisms may coexist within a given bacterium (Fig. 1). Widespread use of antibiotics provides the selective pressure favouring propagation of the resistant organisms.

The rapid evolution of PRSP in the community has been paralleled by the emergence of MRSA and VRE in hospitals. The mechanism of pneumococcal resistance to penicillin involves acquisition of segments of foreign DNA (mosaic genes) that code for alterations in the proteins that bind penicillin and other β-lactams.[14–16] Several mechanisms of methicillin resistance in staphylococci exist,[17] including inactivation by β-lactamase, reduction of penicillin-protein-binding capacity and acquisition of the *mecA* gene, which encodes a penicillin-binding protein with low affinity for β-lactams. The third mechanism accounts for most of the resistance to methicillin and other β-lactams.

Enterococci, notably VRE, have been recognized as increasingly important nosocomial pathogens.[18,19] Enterococci are intrinsically resistant to many antibiotics and have a remarkable capacity to acquire resistance.[20,21] Resistance to vancomycin is due to synthesis of modified precursors that have decreased affinity for this antibiotic,[22] resulting from

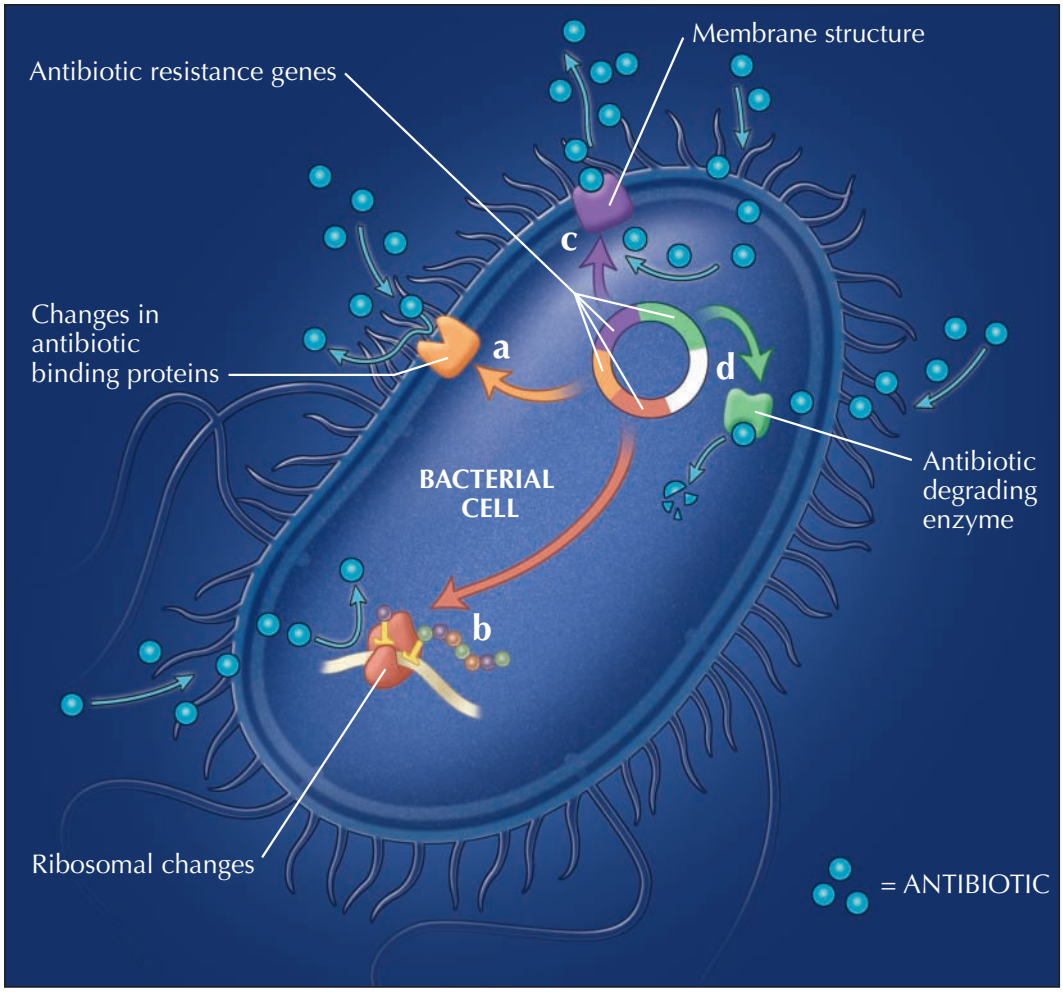

Fig. 1: The main genetic mechanisms leading to antibiotic resistance are genetic mutation (single point mutations or major deletions or rearrangements), expression of a latent resistance gene and acquisition of genes or DNA segments with resistance determinants. Some of the genes are inherited, some emerge through random mutations in bacterial DNA and some are imported from other bacteria. These genetic changes code for changes in binding proteins (a), ribosomes (b), membrane structure (c) or inactivating enzymes (d). Adapted with permission from *Scientific American* (1998;March:46-53).

acquisition of a gene cluster encoding the resistance. The transferability of vancomycin resistance in enterococci was unexpected and raises concern about the dissemination of resistance to other pathogens, notably MRSA.

Epidemiologic features

The prevalence of MRSA was less than 5% in most hospitals worldwide in the early 1970s but a decade later had increased to as much as 40% in many hospitals in the United States and Europe.[23,24] The prevalence differs tremendously between the United States and Canada (Fig. 2).

First reported in Canada in 1981,[25] MRSA has since been reported from both acute care and long-term care facilities.[26,27] Recent data from the Canadian Nosocomial Infection Surveillance Program (CNISP) show that the proportion of *S. aureus* isolates reported as being methicillin-resistant increased from 0.95/100 isolates (0.46/1000 admissions) in 1995[11] to 3.8/100 isolates (1.67/1000 admissions) in 1997,[28] 5.97/100 isolates (4.12/1000 admissions) in 1999[11] and 8.1/100 isolates (5.3/1000 admissions) in 2000 (CNISP, Health Canada: unpublished observation, 2001). Of all the MRSA reports (including those of both colonization and infection), 70% were from central Canada, 26% from western Canada and 4% from eastern Canada. Most of the increase was in Ontario and British Columbia.[29]

> The proportion of *Staphylococcus aureus* isolates in Canada that are methicillin-resistant increased from 0.95/100 isolates (0.46/1000 admissions) in 1995 to 8.1/100 isolates (5.3/1000 admissions) in 2000.

The prevalence of nosocomial VRE in the United States increased from 0.3% in 1989 to 7.9% in 1993 and 23% in 1999.[18,30] The first isolate of VRE in Canada was reported in 1993,[31] and the first outbreak was in 1995.[32] Since then VRE has been recognized in all the provinces, predominantly as colonization, being found in surveillance cultures. The first prevalence survey for VRE in Canada, conducted in 1996, found a rate of 0.1% among high-risk patients in a hospital with no outbreak and 3.7% among high-risk patients in a hospital with endemic VRE.[33] The VRE Passive Reporting Network, established within the CNISP, identified 1315 instances of VRE throughout Canada between 1994 and 1998, less than 5% representing infection.[34] In 1999, the first year of data collection for the VRE Incidence Surveillance Program, also established within the CNISP, a rate of 0.19 per 1000 admissions was reported, representing 0.55% of enterococcal isolates.[35] Data for 2000 are unchanged (CNISP, Health Canada: unpublished observation, 2001). Despite the proximity of Canada to the United States, VRE has not attained the same colonization rate and is rarely a cause of infection (Fig. 3).

After its introduction in the 1940s, penicillin was uniformly effective against *S. pneumoniae*. However, an increasing prevalence of PRSP was noted between 1974 and 1984 in Europe, South Africa and the United States, and then multidrug-resistant strains emerged.[36,37] The prevalence of *S. pneumoniae* with reduced susceptibility to penicillin varies markedly throughout the world, with up to 70% resistance in Korea and 40% in the United States.[36,37] The rates in Canada are much lower: the prevalence of clinical isolates with reduced susceptibility to penicillin (both intermediate-level and high-level resistance) increased from less than 2% in the late 1980s to 16% in 1998,[38,39] with up to 5% of isolates having high-level resistance; during 1999 the PRSP prevalence decreased to 12% and was 12.3% in 2000 (Fig. 4) according to one surveillance system,[39] and 16.5% in 2000 according to another surveillance system.[40]

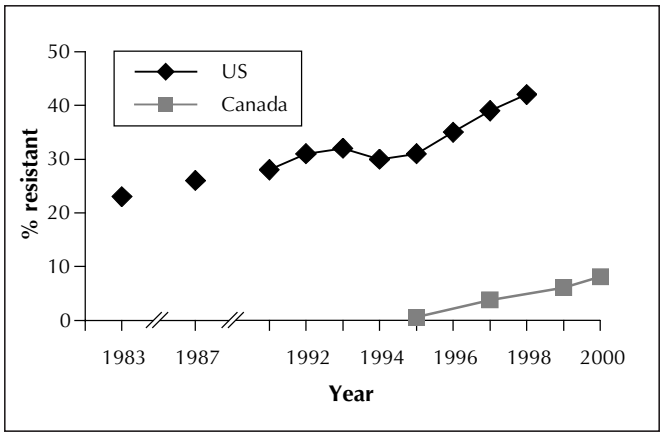

Fig. 2: Proportion of *Staphylococcus aureus* isolates reported as methicillin-resistant from hospitals in the United States (1986–1998) and Canada (1995–2000). Sources: US Centers for Disease Control and Prevention (CDC) data and Canadian Nosocomial Infection Surveillance Program (CNISP) data.

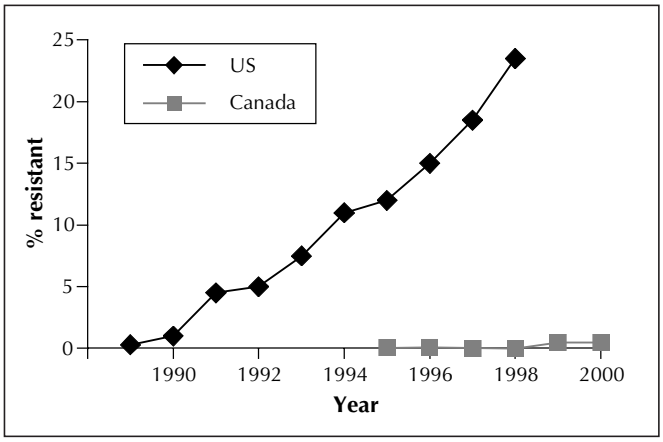

Fig. 3: Proportion of *Enterococcus* isolates from nosocomial infections reported as vancomycin-resistant enterococci (VRE) in the United States (1989–1998) and Canada (1995–2000). Sources: CDC data and data from the VRE Passive Reporting Network (1994–1998) and the VRE Incidence Surveillance Program (1999–2000) of the CNISP.

The proportion of *Streptococcus pneumoniae* strains with reduced susceptibility to penicillin (both intermediate-level and high-level resistance) has increased significantly in Canada, from less than 2% in the late 1980s to 12.3% in 2000.

A multidrug-resistant strain of *Salmonella*, *S.* Typhimurium DT104, is seen with increasing frequency in Canada. This strain emerged in cattle in the late 1980s in England and was subsequently found in meat and meat products from other domestic animals, including swine and chickens.[41–43]

In 1997, a group from Canada, the Netherlands, the United States and the United Kingdom reported a significant increase in the prevalence of these isolates,[44] and fluoroquinolone resistance has been reported from the United Kingdom and Denmark.[45,46]

Economic burden

Very little information has been published about the economic burden of antimicrobial resistance on the health care system in Canada. A recent report[47] summarizing Canadian studies provides some data on the economic burden of MRSA, VRE, multidrug-resistant *Mycobacterium tuberculosis* and multidrug-resistant *Neisseria gonorrhoeae*, but data for other pathogens are lacking. The annual costs of isolating MRSA and managing colonized or infected patients have been estimated at $1363 and $14 360, respectively, the total for all Canadian hospitals being $42–59 million.[48] The incremental annual costs for managing VRE-colonized patients were estimated at $6732 per patient and $5–16 million for all Canadian hospitals.[34,49]

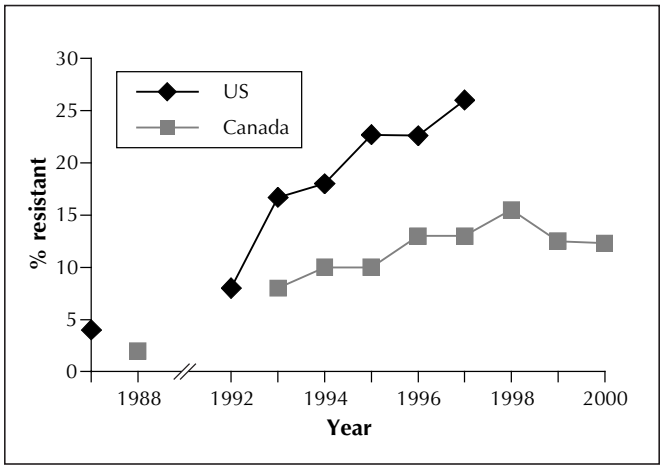

Fig. 4: Proportion of clinical *Streptococcus pneumoniae* strains reported as nonsusceptible (showing both intermediate-level and high-level resistance) to penicillin in the United States (1987–1997) and Canada (1988–2000). Sources: CDC data and Canadian Bacterial Surveillance Network data.

The current overall medical costs of antibiotic resistance to the Canadian health care system, predominantly the institutions, may be as much as $200 million per year.[50] By comparison, the US Office of Technology Assessment has estimated that the costs of managing antibiotic resistance in the United States range from US$0.1–10 billion per year.[51]

Antimicrobial use

Antimicrobials are used in human medicine, agriculture, aquaculture and the agrifood industry. Inappropriate use in any of these settings contributes to the emergence of resistance. The scale of total antimicrobial use across all sectors is enormous. In the United States, 160 million antibiotic prescriptions are written annually for humans; of the 22.7 million kg of antibiotics prescribed, about 50% are for humans and 50% for agricultural and aquaculture purposes.[52] These figures equate to 30 prescriptions and 4.1 kg of antibiotics per 100 persons per year. Among industrialized nations, France, Australia, the United States, Canada, Italy and the United Kingdom have the highest rates of oral antimicrobial prescriptions, ranging from 33 to 16 defined daily doses per 1000 population per day.[53] Data from IMS HEALTH Canada[54] reveal that in 1999 in Canada about 25 million prescriptions for oral antibiotics were dispensed and that, after cardiovascular and psychotherapeutic drugs, antibiotics were the third most commonly prescribed class of agents.

The total number of prescriptions for oral solid and liquid antimicrobial agents dispensed annually per 1000 population in Canada from 1995 to March 2000 declined by 11%.[55] The numbers were adjusted for differences in population.[56] Total β-lactam prescriptions decreased by 20.8% during the same period.[55] Using the moving annual total, a decrease of 24% was noted between 1997 and March 2000, following formulation of the Canadian action plan for controlling antimicrobial resistance.[57]

The scale of total antimicrobial use in Canada across all sectors of human medicine, agriculture, aquaculture and the agrifood industry is staggering. Canada is one of the industrialized countries that prescribes the most oral antimicrobials.

Substantial amounts of antimicrobials are used in the agrifood industry, primarily for disease prevention or growth promotion. Under current Canadian legislation, antimicrobials are acceptable as feed additives, veterinary prescription drugs or over-the-counter drugs. Feed antimicrobials are added through feed mills for growth promotion (usually 2–50 g per tonne), for subtherapeutic use (≤ 200 g per tonne) or for disease treatment (> 200 g per tonne). The recommended levels for growth promotion have increased 10-fold to 20-fold since the 1950s. Detailed estimates of antimicrobial use in agrifood sectors are unavailable for Canada. However, US reports have estimated that nonther-

apeutic use in livestock is one-half to 8 times the use in humans;[58,59] another report estimates that the amount used for agricultural and aquaculture purposes is 100 to 1000 times that used in humans.[60] Although many feed antibiotics are unique to agriculture, others (bacitracin, tetracyclines, sulfonamides, lincosamides, penicillin and aminoglycosides) are used in humans as well. Antimicrobials are also used in the aquaculture and agrifood industries (e.g., spraying of fruit trees, crops and beehives). Although there are examples of resistance development in the agricultural industry leading to resistant *Escherichia coli*, *Salmonella*, *Campylobacter* and *Enterococcus* species affecting humans,[22,46,61,62] the extent to which the use of antimicrobials in the agricultural and aquaculture sectors contributes to antibiotic resistance among bacteria affecting humans has been difficult to establish;[58,63,64] more systematic studies are needed.

Transmission of resistant organisms

The dissemination of resistant microorganisms occurs directly through transmission on the hands of health care workers and other caregivers and indirectly through contaminated or soiled environments. It has been estimated that 30%–40% of endemic institutional antibiotic resistance is caused by the unwashed hands of hospital personnel.[65]

Multiple studies have revealed that health care workers and other caregivers neglect to wash their hands before and after patient contact, physicians being among the least compliant.[66–70] Gloves may not be used appropriately, and health care workers may not even change gloves between patient tasks. The risk of transmission tends to be greatest among patients with more acute illness, immunosuppression, immobility, incontinence, history of frequent admissions to hospital, invasive devices or loss of integrity of normal skin and mucosal barriers, as well as among elderly people[12,71,72] and in settings of understaffing and overcrowding,[73–75] all of which have been compounded by hospital restructuring.[76] The larger variety of health care workers attending to patient needs includes some who are less skilled or working part-time; there may be inconsistencies in training and in compliance with basic hygienic skills. Several studies have demonstrated that lack of familiarity with a required skill set is associated with an increased rate of nosocomial infection.[77,78] Additional practices that may facilitate the dissemination of resistant microorganisms include inappropriate use of flash sterilization, unsafe handling of infectious wastes, inability to group patients affected by a specific organism, lack of dedicated equipment, poor aseptic technique, recirculation of unfiltered air and decreased environmental hygiene.[79]

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Controlling resistance: a multifaceted approach

Controlling antimicrobial resistance is a difficult task that requires a multifaceted approach. Essential components include reducing inappropriate prescribing for both humans and animals, reducing transmission of resistant organisms through enhanced infection control and environmental hygiene, and identifying trends in resistance through surveillance. This 3-pronged approach fits neatly within the classic bug–drug–host paradigm.

The overuse of antibiotics is considered the main factor in the emergence and dissemination of antibiotic resistance. Many factors lead to inappropriate antimicrobial prescribing, including patient expectations and demands, desire of the physician to give the best possible treatment regardless of cost or subsequent effects, failure to consider alternative treatments, inappropriate use of diagnostic laboratory studies, inadequacy of the physician's knowledge and management of patients with infectious diseases, medicolegal considerations and the belief that the newer and broad-spectrum agents represent the most effective treatment.

> Antimicrobial stewardship (careful assessment of the need for and choice of an antibiotic), with reinforcement and involvement at multiple levels (physicians, dentists, nurse practitioners, veterinarians, pharmacists, farmers and the public), may be the key to controlling antimicrobial resistance.

Antimicrobial stewardship may be the key to controlling antimicrobial resistance and achieving an ecologic balance between susceptible and resistant microbes in humans.[80,81] It consists of careful assessment of the need for and choice of an antimicrobial, including its dose and duration and the setting in which it is prescribed. Antimicrobial stewardship requires input from all individuals involved in the drug prescribing process, including physicians, dentists, nurse practitioners, veterinarians, pharmacists, farmers and the public. A multifaceted and multidisciplinary approach, with enabling and reinforcing strategies to encourage change, offers the best hope for success in controlling antimicrobial resistance.[82]

In addition to stewardship, infection prevention and control practices, including environmental hygiene, play an important role in limiting the transmission of antimicrobial-resistant organisms in all health care settings. Proper hand washing, hygienic practices and vaccination programs minimize the spread of microorganisms, reducing the need for antibiotics. Surveillance of resistant strains in both hospital and community settings provides key information for effectively managing patient care and prescribing practices.

The Canadian action plan

Although some efforts to promote judicious prescribing began in the mid-1990s, systematic efforts began only in 1997, following a consensus conference entitled Controlling Antimicrobial Resistance: an Integrated Action Plan for Canada.[57] At this meeting, national goals included reducing the number of antimicrobial prescriptions for respiratory infections by 25%. Many regions and provinces in Canada have initiated programs to promote judicious antimicrobial prescribing and have had significant impact within their jurisdictions.[83–85]

The Canadian action plan[57] emphasizes antimicrobial stewardship, limiting transmission through infection control, and surveillance. A number of national, regional and local efforts have been undertaken, most focusing on communication within target audiences, including physicians, pharmacists and the public. To facilitate the process, the CCAR was formed following the consensus conference to take an active, multifaceted advocacy and promotion role. CCAR activities to date include distributing antibiotic resistance toolkits to all Canadian physicians and veterinarians, hosting a comprehensive Web site (www.ccar-ccra.org) to provide an overview of Canadian antibiotic resistance programs, developing a directory of antibiotic resistance activities, working with the agrifood industry and attempting to establish a national surveillance system. Through an agreement with IMS HEALTH Canada and its Compuscript database, CCAR provides complete human antimicrobial prescription data on all classes of oral antimicrobials in Canada. Reports on current patterns of antimicrobial resistance in Canada from various surveillance systems are posted or linked on the Web site.

Adoption of components of the Canadian action plan and increased awareness are helping physicians, dentists, veterinarians, pharmacists and the public to recognize the vital importance of wise and prudent use of antibiotics as a means to preserve their effectiveness for future generations. The WHO, in its report on the growing threat of antimicrobial resistance, cited the decreases in antimicrobial prescribing in Canada; indeed, the Canadian approach has been suggested as a model for the developed world.[2,86] Despite some apparent progress in Canada's efforts, our country must continue its commitment to the control of antibiotic resistance in the years ahead.

Competing interests: None declared.

Acknowledgements: I acknowledge the critical review of this manuscript by the members of the executive of the Canadian Committee on Antibiotic Resistance (CCAR) — Clare Barry, Kevin Forward, Rebecca Irwin, Mark Miller, Mike Mulvey, Shirley Paton, Anne Phillips and Andrew Simor — as well as by Rick Walter (executive director of the CCAR), Jim Hutchinson and Edith Blondel-Hill, and the administrative and consulting assistance of Dodie Katzenstein.

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