

Antibiotic resistance in Canada at the dawn of the new millennium – A model for the developed world?

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Antibiotic resistance has increased dramatically and rapidly during the 1990s, and it is widely acknowledged to be a serious threat to the treatment of infectious diseases on a global basis (1-6). The morbidity, mortality and economic burden of infections with multiply drug resistant organisms, for which there are no effective therapies, pose an increasing burden for health care systems worldwide; Canada is no exception (7). Without effective public health strategies, grim warnings of a postantibiotic era may become a reality. In addition to significant increases in costs and greater toxicity of newer drugs, antibiotic-resistant organisms are continuously eroding the therapeutic armamentarium, leaving fewer or no alternative agents available. Although much has been written about antibiotic resistance during the past few years, it is noteworthy and relevant that both the World Health Organization (WHO) (8) and the Centers for Disease Control and Prevention (CDC) (9), have released reports on this topic this past June.

The WHO report, entitled *Overcoming Antimicrobial Resistance* (8), gives a stark warning that, at the dawn of a new millennium, humanity is faced with a crisis, where rising rates of drug resistance in many microorganisms could rob the world of its opportunity to cure many common infectious diseases. The report (8) describes multidrug-resistant (two or more first-line drugs) *Mycobacterium tuberculosis* rates of over 10% in Estonia, Latvia, and in parts of Russia and China; complete loss of the three most commonly used antimalarial drugs in Thailand due to resistance; lamivudine resistance rates of 30% to hepatitis B virus; cotrimoxazole-resistant *Shigella dysenteriae* rates of nearly 100% in certain parts of India; and rates of

hospital-acquired, methicillin-resistant *Staphylococcus aureus* (MRSA) of 60% in several industrialized nations. Although the report acknowledges that antibiotic resistance is a natural biological phenomenon, it suggests that it becomes a significant public health burden when it is amplified by human misuse and neglect. Overuse of antibiotics in developed nations and, paradoxically, both misuse and underuse in developing nations have contributed to the burden. Due to fears of resistance, many health care providers are avoiding narrow spectrum drugs in favour of broader spectrum antibiotics that have wider applications and greater impact on the natural flora. The report also indicated that unethical pharmaceutical companies sometimes pay a commission for recommending more expensive broader spectrum medications when cheaper narrow spectrum alternatives would suffice, resulting in a smaller, highly priced pool of antibiotics for a larger spectrum of infectious diseases (8). The WHO report suggests developing a global strategy to contain resistance and to build alliances involving all healthcare providers – countries, governments, international organizations, nongovernmental organizations and both the private and public health care sectors – in an effort to quell the rising tide of resistance. The WHO's *Global Strategy for the Containment of Antimicrobial Resistance* offers a series of recommendations aimed at enabling countries to define and implement national policies designed to maintain antimicrobial efficacy.

In the United States, a draft version of the document entitled *Public Health Action Plan to Combat Antimicrobial Resistance* (9) was also made available in June of this year. The Action Plan, which was developed by an interagency task

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force, including the CDC, the Food and Drug Administration, and the National Institutes of Health, provides a blueprint for specific, coordinated actions to address the emerging threat of antimicrobial resistance. Similar to the WHO report, the document emphasizes that drug-resistant pathogens are a growing menace to all people regardless of age, sex or background. The Action Plan outlines 11 priority items relating to surveillance, prevention and control, research, and new product development. The prevention and control section focuses not only on the human but also on agricultural issues, and the commonalities between the two are being increasingly recognized.

In Canada, systematic efforts for controlling antibiotic resistance began in 1997 following a landmark consensus conference entitled *Controlling Antimicrobial Resistance: An Integrated Action Plan for Canada* (10). The conference, co-sponsored by Health Canada and the Canadian Infectious Disease Society, developed an action plan that emphasized three components – antimicrobial stewardship, infection prevention and control, and surveillance – to monitor resistance trends. The Canadian Committee on Antibiotic Resistance was formed following the national consensus conference; it is a multidisciplinary group performing a collating and coordinating role for stakeholder groups across Canada. With initial funding from Health Canada allowing the recruitment of an executive director, it has taken an active, multifaceted advocacy and promotion role, which includes distributing antibiotic resistance tool kits to all Canadian physicians and veterinarians, hosting a web site (11) to provide an overview of Canadian antibiotic resistance activities, working with the agrifood industry and attempting to establish a national surveillance system. Through an agreement with Intercontinental Medical Statistics (IMS) HEALTH Canada and its CompuScript database, complete antimicrobial consumption data on all classes of oral antimicrobials in Canada are provided to the website. Together with current trending reports of antimicrobial resistance patterns in Canada from various national and regional surveillance systems, either linked or posted on the site, a composite portrait of the Canadian efforts against antibiotic resistance is provided.

Many microorganisms have exhibited increasing rates of resistance to commonly used antimicrobials, including MRSA, vancomycin-resistant enterococci (VRE), multiply antibiotic-resistant *Shigella* species, extended spectrum beta-lactam (ESBL)-resistant enteric Gram-negative bacilli (*Klebsiella* and *Enterobacter* species) and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Some of these organisms such as MRSA, VRE and ESBL are most often associated with patients in health care facilities, whereas PRSP and multiply resistant *Shigella* species are more common in the community. The epidemiology of resistance in the most commonly encountered antibiotic-resistant organisms in Canada and an update of trends in antimicrobial prescribing are described in the ensuing paragraphs.

The prevalence of MRSA was less than 5% in the late 1960s and 1970s in most hospital settings worldwide, but in the 1980s it had increased to as high as 40% in many hospitals in the United States and Europe (12,13). The first MRSA isolate

was reported in Canada in 1981 (14), and since then MRSA has been reported in both acute care and long term care facilities (15,16). Recent data from the Canadian Nosocomial Infection Surveillance Program (CNISP), a collaborative effort between the Population and Public Health Branch (formerly the Laboratory Centre for Disease Control), Health Canada and the Canadian Hospital Epidemiology Committee, a subcommittee of the Canadian Infectious Disease Society has revealed that the proportion of *S aureus* isolates that are reported as MRSA in their respective microbiology laboratories has increased from 0.5% in 1995 to 3.8% in 1997 (17). There was a further increase to 6.1% in 1999 (0.3/1000 admissions in 1995 to 4.3/1,000 admissions in 1999) (18). The rates of MRSA vary markedly across the country, with central Canada (Ontario and Quebec) experiencing the bulk of MRSA, and the eastern and prairie regions experiencing much less. Most of the increase in MRSA has occurred in Ontario and British Columbia. Some of the increase has been attributed to a specific strain described initially in Ontario, which has several features that may ease its spread throughout health care facilities (19).

In recent years, the prevalence of VRE as a percentage of all nosocomial enterococcal infections in the United States has increased from 0.3% in 1989 to 23% in 1999 (20,21). The overall percentage of nosocomial VRE isolates reported to the National Nosocomial Infection Surveillance System of the CDC in intensive care units reveals a similar increase, from 0.4% to 23% between 1989 and 1999. The first isolate of VRE in Canada was reported in 1993 (22), and the first outbreak, reported in 1995, involved 38 patients (23), of whom all but one was colonized. The first prevalence survey for VRE in Canada, conducted over a four-week period between January and March 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 an endemic hospital (24). The second prevalence survey, performed in September 1997, found a rate of only 0.2% (personal communication, M Ofner-Agostini). A VRE Passive Reporting Network established within CNISP identified 1315 cases of VRE throughout Canada between 1994 and the end of 1998, with less than 5% of cases identified as representing infection (25). In the first year of data collection for the VRE Incidence Surveillance Program, 95 cases of VRE were reported, a rate of 0.19/1000 patient admissions and representing 0.55% of enterococcal isolates from the participating facilities (26). Despite the close physical proximity of Canada to the United States, VRE has not attained the same colonization rate in Canada and is very rarely encountered as a cause of infection.

An increasing prevalence of PRSP in Europe, South Africa and the United States was noted between 1974 and 1984, followed by the emergence of strains with resistance to multiple antibiotics. The prevalence of *S pneumoniae* with reduced susceptibility to penicillin varies markedly around the world, with rates of up to 40% in several areas of the United States and to 70% in Korea. Several Canadian studies (10,27,28) reveal that *S pneumoniae* strains with reduced susceptibility to penicillin (both intermediate and high level resistance) have increased significantly, from less than 2% in the late 1980s to 16% in 1998 according to one surveillance system in Canada. Recent

data suggest that up to 5% of isolates have high levels of penicillin resistance. However, in one surveillance system, there has been a decrease in PRSP to 12% during 1999 (28). In addition another Canadian surveillance system has described a decline in PRSP in the past two years (29). It is not known if this is related to changes in beta-lactam prescribing patterns in Canada, which have been declining, or whether it is a spurious decline.

The growth in antibiotic use, and particularly inappropriate use, is a global phenomenon and Canada is no exception. 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/1000 population/day (30). The Compuscript database of IMS HEALTH Canada reveals that approximately 25 million prescriptions for oral antibiotics were dispensed in 1999, making them the third most commonly prescribed class of agents, after cardiovascular and psychotherapeutic drugs (31). Based on recent Canadian data, 51% of antibiotics are being prescribed for patients with upper respiratory tract infections, the common cold and other viral infections for which antibiotics are ineffective (32). These data are consistent with estimates by the CDC suggesting that as many as half of all antibiotic prescriptions are unnecessary. In addition, it is thought that significant costs are being incurred through the excessive use of expensive broad spectrum agents. In Canada, annual expenditures for antibiotics exceed \$485 million (33).

The data for oral antibiotic prescriptions in Canada from 1995 to March 2000 show that there has been a substantial decrease in the number of prescriptions (11,34). By total prescriptions dispensed annually per 1000 population and adjusting for differences in population between 1995 and 2000 (35), oral, solid and liquid antimicrobial consumption in Canada decreased by 11% between 1995 and 2000, with total beta-lactam consumption declining by 16.2% during this same period. Using the number of prescriptions dispensed based on a 12-month moving annual total, the overall decrease between 1995 and 2000 is 29.8% and between 1997 and March 2000 is 24%. Although some efforts to promote judicious prescribing began in the mid-1990s, systematic efforts began in 1997, following the consensus conference (10) where national goals were set to reduce the number of antimicrobial prescriptions for respiratory infections by 25%. Many regions and provinces in Canada have initiated programs to promote judicious antimicrobial prescribing (36-38), and the programs have had significant impact within their respective regions.

With the adoption of the Canadian consensus plan by jurisdictions and regions across Canada, it is hoped that the favourable trends will continue. The WHO, in its report on the growing threat of antimicrobial resistance, cited the recent decreases in antimicrobial prescribing in Canada and suggested that the work done in Canada could be a model for the developed world (8,39).

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