The microbes strike back

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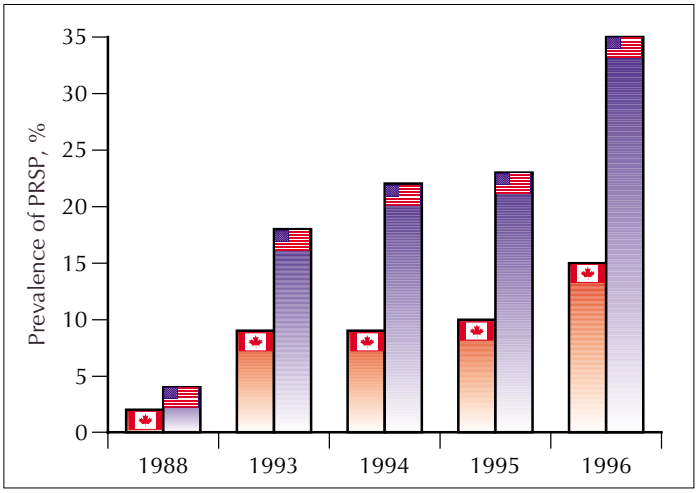
Antimicrobial resistance is a rapidly emerging global problem.[1] In Canada we have so far been spared the scourge of many of the important multidrug-resistant pathogens that have had such an impact on health care in other countries. Unfortunately, this happy circumstance is about to come to an end, unless drastic measures are taken.

Understanding the reasons for the emergence of resistance is essential if we are to develop control strategies. The emergence of resistant bacteria requires both the evolution of resistance mechanisms and their dissemination. The evolution of resistance can occur as the result of frequent spontaneous chromosomal mutations, as occurs in the development of streptomycin resistance in tuberculosis and rifampin resistance in *Staphylococcus aureus* infection, or as the result of a very rarely occurring transfer of genetic material followed by clonal dissemination of the resistant bacteria, the best-recognized examples of which are methicillin resistance in *S. aureus* infection (MRSA) and penicillin resistance in *Streptococcus pneumoniae* infection (PRSP). The former is controlled by avoiding the use of certain drugs or drug regimens for specific pathogens (such as monotherapy for tuberculosis). Controlling the latter involves detecting the introduction of a resistant clone into a susceptible population, implementing appropriate measures to limit transmission, and reducing the use of antibiotics to decrease the size of the niche available to resistant bacteria and the associated likelihood of dissemination.



The evolution of penicillin resistance in *Streptococcus pneumoniae* infection in Canada and the US.

Currently, the most important antimicrobial resistant pathogens in the Canadian hospital setting are MRSA and vancomycin-resistant enterococci (VRE). In the community, the greatest immediate threat is PRSP. Since early 1995 Ontario has witnessed the relentless spread of a clone of MRSA that has been difficult for laboratories to identify, can readily disseminate in hospitals and nursing homes, and is associated with invasive disease.[2] It is estimated that more than 10 000 patients in Ontario will be identified as being infected or colonized with this clone in 1997. Across Canada a steadily increasing number of hospitals have reported dissemination of strains of VRE introduced by patients returning from areas where these strains are endemic. However, the rapid evolution of PRSP in Canada and the US poses even greater problems. In Canada rates of PRSP remained at less than 2% through the late 1980s. However, in the 1990s this situation has changed dramatically. Simor and associates[3] found in a cross-Canada surveillance study that the prevalence of PRSP had increased to 11.7% in 1995, and the increase continues (see figure).

The increase in PRSP is paralleled by an equally important increase in resistance to other antibiotics, including erythromycin, clindamycin, tetracycline and co-trimoxazole. One of the important questions to be faced is, At what level of resistance to an antibiotic in the community should a change in empiric therapy be instituted? The answer obviously depends on the severity of the illness and how likely it is that the change in therapy will affect outcome. Most authorities would agree that the current rates of PRSP require a change in the empiric treatment of suspected pneumococcal meningitis from ceftriaxone alone to ceftriaxone plus vancomycin.[4] Despite widespread use of macrolides to treat community-acquired pneumonia,[5] resistance to

these agents in common pathogens remains low (less than 5%). Because treatment of pneumonia on an outpatient basis has a low mortality rate (less than 1%) no change in approach is necessary.[6]

Finding the means to slow the rise in antimicrobial resistance is as important as appropriately managing individual patients with infections due to resistant pathogens. Fortunately, recent studies have demonstrated that safely reducing antibiotic use is not only feasible but also effective in reducing resistance. Numerous studies have found that physicians routinely prescribe antibiotics for clinical syndromes in which antimicrobials are known to have no effect.[7,8] For instance, Gonzales and associates[8] carried out a sample survey of practising physicians participating in the US National Ambulatory Medical Care Survey. Office visits for colds, upper respiratory tract infections and acute bronchitis, clinical conditions caused by viruses in the vast majority (more than 90%) of cases, accounted for 21% of all antibiotic prescriptions for adults. There are a number of reasons why physicians overprescribe antibiotics: patient expectations, insufficient time to discuss with patients why an antibiotic is not needed and desire to avoid misdiagnosis of bacterial infections for which an antibiotic is indicated.[7] There is therefore an urgent need both to improve prescribing practices and to provide the tools for physicians to diagnose more accurately those conditions for which an antibiotic is indicated. Some of this work is beginning. For instance, McIsaac and associates[9] have developed and validated an age-appropriate score for the management of children and adults with sore throats in general practice. The purpose of the score is to help physicians to minimize unnecessary antibiotic use while appropriately treating streptococcal pharyngitis. These authors projected that using the clinical score would reduce antibiotic prescriptions by 48%.

Programs in both Iceland and Finland have now demonstrated that it is possible to curtail antibiotic use across an entire country and that this results in a decrease in antimicrobial resistance. In Finland, in response to an increase in erythromycin resistance among group A streptococci, nationwide recommendations were issued that called for reduction in the use of macrolide antibiotics for respiratory and skin infections in outpatients.[10] Total consumption of macrolide agents, which had risen steadily to above 2 defined daily doses per 1000 inhabitants per day, fell after the introduction of the program to about 1.4 defined daily doses in 1992. Erythromycin resistance in group A streptococci peaked at 19% in 1993, the year after the reductions in erythromycin use began, and then steadily declined to 0.6% in 1996.

It is possible to curtail antibiotic use across an entire country.

Canada's Laboratory Centre for Disease Control, the United States' Centers for Disease Control and Prevention, and other provincial and state governments have now initiated multidisciplinary partnerships to reduce antimicrobial use. The Canadian goal is to reduce outpatient antimicrobial use by 25% in 3 years, by focusing on community-acquired upper respiratory infection. Our hopes of stemming the tide of antimicrobial resistance in North America depend on the success of these initiatives, on progress in research to understand the evolution and dissemination of resistance, and on the efforts of individual physicians.

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