

# Agricultural antibiotics and resistance in human pathogens: Villain or scapegoat?

Allison J. McGeer, MSc, MD

**D**espite advances in prevention, diagnosis and management, infectious diseases endure as the most common cause of death worldwide and the third most common cause of death in the developed world.<sup>1</sup> The emergence of antimicrobial resistance in human pathogens now threatens to increase overall mortality, morbidity and health care costs around the world.<sup>2</sup> Addressing the issue of antimicrobial resistance has been called one of the most urgent priorities in the field of infectious disease.<sup>3</sup>

Antimicrobial drug resistance arises in populations because of a combination of selective pressure from the use of antimicrobial agents and the import and spread of resistant microbes or genes. Antimicrobial drug use and transmission of resistant pathogens in humans are well-recognized contributors to the increase in antimicrobial resistance. However, the world is not limited to humans, and microbes frequently fail to recognize species boundaries. Thus, as described in this issue by Dr. George Khachatourians (page 1129), the use of antimicrobial drugs in agriculture also has a significant impact on resistance in human pathogens. Nearly half of all antimicrobial use in North America is in agriculture, and the great majority of such use is for promotion of growth in farm animals, rather than for crop treatments or therapy.<sup>4</sup> The volumes used, and the fact that the low doses of antibiotics used for growth promotion may be more effective in inducing resistance than the higher doses used for therapy,<sup>5</sup> mean that this use of antibiotics contributes significantly toward selection for antimicrobial resistance in human pathogens.

What is the most appropriate response to this problem? Last year's Canadian consensus conference on antimicrobial resistance recommended that a national surveillance system be established to monitor antibiotic use and resistance in agri-food and aquaculture.<sup>6</sup> A 1997 meeting of experts sponsored by the World Health Organization recommended in addition that no antimicrobial agent be used in agriculture unless it has been evaluated and authorized by competent national authorities, that a systematic approach to replacing growth-promoting antimicrobials with non-antimicrobial alternatives is essential, and that the use of any antimicrobial for growth promotion be terminated if it is also used for therapeutic purposes in humans or is known to select for cross-resistance to antimicrobial drugs used in human medicine.<sup>7</sup>

The last of these recommendations was initially made in 1969 by the Swann Committee of the United Kingdom and was reiterated in 1994 by a World Health Organization advisory committee.<sup>5</sup> The examples of selection for antimicrobial resistance in livestock and its subsequent transmission to human populations cited by Khachatourians reflect 2 problems with practice related to this recommendation. First, some countries have chosen not to follow it. Other countries, including Canada, have, because of the absence of proof of selection for cross-resistance, continued to use antibiotics that are structurally related to human antibiotics in animal feeds. Unfortunately, research and surveillance data regarding selection for antimicrobial resistance in animals are extraordinarily sparse, and we are just now learning that interpreting the absence of proof as proof of absence may have been an error.

The use of antibiotics for growth promotion is complicated by controversy regarding the need for and cost-effectiveness of this use. It is recognized that the



*Editorial*

*Éditorial*

**Dr. McGeer is a Microbiologist with the Department of Microbiology, Mount Sinai Hospital, and Associate Professor with the Department of Pathobiology and Laboratory Medicine, University of Toronto, Toronto, Ont.**

CMAJ 1998;159:1119-20

‡ See related article page 1129



growth-promoting effect of antibiotics is greatest when primary animal performance is low. In 1986 Sweden became the first country to ban antibiotics for growth promotion. Since then, antibiotic use in animals has decreased by more than 50% in Sweden, and changes in practice have recouped virtually all the productivity losses initially incurred when the ban was imposed.<sup>8</sup> Earlier this year, Denmark followed Sweden's lead. Canada should be joining these countries in setting an example for the world to follow. The change in practice will require considerable effort and a substantial investment into finding alternatives to ensure optimal animal growth. However, as suggested by Witte,<sup>9</sup> such an investment is likely to pay off not only in the protection of our ability to manage human disease but also in more efficient production of food animals in general.

It should be recognized that, important as antibiotic use in animals may be in the evolution of antimicrobial resistance, both antibiotic use and the failure to control the dissemination of resistant clones or genes in human populations are of greater consequence. Human consumption accounts for the majority of all antibiotic use.<sup>4</sup> Antibiotic use not only selects for resistance within a patient's own microflora but also provides a niche for resistant bacteria that come into contact with the patient during therapy. Thus, antibiotic pressure and transmission of resistant clones work synergistically to increase overall resistance. When the overall rate of penicillin resistance in *Streptococcus pneumoniae* is 20% to 40%, recent personal antibiotic use may increase the risk of infection by antibiotic-resistant *S. pneumoniae* as much as 3-fold (US Centers for Disease Control and Prevention, unpublished information).

Until recently, many of us believed that resistant strains were less likely to be virulent than others and that the acquisition of resistance carried with it a price to the organism, such that antibiotic resistance would be lost once antibiotic pressure was removed. There is, however, increasing in vitro data to indicate that neither of these beliefs is true.<sup>10,11</sup> There is also an increasing number of examples of worldwide spread of virulent clones of such multiply-resistant organisms as *Salmonella typhimurium* DT104, *S. pneumoniae* and *Staphylococcus aureus*.<sup>12,13</sup>

Ultimately, the burden of managing the change needed to control antimicrobial resistance will fall on individual farmers, family practitioners and health care institutions. The role of academics, public health departments and governments is to facilitate and support this change and to ensure that the burden is fairly distributed across all of society, to whom the benefit accrues. Although there is a great deal to be done, there is reason for optimism. Experience in other countries has demonstrated that antibiotic use can be reduced, that transmission of hospital pathogens can be controlled and that the overall rate of antimicrobial resis-

tance in bacteria important in human disease can be reduced.<sup>14-17</sup> Health Canada, in collaboration with a variety of national organizations, has created the Canadian Coordinating Committee on Antimicrobial Resistance to coordinate Canadian efforts to reduce antimicrobial resistance. A number of provinces have also initiated programs to complement this effort. Most promisingly, and despite the fact that all these initiatives are in very early stages, recent data suggest that overall outpatient antimicrobial use in Canada has declined steadily since 1995 (unpublished information, IMS Canada). Although the reductions are small, the change indicates that physicians and their patients are already working toward decreased use. With continued work, there is every reason to believe that we can reset the balance and protect ourselves from having to live in the "post-antibiotic" era.

## References

1. World Health Organization. *The World Health Report 1998*. Geneva: The Organization; 1998. Also available: [www.who.ch/whr/1998/reports.html](http://www.who.ch/whr/1998/reports.html)
2. Williams RJ, Heymann DL. Containment of antibiotic resistance. *Science* 1998;279:1153-4.
3. Schwartz B, Bell DM, Hughes JM. Preventing the emergence of antibiotic resistance: a call for action by clinicians, public health officials and patients. *JAMA* 1997;278:944-5.
4. Institute of Medicine. *Human health risks with the subtherapeutic use of penicillin or tetracyclines in animal feed*. Washington (DC): National Academy Press; 1989.
5. WHO scientific working group on monitoring and management of bacterial resistance to antimicrobial agents. Geneva: World Health Organization; 1994. WHO/CDS/BVI/95.7.
6. Controlling antimicrobial resistance: an integrated action plan for Canadians. *Can Commun Dis Rep* 1997;23(Suppl 7).
7. Report of the World Health Organization meeting on the medical impact of the use of antimicrobial drugs in food animals; 1997 Oct 13-17; Berlin. Available: [www.who.ch/programmes/emc/zoo/oct97.pdf](http://www.who.ch/programmes/emc/zoo/oct97.pdf)
8. *Antimicrobial feed additives*. Stockholm: Government of Sweden; 1997. Government Official Reports no 132.
9. Witte W. Medical consequences of antibiotic use in agriculture. *Science* 1998; 279:996-7.
10. Bjorkman J, Hughes D, Andersson DI. Virulence of antibiotic-resistant *Salmonella typhimurium*. *Proc Natl Acad Sci U S A* 1998;95:3949-53.
11. Sayers AA, Amabile-Cuevas CF. Why are antibiotic resistance genes so resistant to elimination? *Antimicrob Agents Chemother* 1997;41:2321-5.
12. Hermans PW, Sluiter M, Dejsirilert S, Lemmens N, Elzenaar K, Van Veen A, et al. Molecular epidemiology of drug-resistant pneumococci: toward an international approach. *Microb Drug Resist* 1997;3:243-51.
13. Simor A, Ofner-Agostini M, Paton S. The Canadian Nosocomial Infection Surveillance Program: results of the first 18 months of surveillance for methicillin-resistant *Staphylococcus aureus* in Canadian hospitals. *Can Commun Dis Rep* 1997;23:41-5.
14. Westh H, Jarlov JO, Kjersem H, Rosdahl VT. The disappearance of multi-resistant *Staphylococcus aureus* in Denmark: changes in the strains of the 83A complex between 1969 and 1989. *Clin Infect Dis* 1992;14:186-94.
15. Vandenbroucke-Grauls CMJE. Management of methicillin-resistant *Staphylococcus aureus* in the Netherlands. *Rev Microbiol* 1998;9:109-16.
16. Ekdahl K, Hansson HB, Molstad S, Soderstrom M, Walder M, Persson K. Limiting the spread of penicillin-resistant *Streptococcus pneumoniae*: experiences from the South Swedish Pneumococcal Intervention Project. *Microb Drug Resist* 1998;4:99-105.
17. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. Finnish Study Group for Antimicrobial Resistance. *N Engl J Med* 1997;337:441-6.

**Reprint requests to:** Dr. Allison J. McGeer, Department of Microbiology, Mount Sinai Hospital, 600 University Ave., Toronto ON M5G 1X5; fax 416 586-3140; [amcgeer@mtsinai.on.ca](mailto:amcgeer@mtsinai.on.ca)