

Antimicrobial Drugs: Miracle Drugs or Pig Feed?

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▪ Introduction

Human medicine is experiencing a crisis because of the increasing emergence of resistance of pathogenic bacteria to antibiotics. The crisis has been caused by a multiplicity of factors, including: use of some drugs for 50 years, excessive use of drugs to treat ear infections in infants in day care centres, and the use in immuno-suppressed people of extremely powerful drugs which kill most of the bacteria in the body, thus leaving it open to be colonized by weakly pathogenic bacteria which are naturally resistant to most antibiotics. As medicine tries to reduce resistance, it is again questioning the widespread use of antimicrobial drugs in farm animals.

Agriculture uses about half of all antimicrobials produced. The extent of the contribution of farm animal use of antimicrobials to resistance in human pathogens has been the subject of vigorous and unresolved debate for several decades. Although it is easy to see how resistant bacteria or resistance genes can get from farm animals to people, the scale and importance of this movement is unclear.

This talk will concentrate on the effect of the European growth promoter, avoparcin, and its role in selecting for vancomycin resistant enterococci (a “superbug”) as an example where surveillance data combined with molecular typing has shown the extent of this movement. It will discuss this in relation to the recent ban on antimicrobial growth promoters in Europe and the proposed format for reexamination of use of individual antimicrobial drugs in animals in the United States. It will also discuss the experiences in Denmark and in Sweden where antimicrobial drug use in swine has been reduced by about half following removal of growth promoters.

▪ **Antimicrobial Resistance: The Crisis in Medicine**

The use of antibacterial drugs selects for resistant bacteria, which tends to occur in stepwise increments. Once a bacterium has acquired a resistance mechanism, it tends to retain it. Use of antibacterial drugs provides the selection pressure for the Darwinian process of natural selection. Only the “fittest” (i.e. resistant) bacteria survive. Antibacterial use over the last 50 years has significantly changed the frequency of different types of bacterial infections observed in animals and humans. Increasing resistance to commonly used antibiotics in common human pathogens has led to the crisis of antibiotic resistance in human medicine. Most of this crisis is the result of just plain use, but in some cases also of overuse and perhaps even of “abuse” of antibiotics in human medicine over the last 50 years. This genuine crisis has led to renewed public questioning about how antimicrobial drugs are used in agriculture and the extent of the agricultural contribution is to this crisis.

Approximately half of all antibiotics produced in North America are said to be used in agriculture, the greatest proportion as growth promoters and disease prophylactics in swine. The swine industry’s use of antibiotics is coming increasingly under scrutiny.

▪ **How Do Bacteria Become Resistant and How Does Resistance Spread?**

The potential for mutation by bacteria, for recombination of genes to form variant genes, and for genetic exchange between bacteria, combined with the short generation time of bacteria, can rapidly produce resistant populations. These bacteria will be selected by the use of antibacterial drugs, although this selection effect is often bacterial species specific and is not inevitable. Acquired, genetically based resistance can arise because of chromosomal mutation or, more importantly, through the acquisition of transferable genetic material. Acquired resistance has been identified in most but not all pathogenic bacterial genera, as well as in the commensal flora. The seriousness of the problem comes both from the fact that once multi-resistant organisms develop they may persist in the host or the environment in the absence of antibiotic selection and because these organisms may act as reservoirs of resistance genes which may spread to other bacteria.

Bacterial populations have remarkable abilities to share genetic information that will promote their survival in adverse environments through specialized genetic elements including bacterial viruses, plasmids, transposons, and integrons. The specialized genetic elements responsible for moving resistance genes between

bacteria seem to have evolved in parallel with, and in response to, the massive antibiotic use, which has occurred in people and in animals in the last 50 years.

Extensive study of antimicrobial resistance in *Escherichia coli*, a common intestinal bacterium, which is easy to track, has shown the relationship between the degree of antimicrobial drug use and the extent of resistance. Resistance is extensive in animals such as pigs kept under intensive conditions where antibiotics are in common use. A high proportion of these normal intestinal *E. coli* shows resistance. In Ontario, it has recently been shown that the extent and type of resistance is directly proportional to the extent and type of antimicrobial use in pigs (Dunlop et al, 1998). Increased resistance of intestinal *E. coli* of animal origin has occurred over the years as a result of the widespread use of antimicrobial drugs in animals. While intestinal *E. coli* coming from pigs are not usually human pathogens, they may be important sources of resistance genes which are transferable. Other bacteria of animal origin such as *Salmonella* serotypes cause serious food borne infections, which may be more difficult to treat because of resistance.

▪ **Antibiotic Resistance in Animal Pathogens and Human Health**

The effect of antimicrobial drug resistance in bacteria of animal origin on human health has been the subject of prolonged and acrimonious debate. In particular, the focus has been on the unrestricted and often widespread use of antimicrobial drugs for growth promotional and disease prophylactic ("subtherapeutic") purposes in food animals. Why antibiotics can be administered to animals on a wide scale in feed to promote growth in animals is not, and never will be, understood by physicians desperate to conserve effective antimicrobial drugs. Besides the crisis of resistance generally in medicine, the recent emergence of vancomycin-resistant enterococci, of multiresistant *S. typhimurium* DT104, and of fluoroquinolone-resistant *Campylobacter*, and the recent ban on growth promoters in the European Union have restimulated discussion of this important issue.

The extent of acquisition by people of bacteria of medical significance which are resistant directly or indirectly as a result of the use of growth promotional and disease prophylactic antibiotics is virtually impossible to quantify. This is because these bacteria may have become resistant as a result of medical use of the same or related antibiotics. It is probably quite low overall (less than 1%?) but is very hard to assess. There is, however, increasing evidence for a contribution to resistance, by selected pathogens, due to the use of certain growth promotional drugs.

Animals and humans do not live in totally separate ecosystems; there are many routes by which resistant bacteria can reach people from animals (Figure 1).

The contribution of agricultural use of antimicrobials to resistance in human pathogens has been the subject of repeated blue-ribbon enquiries for over 30 years, with the general consensus (e.g., National Research Council [NRC], 1999) that use of antimicrobial drugs in food animal production is not without some problems and concerns, but that it “does not appear to constitute an immediate public health concern”. The NRC acknowledged that there are many gaps in knowledge and that additional data might alter this conclusion. It estimated that banning non-therapeutic use of antibiotics in food animals would add \$5- \$10 a year to the cost of food for each United States citizen.

Recent findings in Europe have indicated the scale with which bacteria may reach the people from farm animals fed growth promoters.

Vancomycin-Resistant Enterococci

Enterococci have emerged as a major cause of hospital acquired infection in immunosuppressed human patients treated with broad-spectrum antimicrobial drugs. Enterococci are organisms, which are found normally in the intestines of people and animals. Enterococci are naturally resistant to many commonly used antibiotics, with the exception of vancomycin, but they readily acquire resistance genes (*vanA*, *vanB*) which are found on mobile, transposable elements. Because vancomycin has been virtually the only antibiotic available for treatment of these infections, the emergence of vancomycin resistant enterococci (VREs) (“superbugs”) has become a major problem in hospital acquired infections.

Avoparcin was extensively used as growth promoter in chickens and pigs in Europe precisely because it had no use in human medicine. However, because it is of the same drug class as vancomycin, its use in animals has been associated with the selection of vancomycin resistance in enterococci. The widespread distribution in Europe, but not the United States and Canada, of VREs in farm and pet animals, in fresh meats, and in the human intestine has been accepted as clear evidence that the extensive use of avoparcin as a growth promoter in Europe was responsible for VREs. For this reason avoparcin was withdrawn as a growth promoter in Europe.

Molecular methods of typing VREs have identified that half the isolates obtained from people appear to have originated from chickens and half from pigs. In Muslim countries (where pork is not eaten), the human isolates are, as expected, all the “chicken” type. Preliminary evidence is that a marked decline in intestinal occurrence of VREs in both animals and humans has occurred in Europe following the ban on avoparcin (Klare et al, 1999). This supports the

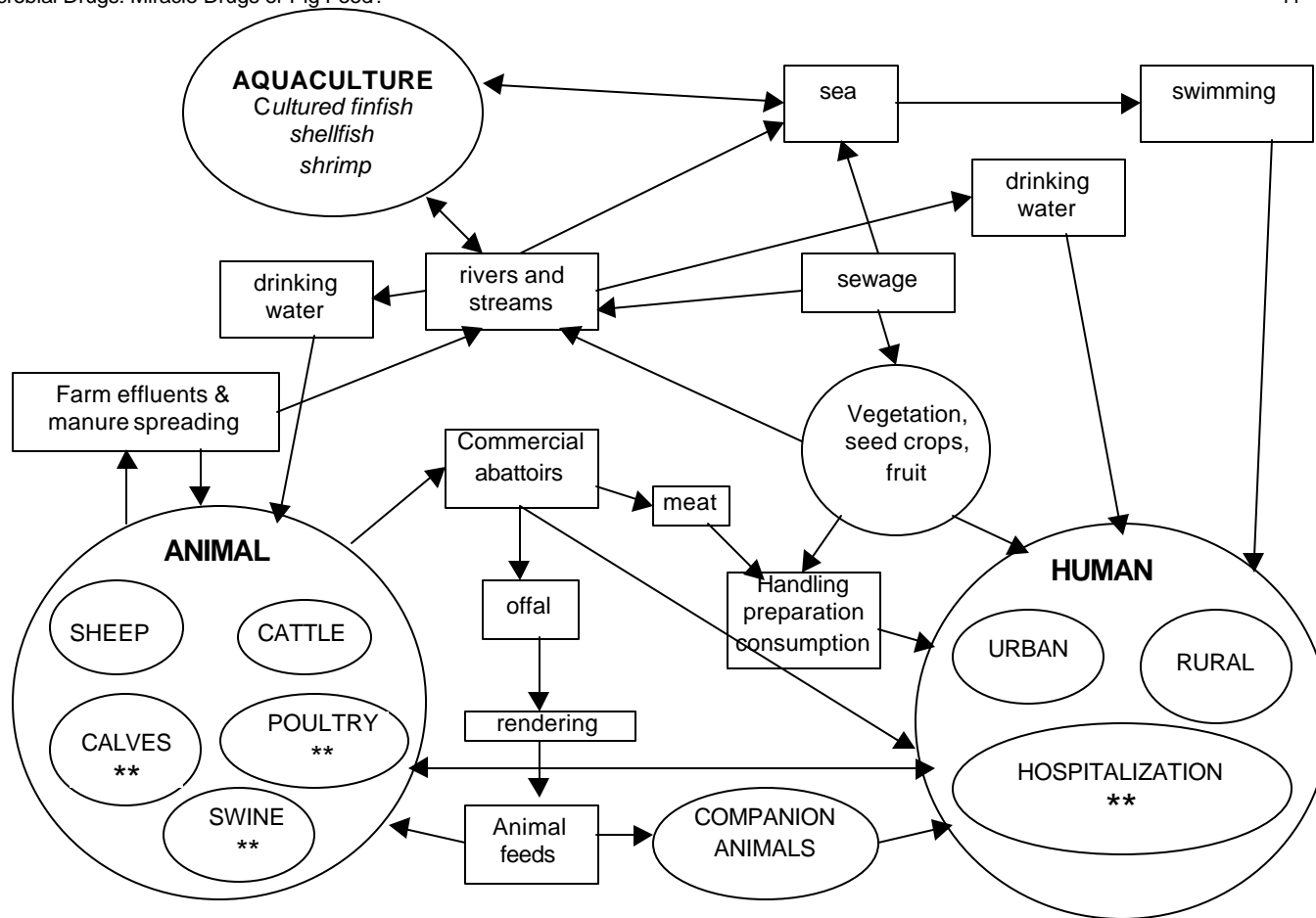


Figure 1. Routes of exchange of *E. coli* between animals and humans. Note the areas where antibiotic selection for resistance is most likely (**). After Linton (1977), as modified by Dr Rebecca Irwin, Health Canada; reproduced with permission.

contention that the acquisition of antibiotic resistant bacteria from animals has probably been more extensive than realized.

Virginiamycin and Synercid resistant Enterococci

Because of the resistance problem in human medicine, a number of novel classes of antibiotics introduced specifically for growth promotion in animals, since they were not at the time used in medicine, have now become the core of some new medically useful drugs. An example is Synercid, which has recently been approved in the United States specifically for treatment of patients with VRE infections. Unfortunately, enterococci resistant to virginiamycin (a growth promoter used in swine and poultry) are also resistant to this drug.

The European Ban

The European Union (1999) has banned avoparcin, bacitracin, spiramycin, tylosin, and virginiamycin as growth promoters. Other growth promoting drugs may follow. The impetus for the ban was the entry of Sweden into the EU. Sweden has banned growth promoters since 1986 but, in order to join the EU, needed to harmonize its regulations with those of the EU. It persuaded the EU to change the regulations, supported by Denmark whose pork producers had, at about the same time, instituted a voluntary ban. The Danish have an unrivalled set of data on antimicrobial resistance in animal derived bacteria, based on an extensive national surveillance system, and have used this to monitor the effects of the ban. Not using growth promoters was seen by Danish pork producers as one factor giving them significant competitive advantage on the world market.

What's Happening in the United States?

This public health issue is being taken very seriously in the United States, where the Center for Veterinary Medicine of the Food and Drug Administration has proposed a framework for evaluating (and re-evaluating) and assuring human safety of antimicrobial drugs used for food animals. The proposed evaluation will depend on the importance of the antimicrobial drug or drug class in human medicine and on the potential human exposure to resistant bacteria acquired from food-producing animals. Drugs may be categorized into 3 groups depending on the value of the drug in human medicine. For example, vancomycin and virginiamycin might be Category I class ("critical" antimicrobial drugs) whereas Category III drugs might be those such as monensin (not used or unimportant in human medicine). Subcategories for each of these 3 groups would depend on the likelihood of human exposure to resistant (usually enteric) pathogens produced by use of these drugs in food animals. In addition, the framework proposes obtaining pre-approval data showing that the level of resistance transfer from proposed use of drugs is safe, and establishing

resistance and monitoring “thresholds” to ensure that approved uses do not result in significant development of resistance in animal-derived bacteria or their transfer to people. A public consultation process is underway.

The proposals of the “framework document” are supported by the national antimicrobial resistance monitoring surveillance (NARMS) program which has been underway for about 3 years in the United States. This program examines resistance in key “target organisms” (e. g., *Salmonella*, *Campylobacter*, *E. coli*, enterococci) isolated from healthy animals and animals, and from people. It also integrates the activities of the US Department of Agriculture with the Centers for Disease Control. These developments are important to Canadian pork producers since it is likely that Canadian regulations will be heavily influenced by developments in the United States.

What's Happening in Canada?

In comparison to Europe, the United States and Australia, Canada has been slow in addressing this issue at a national level. The 1997 Health Canada consensus meeting held in Montreal recommended development of a national surveillance system to monitor antimicrobial resistance in bacteria of animal origin and to monitor use of these drugs in agriculture and aquaculture. This work is being started. An important national conference to define the issue was held in Toronto in October 1999. The first meeting of the Non-human Use of Antimicrobials Steering Committee of Health Canada was held in December 1999. This Committee will prioritize current issues related to agricultural use of antimicrobials, examine international developments, and provide input into policy development of Health Canada relating to agricultural use of antibiotics. The Committee will report to the Bureau of Policy Integration within the Food Directorate.

■ Can We Farm Without Antimicrobials?

No; but we could probably use far less.

Although all are agreed that selective use of antimicrobial drugs is essential in the control of a number of important infectious diseases in animals, it is likely that total antimicrobial drug use in intensively reared animals could be reduced, perhaps by about half its current usage, without significant effects on productivity. The particular target for reduction could be the growth promotional and subtherapeutic use, rather than the therapeutic, use of these drugs.

The experience in Sweden since 1986 and in Denmark since 1997, after the removal of antimicrobial growth promoters, is instructive. In both countries, withdrawal of growth promotional antimicrobials has apparently had negligible

effects on productivity and has reduced vaccine and medical costs of pig production. In Sweden, the greatest effect in pig production was to significantly increase post-weaning diarrhea problems, which have been largely addressed by changes in housing, management (segregated early weaning), hygiene, and feeding practices, as well as by the liberal use of zinc oxide in the rations (now under prescription only). Canadian experimental experience is that it is possible to farm without growth promotional and subtherapeutic feed antibiotics while achieving high productivity (Van Lunen et al, 1999).

▪ **The Future of Antimicrobial Drug Use in Agriculture**

Antimicrobial drugs will always be needed for the treatment of clinical infections in food animals. However, the increasing health status of modern animals, the availability of effective vaccines, and many other approaches should reduce their use. There may be scope for considerable reduction in the total quantity of antimicrobial drugs used in pig production, particularly of the drugs used for growth promotional and subtherapeutic use. It is hard to defend how drugs which select for resistance to the novel classes of antibiotics now being introduced for use in human medicine can continue to be used on a wide scale in food animals. The framework proposed by the United States Food and Drug Administration's Center for Veterinary Medicine for the evaluation and re-evaluation of antimicrobial drug use in food animals appears to be a sensible way to examine drug usage on a drug-by-drug, use-by-use, industry-by-industry basis.

Canadian pork producers, who as a group use a large quantity of antibiotics, could consider following the Danish experience - a national voluntary ban on the use of growth promotional and feed antimicrobials, when these same drugs are significant in human medicine. A national target for a 50% reduction in overall use might be achievable, as it has been in Sweden and Denmark. Such a reduction might be comparable to the 25% reduction target for antimicrobial drug use in human medicine, set at the Montreal Conference of Health Canada in 1997. Alternatively pork producers can wait and watch for the regulators and others to produce the North American evidence on which changes in policies for use of antimicrobial drugs in swine will be based.

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