Ending the Use of Antimicrobial Growth Promoters Is Making a Difference

In Denmark antibiotic resistance levels fell while food productivity remains strong; EU is planning a similar ban by 2006

Henrik C. Wegener

Feeding antibiotics to animals to make them grow faster has been common practice in intensive agricultural production systems since the late 1950s. In the 1980s, our professors told us that such growth promoters bore no resemblance to antimicrobials being used to treat patients, had no direct animal health effects, and were being used in such low doses that they could not influence the development of resistance. We were also told that their major effect was to shift microbial balances in the gut, enabling animals to use feed more efficiently. Little did we know how wrong our professors were.

Nearly 20 years later in December 2002, the European Union (EU) member states agreed that, by January 2006, antimicrobials would no longer be permitted for use as growth promoters for food animals. The main reason for this action is to protect public health against the further development of antimicrobial resistance. What lies behind this dramatic change in attitude, and what will be the consequences—in the microbial world as well as in the animal kingdom?

Evidence Links Farm Antimicrobial Uses to Drug Resistance in Human Pathogens

When Janice Bates and colleagues from Oxford University in the United Kingdom isolated vancomycin-resistant enterococci (VRE) from chickens in 1994, they speculated that farm animals could serve as a reservoir for pathogens causing a rising number of infections among humans in hospitals. Those infections were causing considerable alarm because VRE are resistant to all commonly used antimicrobial drugs, making them virtually untreatable.

Ingo Klare and colleagues from the Robert Koch Institute in Berlin, Germany, in 1995 confirmed the British findings and showed that VRE could be isolated from animals on the farm. Their findings led them to speculate that widespread use of a glycopeptide antimicrobial agent, called avoparcin, to promote growth was responsible for widespread VRE among animals being raised for food production.

Klare and his colleagues contacted scientists in Denmark to ask about VRE in animals being raised on Danish farms. A colleague at the Danish Veterinary Institute (DVI) quickly conducted a survey of VRE in conventionally and organically produced poultry. We learned that, while VRE occurred frequently in birds raised by conventional means, meaning their feed contained antimicrobial growth promoters, birds being raised by organic means and thus not receiving antimicrobials were free of VRE. This study provided us with circumstantial evidence indicating that the use of such growth promoters was producing an animal reservoir for VRE. DVI subsequently conducted large-scale investigations of pig and poultry production farms in Denmark, and findings from those studies substantiated those earlier findings: farm animals receiving avoparcin as a growth promoter harbor VRE.

Other studies documented that the genes encoding resistance to vancomycin in human and animal strains of VRE are identical and may be transferred between animal and human strains. Moreover, detecting VRE in foods and in the gastrointestinal tracts of healthy humans also suggested that VRE infections could be attributable to foodborne transmission of these agents.

Henrik C. Wegener is professor at the Danish Veterinary Institute, WHO Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens, Copenhagen, Denmark.
Taking these findings into account, Danish Minister of Agriculture Henrik Dam Kristensen in 1995 banned further use of avoparcin for growth promotion in animals grown on farms in Denmark. EU rules specify that such a national ban must be followed by an EU-wide ban, provided that the scientific evidence is sufficiently strong to support such a move. If not, the national ban must be lifted. In this case, following substantial scientific debate, the EU Commission in 1997 agreed to ban avoparcin in all EU member states.

In 1997, the World Health Organization (WHO) convened a group of experts in Berlin to consider and evaluate the medical impact of antimicrobial uses in food animals. This group concluded that using antimicrobials to promote growth in such animals contributes to the development of antibiotic resistance and therefore is a major public health concern. In particular, VRE emerged as a consequence of using glycopeptides to promote growth in food animals. The appearance of VRE in such animals brought the risk of its transfer from animals to humans as well as the risk of this resistance disseminating from enterococci to _Staphylococcus aureus_ in the animal reservoir. Subsequent evidence indicated that VRE is transmitted from animals to humans, and vancomycin resistance genes can be transmitted between microbial species within the mammalian gut.

Experts at that WHO meeting recommended that the use of antibiotics for growth promotion should stop in those cases where identical or closely similar antibiotics were also being used to treat animals or humans. They further recommended phasing out the use of other classes of antimicrobials as growth promoters and replacing those drugs with non-antimicrobial alternatives.

Meanwhile, physicians who were treating patients with problematic infections, particularly methicillin-resistant _S. aureus_ (MRSA), were faced with increasingly limited treatment options. In response to this trend, drug companies reevaluated old compounds, some of them previously abandoned because their use triggered adverse side effects, and took new approaches to develop some into safe drugs for clinical use. These efforts led to wider use of the glycopeptide vancomycin and, subsequently, to development of the streptogramin called Synercid. However, in both cases, other members within these two classes of antimicrobial drugs came into use as growth promoters several decades earlier, with their developers then assuming that these drugs were not going to be important in human medicine.

While potential sources of VRE were being thoroughly investigated, microbiologists also were analyzing other classes of antimicrobials being used for animal growth promotion, including virginiamycin, a streptogramin closely related to Synercid, which was being developed to quell otherwise untreatable VRE infections. However, if there were an unrecognized animal reservoir within the agricultural system of Synercid-resistant enterococci because of longstanding use of virginiamycin, it would not bode well for the intended clinical use of Synercid.

Recognizing this threat and after determining that Synercid-resistant enterococci were widespread among farm animals being raised for food production, the Danish Minister of Agriculture unilaterally banned virginiamycin in 1997. Other analysis indicated that genes conferring resistance to virginiamycin are located on transferable genetic elements and that they confer cross-resistance to Synercid. This Danish
During a study tour to India, a local professor told a 20-something Henrik Wegener that, if he wanted to help the developing world, “I shouldn’t scramble around India on a bicycle, but rather go home and educate myself to the highest level attainable in my own country.” Impressed by that advice, he returned to Denmark, and plunged back into his graduate studies in molecular biology and microbiology, and later specialized in food science, focusing on foodborne pathogens and resistance to antimicrobial agents.

Today Wegener, 44, heads the World Health Organization Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens at the Danish Veterinary Institute in Copenhagen, where, earlier, he served as a professor and head of research there. Thus, Wegener was directly involved when Denmark decided to stop using antibiotics to promote growth in food animals—a use that was halted in 1998 for poultry and cattle, and in 2000 for swine.

“In short, the animals are doing well,” Wegener says. “Broiler chickens grow as well as ever, and are healthy as ever. Swine finishers grow as well as ever and are as healthy as before.” Generally, the costs from these changes in farming practice are neutral for food producers and consumers and, in some cases, are offset because of savings from not purchasing antibiotics, he says. “We see much, much less resistant bacteria, such as VRE [vancomycin-resistant enterococci] and synergic resistant enterococci in animals and in the food supply.”

The only noteworthy problems with the antibiotic phase-out have come for those raising baby pigs, whose immature immune systems leave them sensitive to infections when they are weaned at 3–4 weeks of age. Use of growth-promoting antibiotics apparently helped prevent diarrhea among such animals. “Now, occasionally, the veterinarians must prescribe medication for the first few weeks of life—the effect, though, is that before, pigs were on medication all their lives,” Wegener says. “Now, they are on medication an average of 7.9 days of life.”

Wegener spent his childhood summers on a farm, and thought early on that he might become a farmer or veterinarian. “But I ended up in food science, where I divided my interests between nutrition in developing countries and microbiology and hygiene,” he says. “Like most microbiologists, I read Paul de Kruif’s Microbe Hunters as a young person, and it was incredibly inspiring to me.” He received both his master’s and Ph.D. degrees from the Royal Veterinary and Agricultural University in Copenhagen. For his doctoral work, he studied infectious diseases in swine, an effort that stimulated his interest in antimicrobial resistance. Soon after, he began working on the epidemiology of foodborne diseases from the farm to the consumer.

“We initially started looking at resistance in salmonella from animals and humans, and trying to determine the rate and route of transmission,” he says. “But, inspired by work in the U.K. and Germany, we started to investigate vancomycin-resistant enterococci in animals and food. This created major national and international attention—and constitutes a cornerstone in our understanding of the exchange of resistance between animals and humans.” Since then, he has participated in a number of WHO expert consultations on these issues, and helped develop global principles for the prudent use of antibiotics in food animals.

There are no other scientists in Wegener’s family, which instead includes “a lot of bishops and priests,” he says. However, he adds, his wife works in a lab although not at his institute. They have three children—two sons, 10 and 4, and a daughter, 12. “We live in a nice suburb outside the capital, Copenhagen, right by the woods and the big lakes,” he says. Wegener loves skiing and other outdoor sports, and for 16 years played bass guitar in a rock-soul-funk band. But the band was disbanded, he says with remorse. “Traveling and family determined it was time to unplug [quit].”

Marlene Cimons
Marlene Cimons is a freelance writer in Bethesda, Md.

**Resisting Resistance**

During a study tour to India, a local professor told a 20-something Henrik Wegener that, if he wanted to help the developing world, “I shouldn’t scramble around India on a bicycle, but rather go home and educate myself to the highest level attainable in my own country.” Impressed by that advice, he returned to Denmark, and plunged back into his graduate studies in molecular biology and microbiology, and later specialized in food science, focusing on foodborne pathogens and resistance to antimicrobial agents.

Today Wegener, 44, heads the World Health Organization Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens at the Danish Veterinary Institute in Copenhagen, where, earlier, he served as a professor and head of research there. Thus, Wegener was directly involved when Denmark decided to stop using antibiotics to promote growth in food animals—a use that was halted in 1998 for poultry and cattle, and in 2000 for swine.

“In short, the animals are doing well,” Wegener says. “Broiler chickens grow as well as ever, and are healthy as ever. Swine finishers grow as well as ever and are as healthy as before.” Generally, the costs from these changes in farming practice are neutral for food producers and consumers and, in some cases, are offset because of savings from not purchasing antibiotics, he says. “We see much, much less resistant bacteria, such as VRE [vancomycin-resistant enterococci] and synergic resistant enterococci in animals and in the food supply.”

The only noteworthy problems with the antibiotic phase-out have come for those raising baby pigs, whose immature immune systems leave them sensitive to infections when they are weaned at 3–4 weeks of age. Use of growth-promoting antibiotics apparently helped prevent diarrhea among such animals. “Now, occasionally, the veterinarians must prescribe medication for the first few weeks of life—the effect, though, is that before, pigs were on medication all their lives,” Wegener says. “Now, they are on medication an average of 7.9 days of life.”

action was soon followed by an EU-wide ban of virginiamycin as well as three additional antimicrobial growth promoters: tylosin, spiramycin, whose human counterpart is erythromycin, and bacitracin.

**Monitoring Denmark’s Comprehensive Growth Promoter Ban**

In April 1998, Danish poultry, cattle, and pig producers agreed voluntarily to stop using all antimicrobial growth promoters. That ban became effective immediately for all poultry, cattle, and for those pigs weighing more than 35 kg, but was phased into effect for weanling pigs by January 2000. Since that date, farmers in Denmark have not used antimicrobials for growth promotion.

To evaluate the impact of these restrictions and subsequent ban on growth promoter uses on antimicrobial resistance levels and on trends in antimicrobial therapeutic uses, Danish officials and other experts in 1995 established the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP). Its members include the Danish Veterinary Institute, the Danish Veterinary and Food
Administration, and the Statens Serum Institut. DANMAP regularly monitors antimicrobial resistance in pathogenic and indicator bacteria obtained from animals, foods, and humans, and it also tracks usage of antimicrobials in both animals and humans.

Despite an increase in therapeutic drug usage immediately following the withdrawal of antimicrobials as growth promoters, DANMAP figures indicated that the total volume of antimicrobials being used for food animals was reduced by more than 50% (Fig. 1). Some of that initially increased use of therapeutic antimicrobials was to treat diarrheal disease in weanling pigs among those few herds where this problem emerged, whereas some usage was prophylactic (in advance of symptomatic disease) in herds where management strategies were not immediately adjusted to deal with the changing situation.

Ending the use in agriculture of these antimicrobial growth promoters represents a huge reduction in selective pressure for antimicrobial resistance traits. Indeed, resistance to several formerly widely used agents, including tylosin, virginiamycin, avoparcin, and avilamycin, declined dramatically throughout Denmark, particularly among *Enterococcus faecium* isolates obtained from poultry flocks (Fig. 2). This documented decline indicates that the former growth-promotional use of such antimicrobials helped in maintaining high levels of antibiotic resistance among enterococci associated with the food animals. This drop in resistance levels is important in another respect. Earlier, when food producers ceased using chloramphenicol as a growth promoter in animals, high levels of antibiotic resistance in animal-associated bacteria persisted for decades, well after that selective pressure was removed.

Although VRE levels among Danish poultry flocks plummeted almost immediately after avoparcin was withdrawn in 1995, resistance to this drug among bacteria associated with pigs initially changed little if at all (Fig. 2). However, when another growth promoter, the macrolide tylosin, was also removed, VRE levels quickly declined. Because nearly all VRE associated with pigs were also resistant to tylosin, the ongoing use of that drug had effectively maintained high levels of VRE through the mechanism of coselection.

Reduced tylosin selective pressure also has led to a drop in antimicrobial resistance in isolates of *Campylobacter coli* from pigs, a microorganism that can act as a pathogen in humans (Fig. 3). This reduction in macrolide resistance may prove helpful because macrolides are considered a drug of choice for treating humans who become infected with *C. coli* in those relatively few cases where treatment is indicated.

The DANMAP program has not systematically monitored healthy humans in Denmark during this period. However, scientists monitor-
ing VRE trends in three European countries report a consistent decline in VRE carriage by humans. This decline could prove important because VRE carriage is an important risk factor for VRE infections in hospitals (Fig. 4). Since the ban, *Salmonella* prevalence in Danish poultry flocks and swine herds also continues to decline, along with other foodborne pathogens as well as foodborne diseases in humans.

**Farm Consequences following Growth Promoter Ban in Denmark**

When the antimicrobial growth promoter ban was being planned, Danish food producers expressed several concerns, including that it would lead to increased feed consumption, increased morbidity and mortality among herds and flocks, increases in *Salmonella* and other foodborne pathogens, and increased consumption of antimicrobials for therapy. They also suggested that these changes would lead to no or only limited effects on antibiotic resistance levels.

To address some of these issues, my colleagues and I analyzed national poultry productivity data provided by the Danish Poultry Council. This analysis encompassed more than 8,000 flocks for slaughter between November...
1995 and June 2001, for which we tabulated kg of broilers produced per m² (per flock); feed conversion ratios (kg feed/ kg broiler); and mortality rates.

Overall productivity is measured in terms of kilograms of broiler chickens produced per square meter of housing space. By this measure, withdrawing antimicrobial growth promoters did not reduce productivity whatsoever. Similarly, animal mortality rates remained even and, if anything, appeared to decline slightly. Meanwhile, feed efficiency changed slightly, with 16 g more feed now required to add 1 kg of mass to chickens being raised without growth promoters. However, the savings from not having to purchase such antimicrobials offsets the extra cost of feed. The total volume of Danish broiler production has increased steadily since 1998.

We and others also detect little if any effect from the withdrawal of growth promoter use among older, or “finishing” pigs. However, among younger or weanling pigs, some producers report problems such as higher rates of diarrhea, decreases in daily weight gain, and increases in mortality rates. Overall productivity continues to increase steadily since growth promoters were banned, in part due to genetic and other improvements. Nonetheless, pork producers estimate their postban profit losses to be approximately $1 per pig, or about $.01 per kg.

Some observers suggested that withdrawing antimicrobial growth promoters would harm the environment because of increased discharges of nitrogen- and phosphorous-containing animal wastes from farms. This concern arises from the assumption that animals not receiving antimicrobial growth promoters would require 10% more feed intake to reach appropriate slaughter weights. However, data from Danish farms show that changes in feed consumption and feed conversion rates are much smaller than anticipated. In reality, discharges of nitrogen and phosphorous from Danish animal production farms has steadily decreased due to improved feed and waste management programs.

The effects of the antimicrobial growth promoter termination in Denmark have recently been subject to an independent expert review by WHO. The report of this review is available from the WHO website (www.who.int).

SUGGESTED READING


