



# Restricting Antimicrobial Use in Food Animals: Lessons from Europe

Banning nonessential antibiotic uses in food animals is intended to reduce pools of resistance genes

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**A** group of experts, convened last year by the Alliance for the Prudent Use of Antibiotics (APUA), reviewed the impact of the European Union (EU) decision to stop using antimicrobials to promote growth in food animals. The group, which was cochaired by Herman Goossens of the University of Antwerp in Belgium and Christina Greko of the National Veterinary Institute in Uppsala, Sweden, consisted of 16 delegates from 10 EU countries, who met in May 2010.

First Sweden in 1986, then Denmark, the United Kingdom, and other countries of the European Union introduced bans on the use of antibiotic growth promoters (AGPs) in food animal production. Some of these bans were closely monitored from the outset, whereas others were not fully enforced at first. However, in part as a response to the rise of antibiotic resistance in clinical settings, officials have moved to strengthen both monitoring and enforcement efforts involving the agricultural sector. Meanwhile, in general, animal food production in these countries continues to thrive, with appropriate adjustments in practices to ensure continued animal health and safety.

## Several Findings Led EU to Ban Antimicrobials as Growth Promoters

European countries began to raise concerns about the use of antimicrobials as growth promoters in food animal production soon after drugs were first approved for this use in the early 1950s, with the advent of intensive

farming practices to improve feed conversion, speed animal growth, and reduce disease. In 1969, the Swann Committee, established by the British Government, issued a report calling for restricted use of AGPs to reduce the risk of resistance developing to drugs used in human medicine. The committee was formed in response to discovery of transferable oxytetracycline resistance from food animals to *Salmonella enterica* Serovar Typhimurium. Its recommendations led to withdrawal of penicillin, streptomycin, and tetracyclines from the list of authorized AGPs in many European countries in 1972–1974.

In 1980, Swedish officials began to collect data on antimicrobial use in agriculture, and in 1986, Sweden became the first country to regulate withdrawal of AGPs in food animal production. Swedish farmers requested that ban in part

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### Summary

- The first ban on farm use of antibiotic growth promoters (AGPs) was enacted in 1986 in Sweden.
- Studies from several decades ago established that nontherapeutic use of antibiotics selects for resistance, resistance in humans is determined by the same mechanism as in animals, and resistance genes can disseminate via the food chain into the intestinal flora of humans.
- Farm use of AGPs increases selection pressure and fosters the dissemination of resistance.
- A major goal of the European ban on AGPs is to reduce antibiotic resistance traits in the microbial flora of farm animals.

because a 1984 report stated that consumer confidence in meat safety dropped after learning that 30 tons per year of antibiotics were being used in Sweden in food animal production.

During the early 1990s, vancomycin-resistant *Enterococcus* (VRE) was detected among patients in Europe. In the search for a community reservoir of that resistance, VRE was found in meat and also in manure on farms where avoparcin was used as a growth promoter, according to Wolfgang Witte and his collaborators at the Robert Koch Institute. In 1997, the EU banned avoparcin for all uses in agriculture. In 1999, EU officials discontinued further use of AGPs from drug classes also used in human medicine, imposing a ban on tylosin, spiramycin, virginiamycin, and bacitracin. Other antimicrobials were phased out in 2006.

Data gathered by DANMAP, the Danish surveillance system for monitoring antimicrobial use and resistance, facilitated these decisions. Swedish agricultural data, which indicated no loss in production after the ban on AGPs, encouraged other European countries to move forward with similar restrictions.

### Evidence Supporting EU Ban on Antimicrobials as Growth Promoters

When chickens consume low doses of the antibiotic oxytetracycline as part of their feed, multidrug resistance emerges among *Escherichia coli* that are isolated from their feces, according to Stuart Levy at Tufts University School of Medicine in Boston and his collaborators, who conducted prospective studies of this phenomenon beginning in 1975. Those multidrug resistance traits quickly transferred into *E. coli* in fecal samples of nearby farm dwellers, who were not using any antibiotics.

In the 1980s, similar findings came from a large field study involving 35,000 people that was conducted by Ruth Hummel, Helmut Tschäpe, and Wolfgang Witte at the Robert Koch Institute in Wernigerode, then part of East Germany. They focused on transferable streptothricin resistance that was associated with the use of nourseothricin as a growth promoter in farm animals. Their findings corroborated those of Levy and his collaborators. Later, other studies indicated the main selective force for streptogramin resistance genes in *Enterococcus fae-*

*cium* in humans was from use of virginiamycin as a growth promoter in food animal production in Germany and the Netherlands.

Those studies established the link between the use of AGPs in farm animals with the emergence, spread, and transfer of resistance genes from microorganisms associated with those animals to bacterial pathogens that infect humans. Altogether, the studies establish three important principles:

- Low-dose, nontherapeutic use of antibiotics selects for resistance to those antibiotics.
- Resistance to antibiotics used in humans is determined by the same mechanism as those used in animals.
- Resistance genes disseminate via the food chain into the intestinal flora of humans.

### EU Officials Moved To Withdraw Antibiotic Growth Promoters

The goal of the EU and country-specific bans of nonessential antibiotic use in food animal production is to reduce the pool of resistance genes in farm animals and other nonhuman settings. Although a resistance monitoring system was not in place in 1986 when the first European ban took effect in Sweden, the agriculture extension services, efforts to educate farmers, and a system for monitoring antimicrobial use were in place to support the ban. After the ban, antimicrobial consumption fell in that country without a loss in meat production.

In Denmark, DANMAP data demonstrate that the same ban of nonessential antibiotic use in food animal production is working without major consequences for animal health. The Danish approach includes extensive monitoring systems to track drug resistance and antimicrobial use as well as services for research and analysis. Denmark can further reduce antimicrobial consumption by 50%, to 25 mg/kg, by quite simple measures, according to Aaerstrup.

When U.K. officials instituted a ban on nonessential antibiotic use in food animal production, they did not provide resources to establish a monitoring system. Meanwhile, Dutch efforts in this area differ from those in Sweden, Denmark, and the United Kingdom. For example, although Dutch officials promulgated regulations to limit antibiotic usage in animal produc-



## Country-Specific Experiences and Perspectives

**Sweden.** Sweden established SVARM to monitor antimicrobial resistance in farm animals in 2000, although Swedish officials first collected statistics on antimicrobial use in agriculture as early as 1980. After the 1986 ban, sales of antibiotics for animals fell from an average of 45 tons of active substance to about 15 tons by 2009.

To facilitate the move to a new mode of animal husbandry, Swedish officials developed guidelines on feed, medication, management, and hygiene to keep animals healthy and prevent infections. Large efforts were directed to problem-oriented research and to providing extension services for farmers. Early problems following the ban included necrotic enteritis and *Clostridium perfringens*-associated diarrhea in poultry, and weaning diarrhea and dysentery in piglets and slaughter pigs, respectively.

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**Denmark.** In 1995, Denmark established DANMAP, a system for monitoring antibiotic resistance in farm animals, to follow the impact of withdrawing antibiotic growth promoters (AGPs). Comparable monitoring of antibiotic resistance in humans began three years later. The Danes withdrew AGPs from food animal production to reduce an observed reservoir of antibiotic resistance in food animals. Avoparcin use was banned in 1995 and virginiamycin in 1998, with a comprehensive ban on AGPs by 2000. Danish swine and poultry production continues to thrive following the ban. Meanwhile, Denmark has experienced major reductions in antimicrobial consumption and resistance.

Between 1992 and 2008, Danish farmers increased swine production by 47%, maintaining their standing as

being among the largest exporters of pork in the world while exporting 90% of pork they produce. During this period, antimicrobial use in swine was reduced by 51%, from 100.4 to 48.9 mg/kg meat. Since the ban, production in poultry has increased slightly, and there has been a 90% reduction in total antimicrobial usage: from about 5,000 kg used in 1995 to less than 500 kg used (for therapy) in 2008.

Following the ban on AGPs, therapeutic use of antimicrobials gradually increased following outbreaks of *Lawsonia intracellularis* and post-weaning multisystemic wasting syndrome (PMWS) in pigs. However, the overall use of macrolides, which the World Health Organization (WHO) classifies as critically important for human medicine, was reduced.

From 1996–2008, there were major reductions in vancomycin-resistant *E. faecium* from broilers and pigs following decreased use of avoparcin. Similarly, macrolide resistance (tylosin is used for therapy as well as AGP) and avilomycin resistance were reduced in *E. faecium* among broilers.

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**The Netherlands.** Dutch officials established MARAN, a system for monitoring antibiotic resistance in food pathogens, animal pathogens, and indicator organisms in 1999. Dutch sales data indicate that with the termination of growth promoters in 2006, therapeutic drug usage increased to levels that kept total antibiotic use static, highlighting the importance of clearly defining “therapeutic” and “non-therapeutic” use. In 2007, 90% of the 600 tons of antibiotics was administered through oral mass medication.

tion, they did so without a plan to implement or enforce them. Thus, when the AGP ban went into effect, food animal producers were not ready to alter their practices. Subsequently, when the Netherlands experienced high levels of antibiotic resistance in food animals following massive use of these agents, the government intervened by mandating a 50% reduction in antibiotic usage in the next three years through defined daily dosages and transparency in prescriptions.

### Other Risks from Nontherapeutic Uses of Antibiotics in Agriculture

Mutagenesis and horizontal gene transfer do not occur by chance, according to Patrice Courvalin of Institut Pasteur in Paris, France. “Low concentrations of antibiotics induce random mutagenesis,” he explains. “If you use low concentrations of penicillin in pneumococci, you will select for resistance to other drug classes, while strains are still susceptible to penicillin, because

Despite the ban of AGPs, nothing changed in the Dutch food animal production system. Antibiotics were still used extensively to treat infectious diseases, to balance feed quality in broilers, and to treat noninfectious conditions such as dysbacteriosis. Factors contributing to this scaled-up use of antibiotics included farm expansions, poor use of infection control measures, insufficient government control over antibiotic use and sales, and resistance from farmers to mandated changes in their practices.

Nonetheless, the withdrawal of AGPs led to a decrease of VRE in food animals and a decrease in resistance to avilamycin. However, use of high levels of antibiotic continues, while multidrug-resistant bacteria continue to spread among food animals. For example, throughout Dutch farms, there is a high prevalence of fluoroquinolone-resistant *Campylobacter* in poultry, MRSA ST398 in pigs and veal calves, and ESBL-producing *E. coli* and *Salmonella* in broilers, according to a 2008 report from MARAN. The occurrence of methicillin-resistant *Staphylococcus aureus* and extended-spectrum  $\beta$ -lactamase-producing bacteria among food-producing animals has implications for public health in the Netherlands and affects costs in health care settings.

The Dutch experience illustrates that withdrawing AGPs needs to be accompanied by other interventions, including appropriate monitoring and disease control measures in the agricultural sector. Without such measures, bans on AGPs will be replaced by increased therapeutic use of antimicrobials. The Netherlands has responded to its antibiotic resistance crisis with a mandate to reduce their use in food animals by 50% during the next three years and to establish a registration process for veterinary prescriptions of antibiotics.

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**United Kingdom.** Most UK poultry and many swine producers stopped using AGPs before the EU ban in 2006. A government ministry organized a stakeholder meeting, provided general support for farmers as they implemented the ban, and also furnished them with relevant reports from Denmark and the World Health Organization. Pharmaceutical companies also informed farmers about alternative approaches to cope with the move away from AGP use on farms, and the news media invited several farmers to be interviewed; those reports helped in spreading the word about the move from AGPs to alternative strategies for food animal production.

Officials collected antibiotic sales data from pharmaceutical companies, indicating an overall decline in AGP usage from 1998 onwards. In addition, following the ban, total consumption of therapeutic antimicrobials declined in food-producing animals. However, therapeutic use of macrolides increased, possibly to control organisms such as *Lawsonia intracellularis*. Although UK data are incomplete, necrotic enteritis in broilers remained under control, whereas proliferative haemorrhagic enteropathy in pigs and cholangiohepatitis in broilers increased after withdrawal of AGPs.

In the absence of a detailed study, two abattoir surveys of antibiotic use in pigs following the ban on AGPs indicate that resistance to erythromycin in *Campylobacter coli* and *Enterococcus faecium* declined, from 85% in 1999–2000 to 36% in 2007. Vancomycin resistance in *E. faecium* from pigs was less than 1% in both surveys.

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it is just random mutagenesis.” The increased mutation rate may promote horizontal gene transfer. Thus, low concentrations of fluoroquinolone and aminoglycoside resistance genes induce mutations, leading to transfers of these traits. Farm use of AGPs increases selection pressure and fosters the dissemination of resistance. Such findings support the current ban of agricultural use as part of a more general effort to preserve the clinical utility of antibiotics, he says. Other meeting participants said that the

use of low-dose antibiotics in food animal production exerts a particularly strong selective force to develop resistance, which is irreversible, posing treatment problems for the future.

A complex environmental background underlies the emergence and spread of resistance, according to Fernando Baquero of the Ramón y Cajal University Hospital in Madrid, Spain. Antibiotics in agriculture act as ecotoxic agents favoring antibiotic resistance. The dispersal of antibiotics into soil and water enhances the risk



### EU Withdrawal of Nontherapeutic Antibiotics (NTAs) in Food Animal Production Timeline

<b>1963–1965</b>	Epidemic of resistant <i>Salmonella typhimurium</i> in UK
<b>1969</b>	Swann Committee in UK recommends that antimicrobials for animals be divided into two groups: feed additives used without a prescription and therapeutic agents used with a prescription; recommends restricting use of antimicrobial growth promoters.
<b>1972–1974</b>	European bans on use of tetracycline, penicillin, and streptomycin for growth promotion
<b>1986</b>	Sweden bans use of antibiotics for growth-promotion in agriculture, as requested by Federation of Swedish Farmers.
<b>1988</b>	Sweden stops use of all general prophylactic medications.
<b>1993</b>	Vancomycin-resistant enterococci (VRE) is reported in food animals in the UK.
<b>1994</b>	Denmark restricts direct sale of therapeutic antimicrobials from veterinarians and limits veterinary profits from antimicrobial sales.
	Denmark bans routine prophylactic use of antimicrobials.
<b>1995</b>	Denmark bans the use of avoparcin for all purposes in agriculture. DANMAP (Danish Integrated Antimicrobial Resistance Monitoring and Research Program) is initiated.
	Sweden and Finland join the European Union and lobby for EU-wide ban on agricultural growth promoters (AGPs).
<b>1996</b>	Germany bans use of avoparcin.
<b>1997</b>	EU bans use of avoparcin. Netherlands bans use of olaquinox and carbadox. WHO Berlin meeting, “The medical impact of the use of antibiotics in food animals,” concludes that use of medically important antimicrobials as growth promoters should be stopped.
<b>1998</b>	The Copenhagen Recommendations: recognition of antimicrobial resistance as a global threat; call for development of new antimicrobials and establishment of a European Surveillance System
	Denmark bans use of virginiamycin.
<b>1999</b>	Scientific Steering Committee of the European Commission recommends phasing out antimicrobial growth promoters that are medically important and implementing disease-preventive methods. EU bans olaquinox and carbadox; suspends authorization of bacitracin, tylosin, spiramycin, and virginiamycin. EARSS (European Antimicrobial Resistance Surveillance System) established. Sweden bans use of remaining AGPs: flavophospholipol and avilamycin. UK’s Advisory Committee on the Microbiological Safety of Food issues a report recommending improved veterinary training and surveillance of resistance.
<b>2001</b>	ESAC (European Surveillance of Antimicrobial Consumption) launched to collect data on antimicrobial use in ambulatory and hospital care.
<b>2006</b>	EU ban on all AGPs.
<b>2008</b>	ESVAC (European Surveillance of Veterinary Antimicrobial Consumption Project): European Commission asks the European Medicines Agency to harmonize surveillance programs collecting data on antimicrobial sales and usage.

of breaking natural barriers between bacterial groups via horizontal transfer of genes conferring antibiotic resistance. Because agriculture accounts for the highest volume of antibiotic use, the farm environment serves as a reservoir of resistance genes. When transferred to bacterial pathogens that infect humans, drug resistance increases suffering and raises death rates due to treatment failures in patients who become infected with those pathogens.

Because industrialized farming appears to depend on the use of high levels of antibiotics, Wolfgang Witte of the Robert Koch Institute in Berlin, Germany, recommends shifting to alternative systems of farming. Humans exposed to

livestock that are colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) have a 138-fold higher risk of becoming colonized with those bacteria than are nonexposed people, according to Christiane Cuny, who is also from the Robert Koch Institute. Moreover, livestock-associated MRSA is more likely to occur on farms that follow conventional practices.

#### Long-Term Goals of the European Ban

The European ban on the use of low-dose antibiotics to increase food production is part of an effort to restore the microbial flora of animals to an earlier state in which those micro-

organisms did not carry antibiotic resistance traits. More broadly, farm practices involving antibiotics affect patients in the clinic, some of whom are dying as a consequence of resistant infections. This question of how agricultural uses of antibiotics affect their efficacy among humans is part of a multilevel issue. In that sense, it resembles other health issues in which behaviors may lead to important health consequences, albeit through a complex series of imperfectly understood steps. Other examples include the relationship between smoking and lung cancer and consuming cholesterol-rich foods and heart attacks.

Advances in microbial population biology enable us to realize that some bacterial clones that

humans share with animals are more critical than others. In addition, we know more about the microbial connectivity between animals and humans. This knowledge could be applied to develop more targeted interventions to reduce the selection pressure exerted on the emergence, evolution, and spread of antibiotic resistance. It could help inform global policies to improve how farm uses of antibiotics are regulated, with the goal of preserving their effectiveness.

Those interested in learning more about this material are invited to review materials available through the APUA blog: <http://superbug.sanddrugs.blogspot.com>. Additional information on the roundtable program is available under research at <http://www.apua.org>.

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