ENVIRONMENTAL ISSUES

Antimicrobial Resistance Trends in Denmark Following the Ban on Including Antimicrobials in Livestock Feeds

EXPERT REVIEWED

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The use of antimicrobials (substances that kill or inhibit microorganisms) in food animal production is one of the more controversial agricultural practices in the United States. Currently, these antimicrobials are used in two basic ways: 1) in low doses in feed or water to prevent common diseases (see text box) and 2) in higher doses to treat specific diseases after they appear. The first use receives the most attention. Critics contend that using antimicrobials in the feed of healthy animals that show no clinical signs of disease is unnecessary and bad for human health, because it promotes development and spread of antimicrobial-resistant bacteria.

> Because adding antimicrobials to the feed and water of healthy animals often results in improved growth rates, antimicrobials used in this form are sometimes called antimicrobial growth promoters (AGPs).

Beginning in 1999, Denmark began phasing out antimicrobial growth promoters (AGPs). Around the same time, the country started a nationwide program to monitor the amounts and types of antimicrobial substances used in both veterinary and human medicine. They also looked for trends in antimicrobial resistance in microbes from livestock and humans (Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, DANMAP). The following is a summary of eight years of DANMAP data examining how banning the use of antimicrobials in livestock and poultry feeds has affected antimicrobial resistance in Denmark.

Pre-1999 Antimicrobial Use in Food Animal Production

Before 1999, AGPs made up more than half of all antimicrobials used per year in food animal production (Figure 1). After AGPs were banned, the use of antimicrobials to treat established diseases increased by about 40%. Despite the fact that more antimicrobial were used to treat diseases after the AGP ban, total antimicrobial consumption in food animals still decreased from a peak of over 200 tons in 1994 to about 128 tons in 2008.

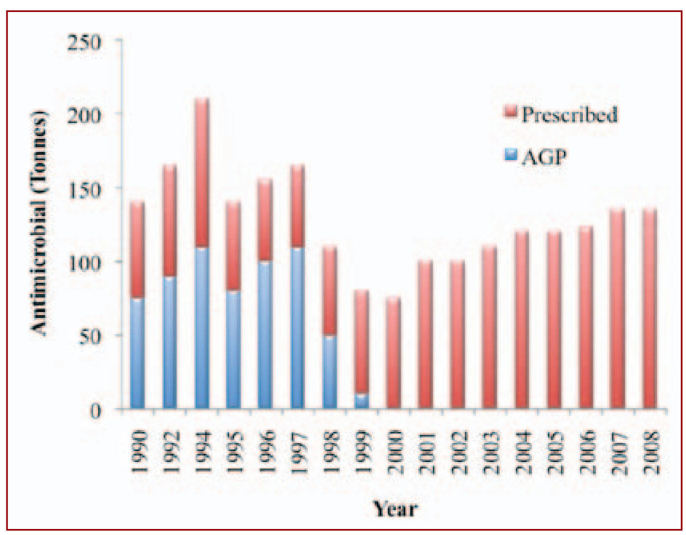


***Figure 1.** Changes over time in antimicrobial use in Danish livestock and poultry production. Adapted from DANMAP figure 43.*

Table 1. Comparison of antimicrobial resistance in E. coli *isolates obtained from food animals prior to banning AGPs and eight years following the ban. Adapted from DANMAP Figure 31. Numbers represent estimates of percentages of isolates resistant to the different antimicrobials.*

Compound	Broilers		Cattle		Pigs	
	1999	2008	1999	2008	1999	2008
Ampicillin	12	10	8	2	12	19
Nalidixic Acid	12	12	0	0	<1	<1
Sulfonamide	22	11	6	5	40	24
Tetracycline	16	10	7	1	34	29
Streptomycin	8	7	7	4	55	26

Antibiotic Resistance in Bacteria Isolated from Livestock

***Generic* E. coli**. DANMAP uses several different types of bacteria to gauge trends in antimicrobial resistance. Generic *E. coli* is used to compare resistance levels to five antimicrobials (ampicillin, nalidixic acid, sulfonamide, tetracycline, and streptomycin). Resistance levels in E. coli from broilers, pigs, and cattle before and following the ban on AGPs are compared in Table 1. Since the ban on AGPs, antimicrobial resistance has decreased in approximately 40% of comparisons. In most cases, antimicrobial resistance in generic *E. coli* isolates has remained unchanged. In the cases of pigs, ampicillin resistance has increased.

***Pathogenic* E. coli.** Resistance trends are also monitored in *E. coli* O149, a more pathogenic type of *E. coli*. Unlike generic *E. coli* mentioned above, *E.coli* O149 isolates are obtained from cattle and swine that show clinical signs of infection and are likely to have been treated with antimicrobials (Table 2). After antibiotic therapy, antimicrobial resistance levels in bacteria isolated from diseased animals are regularly higher than resistance levels in healthy animals. However, since the ban on AGPs, antimicrobial resistance decreased in six of 14 cases. As in generic *E. coli* from healthy pigs, ampicillin resistance increased in *E. coli* O149 from diseased pigs. In all other cases, resistance remained constant.

***Enterococcus* spp.** Many of the banned AGPs are active mostly against a group of bacteria called *gram-positive bacteria*. DANMAP uses *Enterococcus* spp. as an indicator, gram-positive organism when checking for antimicrobial resistance in food animals. In the cases of virginiamycin, avilomycin, avoparcin and macrolides, resistance has decreased in *Enterococcus faecium* from both broilers and pigs. Resistance to tetracycline, a broader spectrum antimicrobial (active against gram-positive and gram-negative bacteria), has increased in *Enterococcus faecium* isolates from pigs.

Foodborne Pathogens. *Salmonella* and *Campylobacter* serve as indicator, gram-negative organisms for monitoring antimicrobial resistance in foodborne pathogens. In contrast to other types of bacteria, antimicrobial resistance in *Salmonella* from pigs either increased (tetracycline, sulfonamide, ampicillin) or

Table 2. Comparison of antimicrobial resistance in E. coli *O149 isolates obtained from cattle and pigs with clinical signs of infection prior to banning AGPs and eight years following the ban. Adapted from DANMAP Figure 41. Numbers represent percentages of isolates resistant to the different antimicrobials.*

Compound	Cattle		Pigs	
	1999	2008	1999	2008
Ampicillin	84	84	23	41
Nalidixic Acid	18	23	21	13
Sulfonamide	79	58	81	62
Tetracycline	69	66	73	63
Streptomycin	81	60	73	63
Gentamicin	18	12	5	7
Neomycin	17	7	30	19

remained the same (nalidixic acid, ciprofloxacin). Similarly, resistance to tetracycline and erythromycin increased in *Campylobacter* from broilers. Resistance to nalidixic acid remained very low. Because far fewer samples of these bacteria were tested, it is hard to draw clear conclusions about what this means.

Antmicrobial Use in Human Medicine Since 1999

There have been no dramatic, intentional changes in antimicrobial use in human medicine in Denmark. However, since 1999, overall antimicrobial use in human medicine has increased, particularly use of cephalosporins, fluoroquinolones and various penicillins (Figure 2).

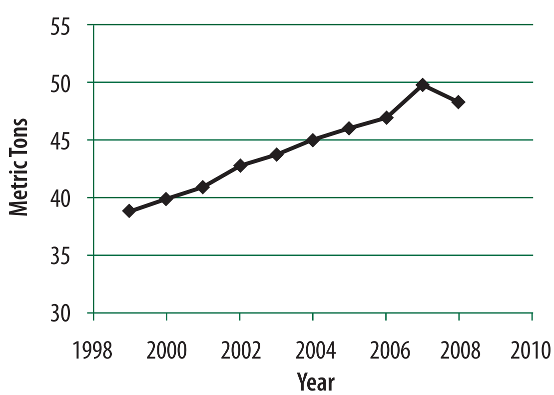
Antimicrobial Resistance in Bacteria Isolated from Humans

DANMAP checks for antimicrobial resistance in *E. coli* found in humans who show clinical signs of infection or disease. Table 3 compares *E. coli* resistance to the antimicrobials ampicillin, ciprofloxacin, nalidixic acid, cefuroxime, gentamicin, mecillinum and sulfonamide in 2000 vs. 2008. In each case, levels of resistance either increased or remained constant.

Antimicrobial resistance levels are also monitored in various gram-positive *Streptococcus* spp. from humans. The largest sample group is *Streptococcus pneumoniae*, where resistance to penicillin and erythromycin did not change significantly between 2000 and 2008. Likewise,

Figure 2. *Antimicrobial consumption in human medicine (Denmark). Adapted from DANMAP Table 13.*

A) *Antimicrobial consumption in metric tons.*



B) *Examples of fluctuations in antimicrobial use in human medicine.*

Antimicrobial	(KG active substance)	
	2000	2008
Tetracylinces	1382	1884
Extended Spectrum Penicillins	5202	6188
Cephalosporins	650	2285
Short acting Sulfonamides	3296	2565
Aminoglycosides	42	27
Fluoroquinolones	383	1162

Table 3. *Comparison of antimicrobial resistance in* E. coli *isolates obtained from humans with clinical signs of infection a year after the ban on AGPs and eight years following the ban. Adapted from DANMAP Figures 33-35. Numbers represent estimated percentages of isolates resistant to different antimicrobials. nt = not tested.*

Compound	Blood (Hospital)		Urine (Hospital)		Urine (Primary Health Care)	
	2000	2008	2000	2008	2000	2008
Ampicillin	41	42	37	40	41	40
Ciprofloxacin	3	12	1	10	2	9
Nalidixic Acid	5	13	4	13	3	12
Cefuroxime	2	6	nt	nt	nt	nt
Gentamicin	1	4	nt	nt	nt	nt
Mecillinum	4	5	6	6	5	5
Sulfonamide	nt	nt	34	34	37	37

resistance levels in *Enterococcus* spp. remained constant with the exception of ampicillin resistance, which has increased. Resistance levels (2004 to 2008) in another gram-positive organism, *Staphylococcus aureus*, have remained constant as well.

Similar Programs in Norway and Sweden

Currently, programs similar to DANMAP are in place in both Norway (NORM-VET) and Sweden (SVARM). The Norwegian program is much smaller in scope than DANMAP, just as the Norwegian livestock industry is smaller than the Danish livestock industry. In most cases, the number of samples taken from livestock and tested for antimicrobial resistance is very low, which makes it difficult to identify trends. However, resistance levels are generally low. In Sweden, the use of AGPs was phased out in the mid-1980s, and several antimicrobial compounds (e.g., amphenicols, nitroimidazoles, streptogramins, quinoxalines) are no longer used in livestock production. Penicillin and cephalosporin use has increased, but overall antimicrobial use is comparatively low in Sweden. Current resistance levels in various indicator bacteria are also low, but SVARM does not include data from before 1986, which makes it difficult to gauge the impact of banning AGPs.

Implications

Denmark banned AGPs because officials wanted to reduce antimicrobial resistance in bacteria from food animals. In this, the ban was largely successful, because resistance in various types of bacteria decreased from 2000 to 2008. Likewise, overall use of antimicrobials in food animal production decreased. The larger question is if this lowered antimicrobial resistance in bacteria from pigs or chickens translates into reduced antimicrobial resistance in bacteria from humans. This does not seem to be the case.

While resistance in bacteria from livestock decreased, resistance in bacteria from humans remained the same or increased in almost every type of bacteria tested. In many cases, the increase in resistance to specific drugs was likely caused by increased use of that drug in human medicine (e.g., fluoroquinolones, cephalosporins). Therefore, it appears that antimicrobial resistance patterns in bacteria from animals and humans are not closely related. That is, antimicrobial resistance patterns in livestock result from antimicrobial use patterns in veterinary medicine and antimicrobial resistance patterns in humans result from antimicrobial use patterns in human medicine. This suggests that changes in antimicrobial resistance patterns in bacteria isolated from livestock have limited influence on antimicrobial resistance patterns in bacteria isolated from humans.

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