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Impacts of antimicrobial growth promoter termination in Denmark

The WHO international review panel's evaluation of the termination of the use of antimicrobial growth promoters in Denmark

Foulum, Denmark
6-9 November 2002

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World Health Organization

Department of Communicable Diseases, Prevention and Eradication

Collaborating Centre for Antimicrobial Resistance in Foodborne Pathogens

With the support of:

Danish Veterinary Institute

Danish Institute of Agricultural Sciences

Contents

Executive Summary

In November 2002, the World Health Organization (WHO) convened an independent, multidisciplinary, international expert panel to review the potential consequences to human health, animal health and welfare, environmental impact, animal production, and national economy resulting from Denmark's program for termination of the use of antimicrobial growth promoters in food animal production, particularly swine and broiler chicken.

Through voluntary and regulatory action, antimicrobial growth promoters were withdrawn from use in cattle, broilers and finisher pigs in February 1998. Use in weaner pigs ceased in the following year. Virtually no antimicrobial growth promoters have been used in Denmark since the end of 1999.

Most information for the review was provided at the *International Invitational Symposium; Beyond Antimicrobial Growth Promoters in Food Animal Production*, held 6-7 November 2002 in Foulum, Denmark, and in meetings with national experts 8-9 November 2002. This was supplemented where necessary by additional published and (rarely) unpublished data.

Impact of antimicrobial growth promoter termination on usage of antimicrobials

Overall, antimicrobial use in food animals in Denmark has been reduced substantially following the discontinuation of antimicrobial growth promoters. This has resulted in both reductions in the total amount of antimicrobials used and in the average duration of exposure of animals to antimicrobials. On a national basis, the quantity of antimicrobials used in food animals in Denmark has declined 54% from the peak in 1994, (205,686 kg) to 2001 (94,200 kg). Prior to antimicrobial growth promoter termination, most pigs and broilers were exposed to antimicrobials for most of their lives, while after termination the average use of antimicrobials declined to 0.4 days in broilers (life span usually about 42 days to 2kg), and 7.9 days in pigs (life span usually about 170 days to 100kg).

Termination of antimicrobial growth promoters in pigs resulted in increases in therapeutic use of some antimicrobials that are also used in humans (e.g. tetracycline, penicillins, macrolides), however use of other drugs of importance to humans (e.g. cephalosporins, fluoroquinolones) was unaffected, and total therapeutic use in 2000 and 2001 was similar to 1994, the peak year of therapeutic use before any antimicrobial growth promoters were terminated. Therapeutic use in poultry appeared to be unaffected by antimicrobial growth promoter termination.

Impact of the termination of antimicrobial growth promoters on antimicrobial resistance

Extensive data were available that showed that the termination of antimicrobial growth promoters in Denmark has dramatically reduced the food animal reservoir of enterococci resistant to these growth promoters, and therefore reduced a reservoir of genetic determinants (resistance genes) that encode antimicrobial resistance to several clinically important antimicrobial agents in humans. Although clinical problems in humans related to resistance to antimicrobial growth promoters were rare in Denmark before and after termination, the principal public health goal of antimicrobial growth promoter termination was to reduce resistance in the food animal reservoir in order to prevent such problems from emerging.

Data from healthy humans however are relatively sparse on which to assess the effect of the termination of antimicrobial growth promoters on the carriage of antimicrobial resistant bacteria. There is some indication that termination of antimicrobial growth promoters in Denmark may be associated with a decline in the prevalence of streptogramin resistance among *E. faecium* from humans. There is also an indication that the termination may be associated with an increase in resistance among *E. faecalis* to erythromycin (a macrolide), which may reflect an increase in the therapeutic use in pigs of tylosin (another macrolide). However, it should be noted that erythromycin is not a very important antimicrobial for the treatment of enterococcal infections in humans; preferred drugs include ampicillin, amoxycillin, vancomycin, streptogramins (for *E. faecium*), and linezolid. Further larger studies are needed to determine how much of an effect the discontinued use of antimicrobial growth promoters in Denmark will have on the carriage of antimicrobial resistance in the intestinal tract of humans in the community.

The antimicrobial growth promoters that were used in Denmark were active mainly against Gram-positive bacteria (with the exception of the quinoxalines). Therefore, direct effects of the termination of growth promoters on resistance in Gram-negative bacteria (e.g. *E. coli*, *Salmonella*) were neither expected nor observed. It is probable, however, that termination of antimicrobial growth promoters had an indirect effect on resistance to tetracycline resistance among *Salmonella* Typhimurium because of an increase in therapeutic tetracycline use in food animals. The clinical consequence of increased tetracycline resistance is, however likely to be minimal for the therapy of *Salmonella* infections. This is because patients with gastroenteritis are unlikely to be treated empirically with tetracycline (and tetracycline is no longer used to treat persons with diagnosed *Salmonella* infections in Denmark). Increased tetracycline resistance among *Salmonella* is therefore not likely to result in ineffective treatment of *Salmonella* infections. Increased tetracycline resistance among *Salmonella* may result in additional human *Salmonella* infections, however, since persons who take tetracycline for other reasons are at increased risk of becoming infected with tetracycline-resistant *Salmonella*.

Impact of the termination of antimicrobial growth promoters on human health (other than resistance)

Overall, termination of antimicrobial growth promoters appears not to have affected the incidence of antimicrobial residues in foods or the incidence of human *Salmonella*, *Campylobacter*, or *Yersinia* infections in humans. These are the major zoonoses in Denmark that may be associated with consumption of pork and poultry. In an industry aggressively pursuing successful *Salmonella* reduction strategies, antimicrobial growth promoter termination appears not to have affected the prevalence of *Salmonella* in pig herds, pork, broiler flocks and poultry meat, or the prevalence of *Campylobacter* in poultry meat.

Impact of the termination of antimicrobial growth promoters on animal health (morbidity) and welfare

In swine, there was a significant increase in antimicrobial treatments for diarrhea in the post-weaning period after the termination of antimicrobial growth promoters. A less pronounced and transient increase in antimicrobial treatment for diarrhea was also observed in finishers. In broilers, necrotic enteritis was at most a minor broiler health problem following the termination of antimicrobial growth promoters, largely because producers continued to use ionophores for the prophylaxis of necrotic enteritis and coccidiosis.

Impact of the termination of antimicrobial growth promoters on the environment

There was no evidence of any adverse environmental effects due to the termination of antimicrobial growth promoters, although there is very little data available with which to make an assessment. The effects of antimicrobial growth promoter termination on total nitrogen and phosphorus output in animal manure appear to be negligible. Available national data indicate that surpluses of these nutrients from agriculture continued to decline following termination.

Impact of the termination of antimicrobial growth promoters on animal production

The termination of antimicrobial growth promoters resulted in some loss of productivity, primarily in weaners. There has been no major effect of the antimicrobial growth promoter termination on productivity or feed efficiency in finishers. The economic effects of the antimicrobial growth promoter termination on the pig producer would have been variable and presumably may have included some or all of the following: costs associated with modifications of the production systems to increase pig health, decreased feed efficiency, reduced growth rate and increased mortality in weaners, increased use of therapeutic antimicrobials and costs associated with purchasing alternatives to antimicrobial growth promoters. Some of these costs (e.g. increased therapeutic antimicrobials, reduced growth rate) have been measured and were not large, but others, especially some costs associated with modifications of the production systems, are difficult to measure and were not included in this report, although they may have been substantial for some producers. These costs would have been at least partially offset with savings associated with not purchasing antimicrobial growth promoters. Overall, total volume of pork production in Denmark continued to increase in the period following the termination of antimicrobial growth promoters.

Based on available data, the effects of antimicrobial growth promoter termination on poultry production appear to be small and limited to decreased feed efficiency (-2.3%) that is offset, in part, by savings in the cost of antimicrobial growth promoters. There were no changes in weight gain or mortality in broilers that appeared to be related to the termination of antimicrobial growth promoters.

Economic impacts of the termination of antimicrobial growth promoters in Denmark

The net costs associated with productivity losses incurred by removing antimicrobial growth promoters from pig and poultry production were estimated at 7.75 DKK (1.04 €) per pig produced and no net cost for poultry. This translates into an increase in pig production costs of just over 1%. Some of these costs (e.g. increased therapeutic antimicrobials, reduced growth rate) have been measured and were not large, but others, especially some costs associated with modifications of the production systems, are difficult to measure and were not included in this report, although they may have been substantial for some producers. Results from using a general equilibrium model of the Danish economy suggest that, as a result of this change in costs, pig production would be around 1.4% per annum lower than might be expected and poultry production 0.4% per annum higher due to termination of antimicrobial growth promoters. The latter result is because poultry production is a competitor to pig production both for inputs and consumption and so indirectly benefits from lower pig production. The overall estimated impact for the Danish economy of antimicrobial growth promoter termination is a reduction of 0.03% (363 million DKK (48 million€) by 2010 at 1995 prices) in real Gross Domestic Product (GDP).

Any additional cost to production and the national economy may be, at least partially, offset by the benefits of increased consumer confidence in, and demand for, Danish pig and poultry meat produced without antimicrobial growth promoters. Also to be set against the cost are the likely human health benefits to society of antimicrobial growth promoter termination.

Applicability to other countries

The consequences of antimicrobial growth promoter termination in other countries should be broadly similar to Denmark, but may vary in some respects depending on the health status of animals and prevailing animal husbandry conditions. In addition, the effects of termination on disease and productivity may vary depending on the type of antimicrobials (e.g. pharmacological properties, spectrum of activity against bacteria) that are currently used in a country. The economic effects will depend upon several factors including the effects on performance levels, the cost of any technologies adopted to compensate for the termination of antimicrobial growth promoters, and these costs may be offset by the benefits of increased consumer confidence and public health.

Conclusions

Internationally, there has been considerable speculation about the effects of antimicrobial growth promoter termination on efficiency of food animal production, animal health, food safety and consumer prices. These issues have been addressed in the "Danish experiment", and there have been no serious negative effects. We conclude that under conditions similar to those found in Denmark, the use of antimicrobials for the sole purpose of growth promotion can be discontinued. Denmark's program to discontinue use of antimicrobial growth promoters has been very beneficial in reducing the total quantity of antimicrobials administered to food animals. This reduction corresponds to a substantial decrease in the overall proportion of individual animals given antimicrobials, and in the duration of exposure among animals given antimicrobials. This represents a general change in Denmark from continuous use of antimicrobials for growth promotion to exclusive use of targeted treatment of specific animals for therapy under veterinary prescription. The program has also been very beneficial in reducing antimicrobial resistance in important food animal reservoirs. This reduces the threat of resistance to public health. From a precautionary point of view, Denmark's program of antimicrobial growth promoter termination appears to have achieved its desired public health goal.

The phasing out of antimicrobial growth promoters was done without major consequences. Under Danish conditions, the negative impacts of antimicrobial growth promoter termination are largely attributable to their disease prophylaxis (i.e. disease prevention) properties, with no effect on growth in broilers and only a small effect on growth in pigs. In pigs, where most antimicrobials were used in Denmark, antimicrobial growth promoter termination was associated with a reduction in growth rate and an increase in mortality and diarrhoea in weaners, but these changes were not detectable in finishers. Many of these effects were probably due to termination of olaquindox and carbadox. Even if the pig industry had not decided to voluntarily cease antimicrobial growth promoter use in 1998/99, olaquindox and carbadox would still have been withdrawn in 1999 by EU regulation over concerns about potential toxicity to humans from occupational exposure. The other antimicrobial growth promoters have little or no activity against the gram-negative bacterial infections believed to be most important in post-weaning diarrhea of pigs (tylosin may have activity against *Lawsonia*, but it was banned as an antimicrobial growth promoter by the EU in 1999). Therefore, even if there had been no voluntary discontinuation of antimicrobial growth promoter use, other solutions to the problem of increased post-weaning diarrhea would have been needed. In finisher pigs, antimicrobials did not appear to have these disease prophylaxis benefits and discontinued antimicrobial growth promoter use was not associated with a sustained increase in morbidity or mortality. In broilers, antimicrobial growth promoter termination was not associated with increases in morbidity and mortality, however, ionophores (a drug class not used in humans) were used routinely in feed to prevent the parasitic disease coccidiosis, and this probably also provided some protection against the bacterial disease necrotic enteritis. Savings in antimicrobial growth promoter costs largely offset losses in feed efficiency in broilers.

Introduction

In the context of the "WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food", and with a focus on swine and broiler chicken, the objectives of the review panel were:

- To assess the impacts of the termination of antimicrobial growth promoters on:
  - Usage of antimicrobials and antimicrobial resistance in bacteria in animals, food and humans;
  - Animal production;
  - Animal health and welfare, human health and environmental impact
- To discuss the implications of termination of antimicrobial growth promoters for other countries including developing countries

Preamble

As a result of the growing concern of the impact of antimicrobials used in animals on human health and food safety, the World Health Organization (WHO) published the *WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food* (Global Principles) in June 2000 (WHO, 2000). Previously the risks regarding the use of antimicrobials in food animals were discussed in WHO meetings in Berlin in 1997 (WHO, 1997) and in a meeting in Geneva in 1998 (WHO, 1998). Once the areas of particular concern were identified, WHO proceeded into publishing the Global Principles. These are a part of the *WHO Global Strategy for Containment of Antimicrobial Resistance* (Global Strategy) released in 2001 (WHO, 2001). The issue of monitoring the use of antimicrobials in food animals was specifically addressed in a WHO meeting in Oslo in 2001 (WHO, 2002). The *International Invitational Symposium; Beyond Antimicrobial Growth Promoters in Food Animal Production* in Foulum, Denmark, in November 2002 and this resulting document are a step towards the implementation of recommendations of the Global Principles.

Antimicrobial resistance is a multifactorial problem and thus requires a multidisciplinary approach. In this document the potential consequences to human health, animal health and welfare, environmental impact, animal production, and national economy resulting from Denmark's program for termination of the use of antimicrobial growth promoters in food animal production, particularly swine and broiler chicken, was reviewed by an independent, multidisciplinary, international expert panel, and results of that review are described in this report.

The outcome has been intended to develop, in the relation to the Global Principles and where appropriate, recommendations for further improvement of national implementation strategies for the containment of antimicrobial resistance, implementation of the Global Principles, and to support other countries in their endeavors to establish programs towards prudent use of antimicrobials in food animals.

Chronology of events and infrastructure in Denmark

May 1995, Denmark banned the antimicrobial growth promoter avoparcin, a member of the glycopeptide class of antimicrobials, in response to concerns that its use contributed to the creation of an animal reservoir of glycopeptide-resistant enterococci (vancomycin resistant enterococci or VRE), which posed a potential risk to public health.

December 1997, The Commission of the European Union banned avoparcin in all European Union member states.

January 1998, Denmark banned the antimicrobial growth promoter, virginiamycin, a member of the streptogramin class of antimicrobials, in response to concerns that its use contributed to creation of an animal reservoir of streptogramin-resistant *Enterococcus faecium* which posed a potential risk to public health.

February 1998, The Danish cattle and broiler chicken industries voluntarily stopped the use of all antimicrobial growth promoters in response to consumer concerns that the use of antimicrobial growth promoters posed a potential risk to public health. At this time, the Danish swine industry also voluntarily stopped the use of all antimicrobial growth promoters in pigs over 35 kg (finishers).

July 1999, The Commission of the European Union banned another four antimicrobial growth promoters, tylosin, spiramycin, bacitracin and virginiamycin, because they belonged to classes of antimicrobial drugs also used in human medicine.

September 1999, The Commission of the European Union banned another two antimicrobial growth promoters, olaquindox and carbadox, in response to concerns of toxicity to humans from occupational exposure.

December 1999, The Danish swine industry voluntarily stopped the use of all remaining antimicrobial growth promoters in pigs under 35kg (weaners).

In 1995 the Danish Ministry of Food Agriculture and Fisheries and the Danish Ministry of Health jointly sponsored the establishment of the Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP). DANMAP, which includes pathogenic and indicator bacteria sampled from animals, food and humans, has reported annual resistance prevalence data each year since 1996. DANMAP furthermore collects and reports data on antimicrobial usage from animals and humans.

In 1997, the Ministry of Food Agriculture and Fisheries funded a four-year research programme, at the Danish Veterinary Institute and the Danish Institute of Agricultural Sciences to investigate the effects of the discontinuation of the use of antimicrobial growth promoters in Danish animal husbandry, and to promote research in alternatives to antimicrobial growth promoters.

On 6-7 November 2002, an international invitational symposium “Beyond Antimicrobial Growth Promoters“ was held at the Danish Institute of Agricultural Sciences. A total of 140 participants from 12 different countries participated in the symposium, which had 32 scientific presentations in 6 scientific sessions with the following headings:

- Effects of the termination of antimicrobial growth promoter use on bacterial resistance to antimicrobials
- Effects of the termination of antimicrobial growth promoter use on animal welfare and productivity
- Consequences of termination of antimicrobial growth promoter use for animal health and the use of antimicrobials in food animals for therapy and prophylaxis
- Effects of the termination of antimicrobial growth promoter use on food prices and the competitiveness of agricultural industries
- Consequences of termination of antimicrobial growth promoter use for the environment
- Alternatives to the use of antimicrobial growth promoters

The World Health Organization (WHO) organized an independent expert review of the Danish experiences in conjunction with the symposium. The review panel consisted of the following experts (In alphabetical order, see Annex 2):

Dr. Fred Angulo, Centers for Disease Control and Prevention, Atlanta, USA

Dr. Richard Bennett, The University of Reading, Reading, England

Prof. Peter Collignon, The Canberra Hospital, Canberra, Australia

Dr. Andrzej Horszowski, National Veterinary Research Institute, Pulawy, Poland

Dr. Defa Li, China Agricultural University, Beijing, China

Prof. Scott McEwen, University of Guelph, Guelph, Canada (Chairman)

Prof. Eric Mitema, University of Nairobi, Nairobi, Kenya

Prof. Jim Pettigrew, University of Illinois, Illinois, USA

Prof. David Taylor, University of Glasgow, Glasgow, Scotland (Rapporteur)

Prof. Martin Wierup, University College Dublin, Dublin, Ireland

Expert Reviewer's Report

Our review took place 8-9 November 2002 in Foulum, Denmark. We worked as a single group throughout and based our review on the national experts' working papers (listed in the bibliography), the oral presentations during the symposium and a three-hour meeting with the Danish national experts on the morning of the 8th November. We point out that the national experts were in a position to give overviews and summaries using national average data. It is apparent that these overviews may not always have revealed or highlighted specific effects on individual producers, nor the full range and types of effects experienced. For example, in weaner pig production (described below) it is likely that some producers experienced substantial problems resulting from termination of antimicrobial growth promoters, while others experienced few or no problems, most likely a result of the prevailing status in management, housing and exposure to disease agents and perhaps also of a naturally-occurring biological range of variability.

Our review focused almost entirely on effects of antimicrobial growth promoter termination in pig and broiler production. The vast majority of antimicrobial growth promoters were used in these industries, and these industries were the subjects of nearly all the monitoring and associated research. Some, but not all of the data presented to us were subjected to statistical analyses, and where appropriate we draw attention to results of these analyses.

Demographic data

In 2001, Denmark had a population of 5.35 million people. Although Denmark imported 27% of its poultry and 10% of pork, overall, Denmark is a net exporter of both poultry and pork (approximately 50% of poultry production and 80-85% of pork production).

Broilers and pigs are raised intensively in Denmark. More than 130 million broilers are produced annually and typically, broilers are raised using "all-in-all-out" (AIAO) management and barns are cleaned and disinfected between flocks (Tornoe, 2002). Approximately 13,500 pig producers raise 22.5 million pigs annually and 95% are slaughtered in two farmer-owned cooperative slaughterhouses (Callesen, 2002). Most new pig facilities use AIAO management and approximately 22% of pigs slaughtered are raised in specific-pathogen-free (SPF) or similar facilities (Baekbo, 2002).

Impact of the termination of antimicrobial growth promoters on usage of antimicrobials

Data

Antimicrobial use data from the following sources were presented at the meeting and included in this report: (1) Danish national surveillance (DANMAP, including VETSTAT) (Bager et. al, 2002); (2) a research study on selected swine farms in Denmark (Larsen, 2002), and (3) a survey of the quantities of antimicrobials used in European Union countries (EMEA, 1999). We also used data from DANMAP and the Federation of Danish Pig Producers and Slaughterhouses (Rønn and Jacobsen, 1995) to identify trends in usage of oral antimicrobials in Danish pig production 1986-2001.

1. Danish national surveillance

The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) conducts surveillance on antimicrobial use in animals and humans in Denmark. These data are collected from several sources and summarized in annual reports. The DANMAP annual reports from 2000 and 2001 were utilized during the review. Details on the DANMAP data collection methods for antimicrobial use in animals and humans are listed in the annual reports. These reports also contain summaries of the quantities of antimicrobial agents used, including quantities used as antimicrobial growth promoters, coccidiostats, therapeutic antimicrobials in animals, and therapeutic antimicrobials in humans.

Antimicrobial growth promoters

DANMAP receives data from the pharmaceutical industry on the quantities of antimicrobial growth promoters sold in Denmark. A summary of the quantities of antimicrobial growth promoters, in kilograms of active ingredient, sold in Denmark from 1990 to 2001 is shown in table 1.

Table 1. Usage of antimicrobial growth promoters in Denmark 1990 to 2002 (kg active compound) (Danmap 2002).

Antibiotic group	Growth promoter	1990	1992	1994	1996	1998	1999	2000	2001	2002
Bacitracin	Bacitracin	3,983	5,657	13,689	8,399	3,945	63	n a)	-	-
Flavofosfolipol	Flavomycin	494	1,299	77	18	6	665	n	11	15 b)
Glycopeptide	Avoparcin	13,718	17,210	24,117	-	-	-	n	-	-
Ionophores	Monensin	2,381	3,700	4,755	4,741	935	-	n	-	-
	Salinomycin	12	-	213	759	113	-	n	-	-
Macrolides	Spiramycin	-a)	-	95	15	0,3	-	n	-	-
	Tylosin	42,632	26,980	37,111	68,350	13,148	1,827	n	-	-
Oligosaccharides	Avilamycin	10	853	433	2,740	7	91	n	3	-
Quinoxalines	Carbadox	850	7,221	10,012	1,985	1,803	293	n	-	-
	Olaquindox	11,391	21,193	22,483	13,486	28,445	9,344	n	-	-
Streptogramins	Virginiamycin	3,837	15,537	2,801	5,055	892	-	n	-	-
Total		79,308	99,650	115,786	105,548	49,294	12,283	n	14	15

a) n = not monitored, assumend to be zero

b) Sold to an exporting feed mill company and a farm near the border to Poland/Germany (pigs treated are presumed exported for slaughter)

Antimicrobial growth promoters were withdrawn from use in cattle, broilers and finisher pigs in February 1998. Use in weaner pigs ceased in the following year. A small quantity (14 kg), however, of EU-approved antimicrobial growth promoters was used in 2001 for the purpose of growth promotion.

Coccidiostats

Coccidiostats are primarily used in chickens and turkeys in Denmark. Prior to 2001, DANMAP received data from the Danish Plant Directorate on the quantities of coccidiostats sold in Denmark. In 2001, these data were obtained through VETSTAT. The quantities of coccidiostats, in kilogram of active ingredient, used in poultry in Denmark from 1991 to 2001 are shown in Table 2.

Therapeutic antimicrobials in animals

Trends in quantities of therapeutic antimicrobials used in food animals are shown in Table 3. The data originate from two sources. Prior to 1995 the data were collected by the Federation of Danish Pig Producers and Slaughterhouses and by the Danish Pharmacy Association and reported to Danish Medical Statistics (they may be incomplete). After 1995 the data were collected through compulsory reporting by the pharmaceutical industry to the DMA (Danish Medicines Agency) of quantities sold to wholesalers and pharmacies (DANMAP 2000).

DANMAP began VETSTAT, a special antimicrobial use monitoring program, in 2000. Antimicrobial use data are collected close to the point of use, and include information on target animal species, and age group of animals. VETSTAT data are prescription-based and are collected from pharmacies, veterinary practices, and feed mills. VETSTAT data are comprehensive because antimicrobials for therapeutic use can only be legally obtained from veterinarians or, on the basis of a prescription from a veterinarian, through pharmacies or from a feed mill as medicated feed. A summary of the quantities of therapeutic antimicrobials, expressed in animal defined doses (ADDs), used in animals in 2001, is shown in Table 4.

Table 2. Usage of coccidiostats in poultry in Denmark 1990 to 2002 (kg active compound) (Danmap, 2002).

Coccidiostats	1990	1992	1994	1996	1998	1999	2000	2001 a)	2002 a)
Amprolium/Ethopabat	3,562	2,716	2,342	1,339	275	839	-	13	-
Dimetridazol	-	-	-	38	-	106	-	-	-
DOT	-	-	300	-	-	13	-	-	-
Monensin	-	108	1,016	3,405	3,709	8,664	3,962	1,361	1,159
Robenidin	33	295	858	293	367	85	-	2	41
Metichlorpindol/ Methylbenzoat	89	1,503	3,360	4,857	930	155	-	-	-
Lasalocid	75	-	5	773	1,677	895	606	872	760
Halofuginon	-	-	19	8	-	2	-	-	-
Narasin	1,588	5,157	6,370	3,905	3,177	5,806	5,073	2,687	863
Salinomycin	7,783	10,298	6,018	4,531	7,884	8,812	6,338	12,801	11,213
Nicarbazin	-	-	-	115	36	4	-	-	-
Narasin/Nicarbazin	-	-	-	-	-	32	20	1	-
Nifursol	-	395	-	146	234	79	-	-	-
Diclazuril	-	-	18	34	3	1	-	2	5
Total	13,569	20,472	20,306	19,444	18,292	25,493	15,999	17,739	14,043

a) Based on VetStat data

Table 3. Trends in the total usage of antimicrobials for treatment of all food animals. Data 1986-1994: Use of antibiotics in the pig production. Federation of Danish pig producers and slaughterhouses. N.E. Rønn (Ed.). Data 1996-2002: Danish Medicines Agency.

Compound a)	1990	1992	1994	1996	1998	1999	2000	2001 b)	2002 b)
Tetracyclines	9,300	22,000	36,500	12,900	12,100	16,200	24,000	28,300	24,300
Penicillins, beta–lactamase sensitive	5,000	6,700	9,400	7,200	14,300	14,700	15,100	16,000	16,900
Other penicillins, cephalosporins	1,200	2,500	4,400	5,800	6,700	6,600	7,300	8,700	9,800
Sulfonamides + trimethoprim c)	3,800	7,900	9,500	4,800	7,700	6,800	7,000	9,400	10,400
Sulfonamides	8,700	5,900	5,600	2,100	1,000	1,000	1,000	900	850
Macrolides, lincosamides, tiamulin	10,900	12,900	11,400	7,600	7,100	8,700	15,600	19,900	21,200
Aminoglycosides	7,700	8,500	8,600	7,100	7,800	7,500	10,400	9,600	9,200
Others c)	6,700	6,800	4,400	600	650	350	300	900	1,600
Total	53,400	73,200	89,900	48,000	57,300	61,900	80,700	93,700	94,300

For comparability between VetStat data and previous data, see DANMAP 2000.
Only veterinary drug are included, excluding human drugs and veterinary drugs obviously used in pets (tablets, capsules, ointment, eye and ear drops) .
a) Only the major contributing ATC-groups are mentioned.
b) Does not include consumption in aquaculture (sale through feed mills and sale of oxolinic acid from pharmacies) before 2001.
c) Data from VetStat 2001-2002. Aquaculture is included.

Table 4. Usage of therapeutic antimicrobials in Animal Defined Dosages (DANMAP 2001).

Animal species	Age group	Standard weight (kg)	Kg antimicrobial	ADD (1000's)	Kg animal treated (1000's)
Pigs	Breeders and suckling pigs	200	18,617	6,787	-
	Weaners	15	27,918	151,740	-
	Slaughter pigs	50	22,028	37,371	-
	Age not given	-	854	-	71,230
Cattle	Cows, bulls	600	112	30	-
	Calves < 12 months	100	1,333	946	-
	Heifers, steers	300	29	9	-
	Age not given	-	64	-	4,219
Small ruminants	> 12 months	50	11	12	-
	< 12 months	20	1	2	-
	Age not given	-	6	-	185
Poultry	Broilers	0.2	161	56,764	-
	Layers	1	29	1,698	-
	Rearing flocks	1	116	3,640	-
	Age not given	-	23	-	1,132
Horses		-	144	9	-
Mink		1	659	36,604	-
Total kg antimicrobial		-	72,380	-	-

Relative quantities used for antimicrobial growth promoters, and animal and human therapy

DANMAP receives data on antimicrobial use in humans from the Danish Medicines Agency which receives monthly reports from all pharmacies, including hospital pharmacies, in Denmark. These data are comprehensive because antimicrobials used in humans are prescription only medicines in Denmark. A summary of the quantities of antimicrobial agents, in kilograms of active ingredient, used in animals (as antimicrobial growth promoters and for therapy) and in humans from 1990 to 2000 is shown in figure 1 (DANMAP 2000; Bager, 2002).

Trends in usage of oral antimicrobials in Danish pig production 1986-2001 calculated as animal daily dosages (ADD)

DANMAP 2001 presents an analysis of usage trends of veterinary therapeutic antimicrobials by route of administration between 1996 and 2001 (Figure 2, DANMAP 2001). The group of oral formulations accounts for most of the increase in total quantity of antimicrobials seen in recent years. The largest proportion of medicines in this group (83 % in 2001, based on VETSTAT data) is used in pigs. In the few countries where data are available, changes in usage trends over

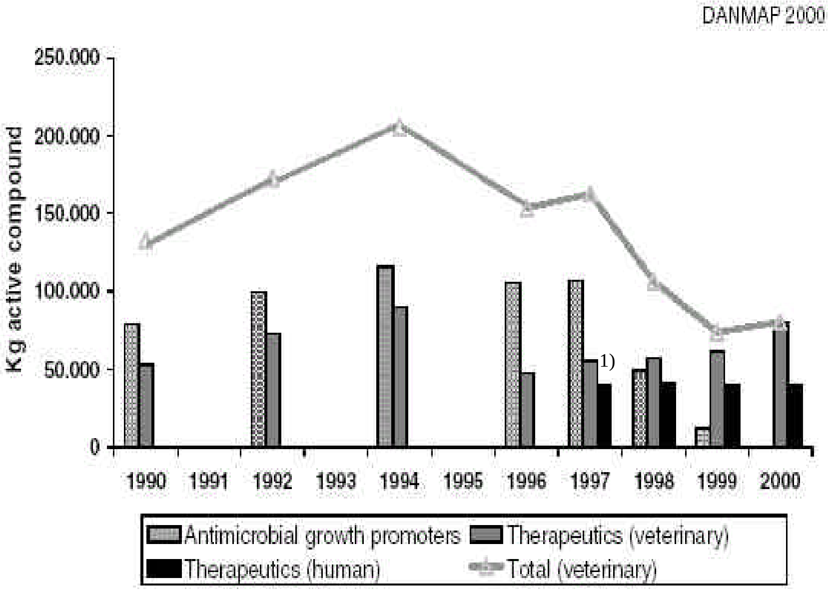


Figure 1. Trend in usage of antimicrobials in kilogram active ingredient for growth promotion in food animals and therapy in food animals and humans in Denmark 1990-2000 (1. Human data is not avaiable before 1997).

time are usually only compared by examining the total volumes of antimicrobials used on a weight basis (because in most of these countries there are insufficient data available on how and in which animals these antimicrobials are used). Comparing usage trends on the basis of the quantity of active compound however can be misleading because of the different formulations and weights needed for therapy of different antimicrobials– for example, the recommended dosage for treatment with tylosin premix is 4 mg per kg. body weight in pigs, compared with 25 mg per kg recommended for chlorotetracycline. To overcome this problem animal daily dosages (ADD) can be calculated if there are sufficient data available (as is the case in Denmark).

In order to calculate usage as ADD (animal daily dosages) we need to know also the target animal species, as the ADD varies between species. Complete information has only become available with VETSTAT, i.e. from 2001 onwards. Recalculation of usage statistics before 2001 to ADD's is therefore difficult. There are, however, in Denmark a number of oral therapeutics that are almost exclusively used in pig production and for such therapeutics the ADD can be estimated also for periods before 2001 on the basis of data collated for DANMAP. These therapeutics include tylosin, tilmicosin, chloro- and oxytetracycline, doxycycline, the pleurmutilins (e.g. tiamulin), lincomycin, spectinomycin and neomycin. In the year 2001 these antimicrobials accounted for over 80% of all oral antimicrobials used, although in 1990 only for 50% of total oral use.

Data for 1996 onwards are from usage statistics collated by the Danish Medicines Agency for DANMAP. Data for the period from 1986 to 1994 were collated by the Federation of Danish Pig Producers and Slaughterhouses (Rønn and Jacobsen, 1995). In this report, usage data for individual agents are not presented separately, even though separate statistics are presented for oral and injectables. We have been given access to the detailed statistics of Rønn and Jacobsen (1995) and therefore have been able to re-calculate usage of the 'pig specific' therapeutics shown in Table 5 as ADD. In the calculation we have used the daily dosages shown in Table 5 for use in a pig of 50 kg body weight. Accordingly, the ADD is calculated as:

$$\frac{\text{(quantity of active compound in mg)}}{\text{(daily dose in mg) * (weight of standard animal in kg)}}$$

Table 5. Daily dosages (mg/kg) used for calculation of usage trends of therapeutic antimicrobials as ADD's.

Therapeutic	Mg per kg. body weight	Mg per 50 kg pig
Doxycycline	12.5	625
Chloro- and oxytetracycline	25	1,250
Lincomycin, lincospectin	10	500
Neomycin	15	750
Tiamulin and valnemulin	6.5	325
Tilmicosin	16	800
Tylosin	4	200

Figure 2 shows the results of the calculation. To maintain comparison, we have used the same daily dosages throughout, even some of them may have been adjusted over time

There are difficulties in comparing antimicrobials used for growth promotion to those used for therapy by the use of ADDs because different drugs are usually used for these different purposes and the daily doses for growth promotion are usually much lower than with therapeutic use. However, tylosin presents a partial exception to these problems because in Denmark and other countries it has been approved for use both in therapy and for growth promotion. Figure 3 is identical to Figure 2, except that we have included data on tylosin use for growth promotion. The ADDs calculated for growth promotion used the same daily dose as that used for tylosin therapy (even though the daily dose for growth promotion purposes is lower).

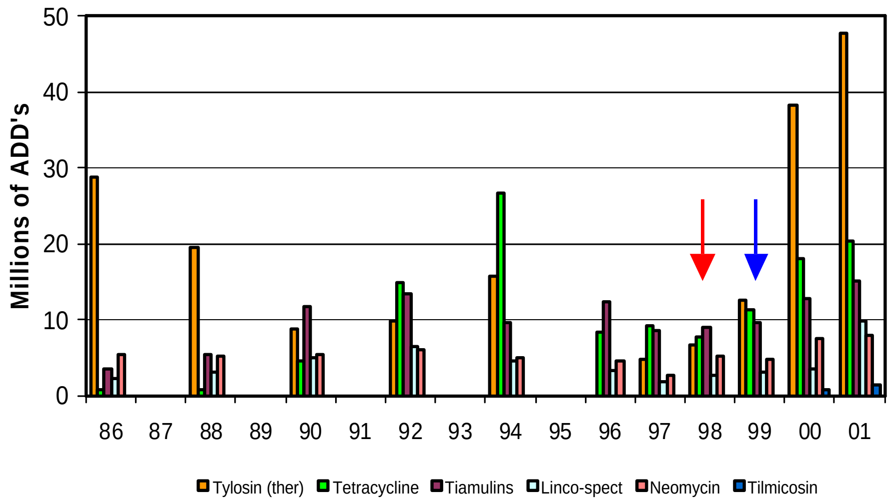


Figure 2. Trend in usage of important therapeutic antimicrobials for oral use in Danish pig production between 1986 and 2001. The bars represent millions of ADD for 50 kg pigs. The arrows indicate date of termination of antimicrobial growth promoters in finisher pigs (red) and in weaner pigs (blue).

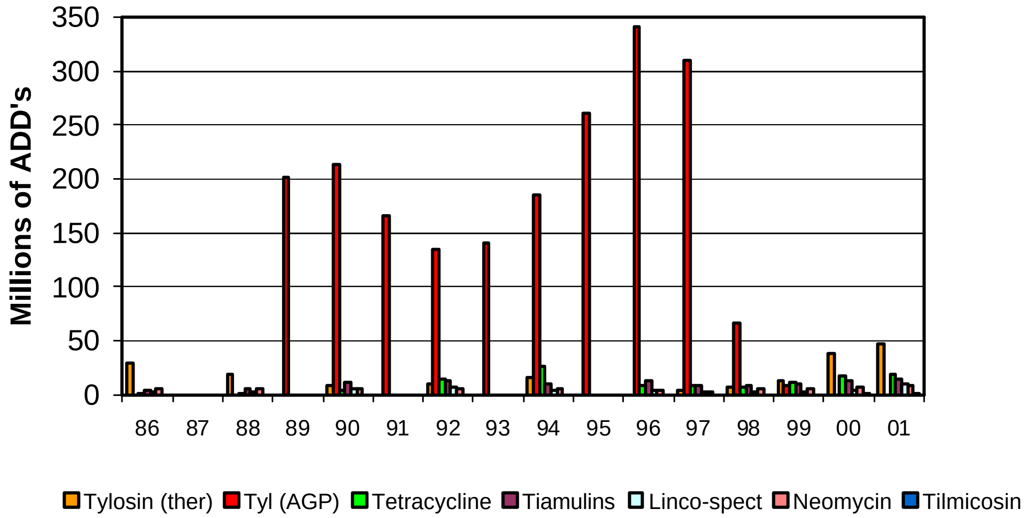


Figure 3. Trends in usage as shown in Figure yy, but with usage of Tylosin for growth promotion (Tyl (AGP)) included for comparison.

2. Research study on selected swine farms in Denmark

After antimicrobial growth promoters were discontinued in finisher pigs, a research project intended to determine the effects of antimicrobial growth promoter termination in weaner pigs on several outcomes including therapeutic antimicrobial use was conducted in approximately 120 Danish farrow-to-finish swine farms from 1998 to 2000. The farms were nominated by sixteen veterinary practices that specialized in swine from among the farms to which the veterinary practices routinely provided medical care. The veterinary practices were contacted monthly to ascertain antimicrobial use information. The producers were asked to record antimicrobial treatments, reasons for treatment and quantities of antimicrobial used. In order to compare amounts used among classes of antimicrobials, usage incidences in weaners and finishers were expressed as animal daily dosages (ADD). An ADD was defined as the average labelled daily dose for the major indication in weaners (average 15 kg) and in finishers (average 50 kg). Average monthly treatment incidences for various therapeutic antimicrobials before and after antimicrobial growth promoter termination in weaner rations were calculated for both weaners and finishers (Figures 4 and 5).

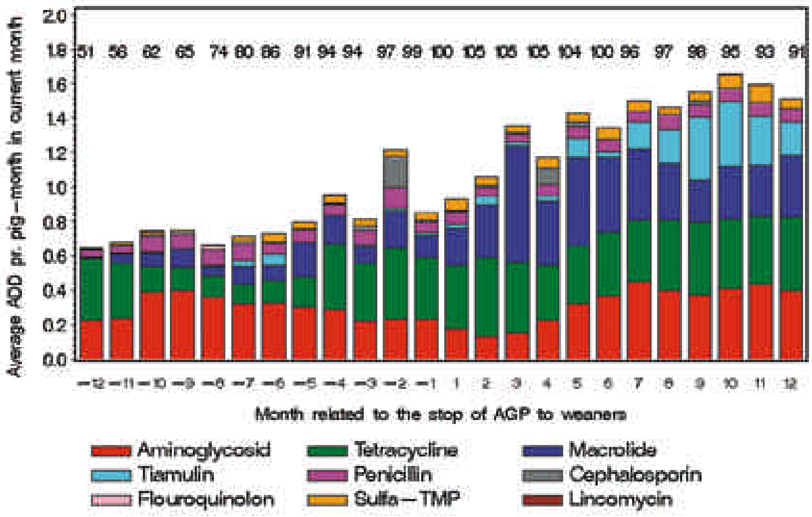


Figure 4. Average ADD consumption in weaners per pig-month before and after antimicrobial growth promoter termination in weaner rations on study farms (number of farms contributing data per month listed at top).

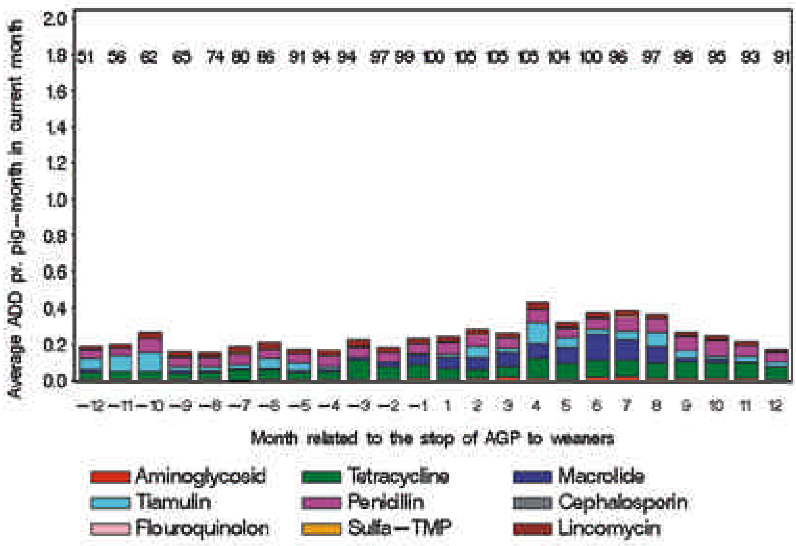


Figure 5. Average ADD consumption in finishers per pig-month before and after antimicrobial growth promoter termination in weaner rations on study farms (number of farms contributing data per month listed at top).

3. Survey of the quantities of antimicrobials used in European Union countries

A survey on the quantities of antimicrobials used in European Union countries was included in a July 14, 1999 report by the European Agency for Evaluation of Medical Products (EMEA, 1999) We reviewed some of the data from this report, specifically a summary of milligrams of therapeutic antimicrobials used in animals per kilogram of slaughter animal produced in 1997 for each of the European Union countries (Figure 6). Although no more recent data were presented for other European countries, it was calculated that approximately 40 mg of therapeutic antimicrobials per kg of slaughter animal produced were used in Denmark in 2001 (DANMAP unpublished data), compared to 24 mg/kg meat reported for Denmark in the 1997 survey.

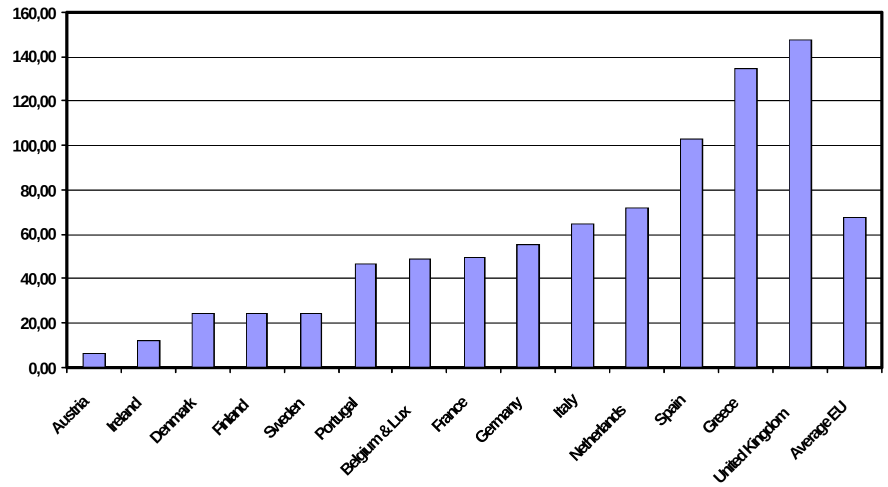


Figure 6. Consumption of therapeutic antimicrobials in animals (including food animals, companion animals, horses and other animals), EU 1997 (mg/kg liveweight of slaughtered animals/year).

[1] We note that for some countries there are discrepancies between the estimates of antimicrobial consumption found in this report and those from other sources. For example, the therapeutic antimicrobial consumption estimate for the UK in this figure (147.7 mg/kg) is higher than that derived from data available from the U.K. Veterinary Medicines Directorate (89.9 mg/kg, not including antimicrobials for fish) (Veterinary Medicines Directorate, 2003). Furthermore, the antimicrobial consumption estimates for Denmark, Finland and Sweden differ somewhat from data available from their respective national sources (DANMAP (1999), FINRES (2000) and SVARM (2001)). Values for other countries may also differ from estimates from their national sources. We do not know why these discrepancies exist, but presume it relates to different methods of data collection and/or reporting. For further information concerning antimicrobial use in a particular country, we recommend contacting the relevant national authority.

Interpretation

1. Danish national surveillance

Antimicrobial growth promoters

Through voluntary and regulatory action, virtually no antimicrobial growth promoters have been used in Denmark since 1999. Prior to the ban on quinoxaline antimicrobial growth promoters (e.g., carbadox and olaquindox) by the European Union due to concerns about toxicity to humans from occupational exposure, olaquindox was the most commonly used antimicrobial growth promoter in weaners, in terms of total kilograms of antimicrobial growth promoters used (DANMAP, 2002).

Although DANMAP has ascertained the kilograms of antimicrobial agents, including growth promoters, used in food animals in Denmark for many years, data were not collected on how these antimicrobial agents were used in food animals until VETSTAT was initiated in 2001. Therefore, it is not known exactly what proportion of food animals were fed rations containing antimicrobial growth promoters prior to the termination of these drugs. It is also not known exactly how many days, on average, pigs and broilers who received antimicrobial growth promoters were fed rations containing antimicrobial growth promoters. It is likely, however, based on indirect evidence[1], that prior to the terminations of antimicrobial growth promoters, most pigs and broilers on conventional (not organic) farms in Denmark were fed rations containing antimicrobial growth promoters for most of their lives (approximately 145 days for pigs to reach 100 kg from weaning at four weeks, and 42 days for broilers to reach 2 kg).

Coccidiostats

There was an increase in quantity of coccidiostats used in poultry in 1999 following the termination of antimicrobial growth promoters, primarily due to an increased quantity of ionophores (i.e. monensin, narasin, salinomycin) used. Ionophores are a class of antimicrobial agents not currently used in humans. In 2000 and 2001, however, quantities of coccidiostats used declined to pre-antimicrobial growth promoter termination levels. Moreover, after 1999, the vast majority of coccidiostats used in poultry were ionophores, and there were marked fluctuations in quantities of specific ionophores used each year. For example, the quantity of salinomycin used in poultry increased sharply in 2001, while use of narasin and monensin declined. Despite the fluctuations in the quantities of individual coccidiostats used in poultry between 1990 and 2001, the only discernable changes in the overall quantity of coccidiostats used in poultry after the discontinued use of antimicrobial growth promoters in 1998 was a moderate increase in 1999 followed by substantial decline in 2000 and 2001 (DANMAP, 2002).

Therapeutic antimicrobials

Broiler chickens

Therapeutic antimicrobial use in broiler chickens in 2001 was low and did not appear to increase following the termination of antimicrobial growth promoters (DANMAP, 2002; Tornøe, 2002). During 2001, Danish broiler chickens were given a total of 56.764 million Animal Defined Dosages (ADD) of therapeutic antimicrobials (DANMAP 2001, Table 6). Denmark produced 130 million broilers that year, so on average each broiler chicken received 56.764/130 = 0.4 ADD (was treated for 0.4 days). The number of ADD is calculated assuming an average body weight of treated birds of 200 g. If most treatments occurred either before or after 200 g, the average number of days treated would have to be adjusted accordingly. Using the above data, and assuming it took approximately 45 days for broilers to reach 2 kg, we also calculated that, on average, an estimated 1% of broilers in Denmark were on therapeutic antimicrobials at any given time in 2001.

Swine

While antimicrobials are used in pigs of all ages and types (sows, boars, piglets, weaners, finishers), the vast majority is used in weaners and finishers. Therapeutic antimicrobial use in pigs increased following the termination of antimicrobial growth promoter use in Denmark in 1998 (finishers) and 1999 (weaners) (Figure 1). In pigs this increase was principally with tetracyclines, penicillins and macrolides, however there were also modest increases with aminoglycosides (e.g. neomycin, streptomycin, spectinomycin, apramycin) and sulfonamide/trimethoprim combinations, while sulfonamide use was unchanged (Table 3). Usage of fluoroquinolones, in contrast, decreased markedly from 1998 to 1999 and has remained at low levels, in large part because a pharmaceutical company withdrew from the market a fluoroquinolone-containing feed premix for pigs out of resistance concerns, and because the Danish Veterinary and Food Administration recommended in 1998 that veterinarians restrain prescription of

[1] Based on DANMAP data, 107,000,000,000 mg of active antimicrobial growth promoters were used to produce 2,000,000,000 kg of meat (pork and broiler meat) in 1997. Assuming a feed/gain ratio of 2.4 for the wean-to-slaughter period, it required an estimated 4,800,000,000 kg of feed for broilers and for pigs from weaning to slaughter to produce this meat. Therefore, on average, feedstuffs contained approximately 22 mg of active antimicrobial growth promoter in 1997. Concentrations of drug in feed varied somewhat by drug, species and class of animals, however, the greatest volume of animal feedstuffs was used in finisher pigs and 20 mg/kg tylosin (maximum) was the principal antimicrobial growth promoter used in finishers in 1997 (see figure 3).

fluoroquinolones (DANMAP 2000). Very little cephalosporin was used in food animals before and after antimicrobial growth promoter termination. The total quantities of all antimicrobials used therapeutically in 2001 and 2002 were similar to the quantity used in 1994, the peak year of usage prior to termination of any antimicrobial growth promoters. During 2001, Danish weaner pigs were given a total of 151.74 million ADD of therapeutic antimicrobials (DANMAP 2001, Table 6). Denmark produced 24.5 million pigs that year, so on average each weaner pig received 151.74/24.5 = 6.2 ADD (was treated for 6.2 days) during the weaner period. The number of ADD is calculated assuming an average body weight of treated pigs of 15 kg. If most treatments occurred either before or after 15 kg, the average number of days treated would have to be adjusted accordingly Using the above data and assuming a 55 day period from 7-30 kg, we calculated that, on average, an estimated 11.3% of weaners in Denmark were on therapeutic antimicrobials at any given time in 2001.

During 2001, Danish finisher pigs were given a total of 37.371 million ADD of therapeutic antimicrobials (DANMAP 2001, Table 6). Denmark produced 22.5 million pigs that year (fewer than the number of weaners produced because some live pigs were exported), so on average each pig received 37.371/22.5 = 1.7 ADD (was treated for 1.7 days) during the finishing period. The number of ADD is calculated assuming an average body weight of treated pigs of 50 kg. If most treatments occurred either before or after 50 kg, the average number of days treated would have to be adjusted accordingly. Using these data and assuming a period of 85 day period from 30-100kg, we calculated that, on average, an estimated 2.0% of finishers in Denmark were on therapeutic antimicrobials at any given time in 2001.

Trends in usage of oral antimicrobials in Danish pig production 1986-2001 calculated as animal daily dosages (ADD)

The calculations shown in figures 2 and 3 are based on the assumption that all the specified oral antimicrobials were used in pigs. This is likely to be true for some of these antimicrobials (e.g. tylosin, tiamulin) , while for others the proportion used in other animal species may be 15-30% (e.g. neomycin). Therefore, the calculations will slightly overestimate the usage in pigs for these latter agents in the years prior to VETSTAT (2001).

In the late 1980's the 'pig specific' antimicrobials recalculated as ADD's accounted for a much lower proportion of total oral usage (25-30 percent) than was the case in the most recent years. This is mainly because dimetridazol and sulfadimidine were heavily used in pig production the late 1980's and accounted for a significant proportion of total usage of oral therapeutics. They were phased out around 1990.

From 1998 to 2001, tylosin (a macrolide) was the most commonly used therapeutic antimicrobial agent when calculated as standard dosages. The increase in tylosin use was larger than the increase in use of tetracycline. However despite this increase in the use of tylosin as a therapeutic agent in pigs the overall therapeutic use was small compared to its previous use for growth promotion purposes. There were approximately 350 million ADDs of tylosin used for growth promotion in 1996 compared to approximately 50 million ADDs used for therapeutic purposes in 2000 (see Figure 3). In this comparison we have used a daily dose of 4 mg/kg body weight both when tylosin was used to treat disease and when used for growth promotion, even though in the latter case the dose used was approximately half of that used for therapy. Had the growth promotion dosage been used, it is clear that our calculations would have shown an even higher number of ADDs of tylosin used for growth promotion than the estimate of 350 million. In addition to tylosin, bacitracin zinc, avilamycin and olaquindox were used for growth promotion in pig production (DANMAP, 2002).

2. Research study on selected swine farms in Denmark

In the study of selected swine herds, the incidence of antimicrobials treatments in weaners increased from approximately 0.8 ADD per pig-month prior to antimicrobial growth promoter termination in weaners, to approximately 1.5 ADD after antimicrobial growth promoter termination, and remained at this level after 12 months (Figure 4) (note: the ADD calculations in this selected study should not be confused with the national figures presented previously). With respect to antimicrobials used, increases were most evident in aminoglycoside, macrolide, tetracycline and tiamulin. In finishers, the incidence of antimicrobials treatments increased from approximately 0.2 ADD per pig-month prior to antimicrobial growth promoter termination in weaners, to approximately 0.4 ADD after antimicrobial growth promoter termination, however the frequency returned to pre-termination levels within 12 months (Figure 5). Increases in this group were most evident in macrolide, tetracycline and tiamulin (Larsen, 2002).

3. Survey of the quantities of antimicrobials used in European Union countries

We were not able to sufficiently compare the antimicrobial use in food animals in Denmark with antimicrobial use in food animals in other countries because limited antimicrobial use data from other countries was presented at the meeting. However, results from the

1997 survey of antimicrobial use in animals in European Union countries indicate that the therapeutic antimicrobial use in food animals was low in Denmark compared to other European Union countries (EMEA, 1999). Although therapeutic antimicrobial use in food animals has increased in Denmark since 1997, and although we do not have more recent consumption data in other countries, we believe that the quantity of therapeutic antimicrobials used in food animals is still likely to be low in Denmark compared to most other European countries.

Although we found discrepancies in the 1997 survey data compared with information from other sources, these discrepancies do not affect the above interpretation. They do however, point to the need for high quality, international antimicrobial use data that are collected and reported using comparable and transparent methods, and which take into account differences in animal husbandry and antimicrobial treatment practices in different countries. This is the subject of a recent WHO publication entitled “Monitoring Antimicrobial Usage in Food Animals for the Protection of Human Health: Report of a WHO Consultation, Oslo, Norway, 10-13 September 2001”.

Conclusion

DANMAP and VETSTAT were both very useful in allowing examination of antimicrobial use over time from 1990 to 2001, and in different animal species in 2001, respectively. Overall, antimicrobial use in food animals in Denmark has been reduced substantially following the discontinuation of antimicrobial growth promoters. This has resulted in both reductions in the total amount of antimicrobials used and in the average duration of exposure of animals to antimicrobials. On a national basis, the quantity of antimicrobials used in food animals in Denmark has declined 54% from the peak in 1994, (205,686 kg) to 2001 (94,200 kg). Prior to antimicrobial growth promoter termination, most pigs and broilers were exposed to antimicrobials for most of their lives, while after termination the average use of antimicrobials declined to 0.4 days in broilers (life span usually about 42 days to 2kg), and 7.9 days in pigs (life span usually about 170 days to 100kg).

Termination of antimicrobial growth promoters in pigs resulted in increases in therapeutic use of some antimicrobials that are also used in humans (e.g. tetracycline, penicillins, macrolides), however use of other drugs of importance to humans (e.g. cephalosporins, fluoroquinolones) was unaffected, and total therapeutic use in 2000 and 2001 was similar to 1994, the peak year of therapeutic use before any antimicrobial growth promoters were terminated. Therapeutic use in poultry appeared to be unaffected by antimicrobial growth promoter termination.

Impact of the termination of antimicrobial growth promoters on antimicrobial resistance

Data

DANMAP conducts surveillance on antimicrobial resistance on bacteria isolated from food animals, food, and humans. These data are summarized in annual reports. The DANMAP annual report from 2001 was utilized for this section of the review. Details about the source of the bacteria isolates and antimicrobial susceptibility testing methods used by DANMAP, including breakpoints for each of the genera of bacteria tested, are included in the report (DANMAP, 2002).

DANMAP monitors antimicrobial resistance among several bacteria including enterococci, *Campylobacter*, *Escherichia coli*, and *Salmonella*. Enterococci are Gram-positive bacteria. Most of the antimicrobial agents used as growth promoters in Denmark (avilamycin, avoparcin, tylosin, virginiamycin) have a Gram-positive spectrum of activity and could therefore be expected to select for resistance among enterococci. There are, however, some differences among the enterococci species. For example, *Enterococcus faecalis* is intrinsically resistant to streptogramins (e.g., virginiamycin). *Campylobacter* and *Salmonella* are Gram-negative bacteria and intrinsically resistant to most of the antimicrobials agents used as growth promoters in Denmark. The quinoxalines (carbadox and olaquindox) have a broad spectrum of activity. Macrolides (e.g., tylosin) are also active against *Campylobacter*. There is cross-resistance between the glycopeptides avoparcin (used in animals) and vancomycin (human), between the streptogramins virginiamycin (animal) and quinupristin-dalfopristin (human), and between the macrolides tylosin (animal) and erythromycin (human).

Bacteria isolates from animals

Samples from animals at slaughter were collected by meat inspection staff or company personnel and sent to the Danish Veterinary Institute for isolation of enterococci, *Campylobacter*, *Escherichia coli*, and *Salmonella*. The number of samples for each slaughter facility is determined in proportion to the number of animals slaughtered each year. The slaughter facilities from which broiler chicken, cattle, and swine samples are collected and included in DANMAP account for 98%, 80%, and 95%, respectively, of the total production of these animal species in Denmark. The *Salmonella* isolates included in DANMAP are a random sample of the *Salmonella* isolates serotyped at the Danish Veterinary Institute. The occurrence of antimicrobial resistance in isolates of enterococci, *Campylobacter*, *E. coli*, and *Salmonella* tested, because of the method of sampling, provides an estimate of the true prevalence of antimicrobial resistance in these bacteria in broiler chicken, cattle and swine in Denmark.

Escherichia coli isolated from clinical specimens of chickens with septicaemia, and cattle and pigs with diarrhea are submitted, usually under the direction of a veterinarian, to the Danish Veterinary Institute, the Cattle Health Laboratory in Ladelund, and the laboratory of the Federation of Danish Pig Producers and Slaughterhouses in Kjellerup. Isolates are forwarded to the Danish Veterinary Institute for susceptibility testing.

Plate dilution was used to test the susceptibility of *Campylobacter* isolates. All other susceptibility testing was done with broth microdilution (Sensititre, Trek Diagnostic System). The minimum inhibitory concentration (MIC) is the lowest concentration of antimicrobial with no visible growth. The Danish Veterinary Institute conducted *Enterococcus* species identification.

Bacteria isolates from food

Regional Veterinary and Food Control Authorities collected food samples at wholesale and retail outlets. The collected food samples consisted of both Danish and imported foods. Enterococci isolated from food samples were forwarded to the Danish Veterinary and Food Administration for species identification and susceptibility testing. From many foods there were no enterococci isolated. If isolated however only one isolate of enterococcus from each food sample was tested for antimicrobial susceptibility. Susceptibility testing was performed with broth microdilution (Sensititre, Trek Diagnostic System).

The following six figures (Figures 7-12), taken from DANMAP 2001, depict the trend in antimicrobial resistance to an antimicrobial agent among *Enterococcus faecium* in samples collected from animals at slaughter, and meat collected at wholesale or retail, and the quantity (in kilograms of active compound) of that antimicrobial agent used as a growth promoter in Denmark, from 1994 to 2001. The first three figures (Figures 7-9) concern broilers and broiler meat, the final three figures (Figures 10-12) concern pigs and pork.

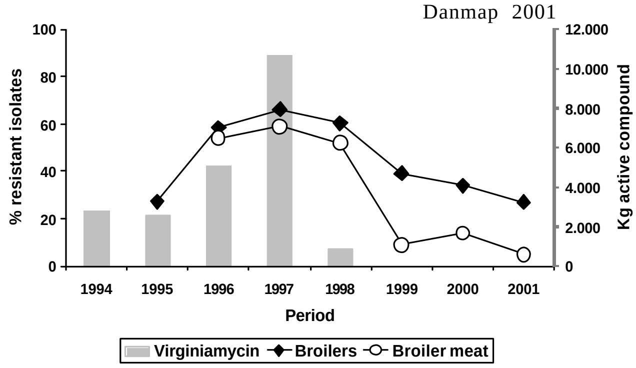


Figure 7. Trend in virginiamycin resistance among Enterococcus faecium *from broilers and broiler meat and usage of the growth promoter virginiamycin, Denmark.*

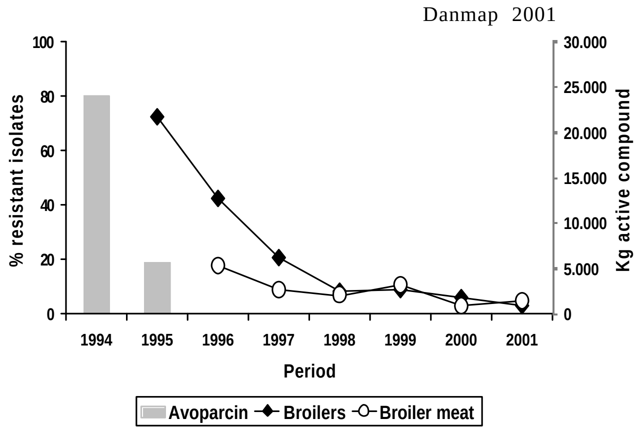


Figure 8. Trend in avoparcin resistance among Enterococcus faecium *from broilers and broiler meat and usage of the growth promoter avoparcin, Denmark.*

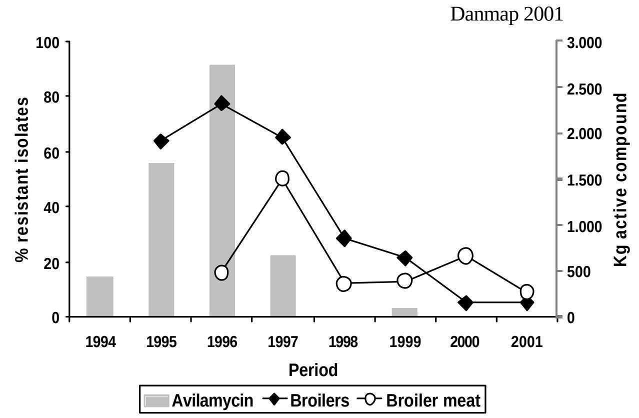


Figure 9. Trend in avilamycin resistance among Enterococcus faecium *from broilers and broiler meat and usage of the growth promoter avilamycin, Denmark.*

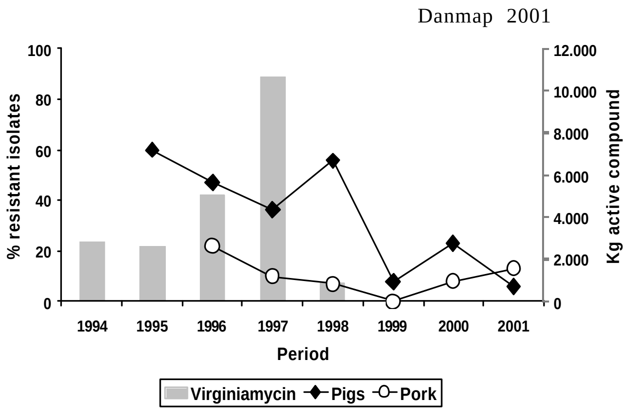


Figure 10. Trend in virginiamycin resistance among Enterococcus faecium *from pigs and pork and the usage of the growth promoter virginiamycin, Denmark.*

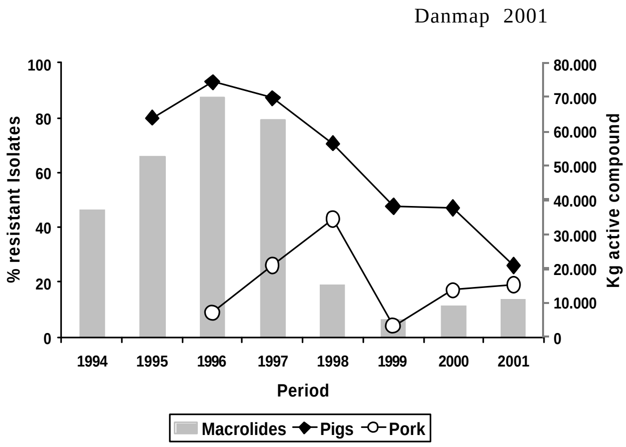


Figure 11 . Trend in erythromycin resistance among Enterococcus faecium *from pigs and pork and the total usage of macrolides, both as growth promoters and therapeutics, Denmark.*

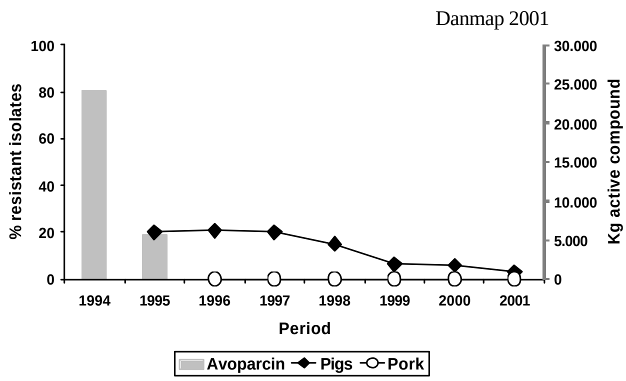


Figure 12. Trend in avoparcin among Enterococcus faecium *from pigs and pork and the usage of the growth promoter avoparcin, Denmark.*

The following figure shows the trends in tylosin use for growth promotion and erythromycin resistance among *Enterococcus faecalis* and *Enterococcus faecium* isolated from pigs at slaughter from 1995 to 2001 (Figure 13).

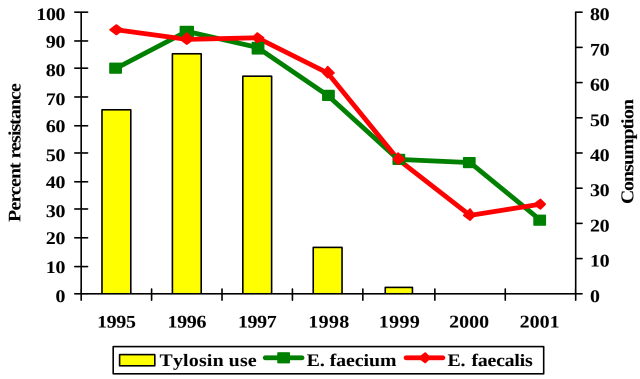


Figure 13 . Trends in erythromycin resistance in enterococci from pigs and tylosin use for growth promotion in Denmark.

The following two figures, taken from DANMAP 2001, depict the trends in antimicrobial resistance to selected antimicrobial agents among *Escherichia coli* isolated from samples collected from animals at slaughter, and from samples collected from ill animals in Denmark, from 1996 to 2001 (Figure 14 & 15).

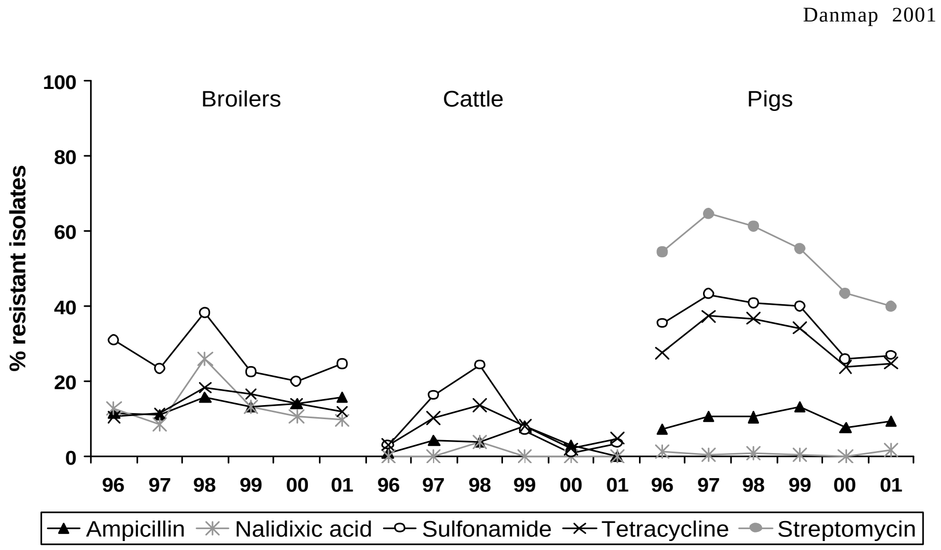


Figure 14. Trend in antimicrobial resistance to selected antimicrobial agents among E. coli *isolated from samples collected at slaughter from broilers, cattle and pigs, Denmark.*

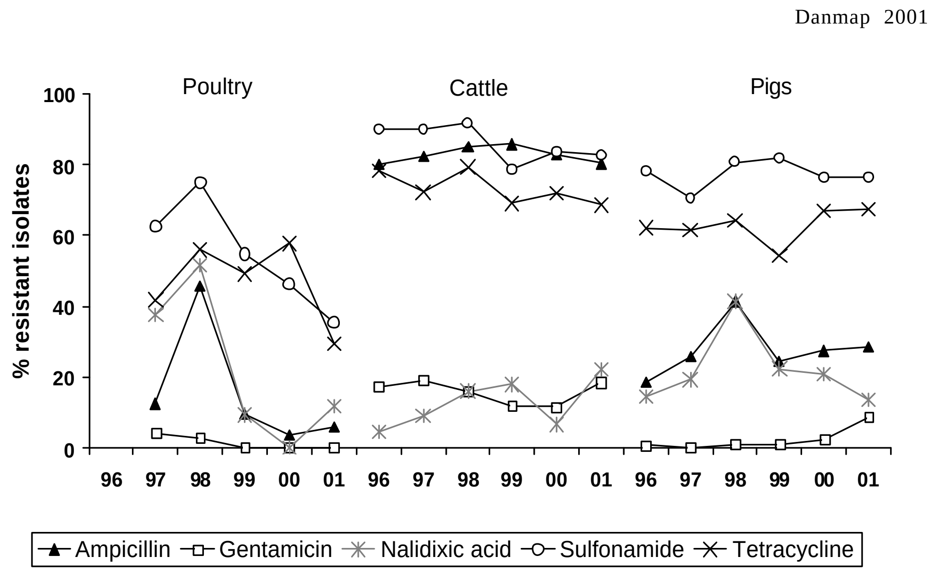


Figure 15. Trend in antimicrobial resistance to selected antimicrobial agents among E. coli *isolated from samples collected from poultry with septicemia, and cattle and pigs with diarrhea, Denmark.*

Bacteria isolates from humans

All isolates of *Salmonella* serotype Typhimurium were tested for antimicrobial susceptibility. For other *Salmonella* isolates and *Campylobacter* isolates from humans a random sample of isolates grown from faeces samples submitted for microbiological diagnostics to the Statens Serum Institute were tested for antimicrobial susceptibility. Susceptibility testing was performed using the tablet diffusion method (Neo-Sensitabs, A/S Rosco).

The following figure, taken from DANMAP 2001, depicts the trends in antimicrobial resistance to selected antimicrobial agents among *Salmonella* isolated from samples collected from animals at slaughter, and from samples collected from ill humans, stratified by history of travel abroad, in Denmark from 1996 to 2001(Figure 16).

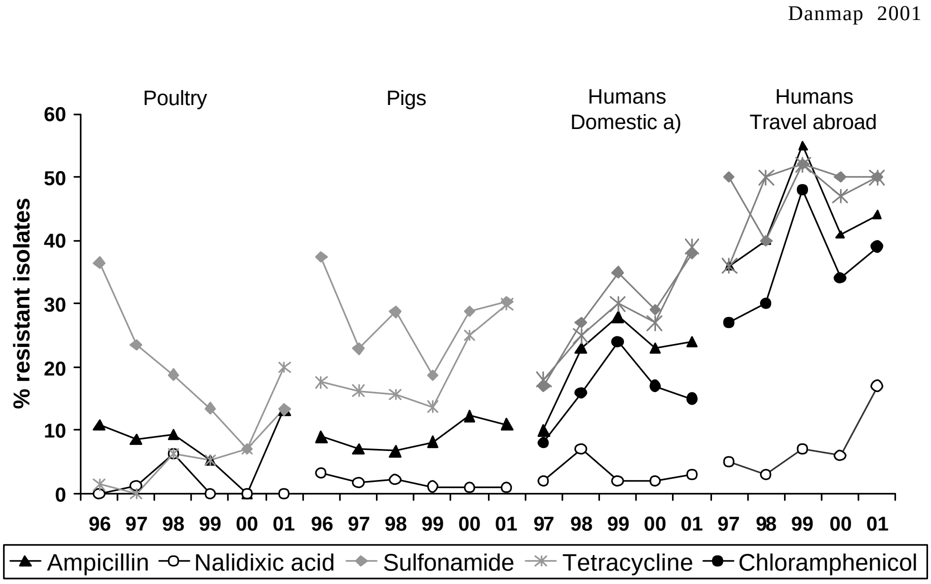


Figure 16 . Trend in antimicrobial resistance to selected antimicrobial agents among Salmonella *Typhimurium isolated from samples collected at slaughter from poultry and pigs, and from ill humans, Denmark*
a) Includes cases where origin of infection is non-documented and may therefore include some isolates acquired abroad but not documented as such.

The following two figures, taken from DANMAP 2001, depicts the trends in antimicrobial resistance to selected antimicrobial agents among *Campylobacter* isolated from samples collected from animals at slaughter, and from samples collected from ill humans, in Denmark from 1996 to 2001 (Figures 17 & 18).

Danmap 2001

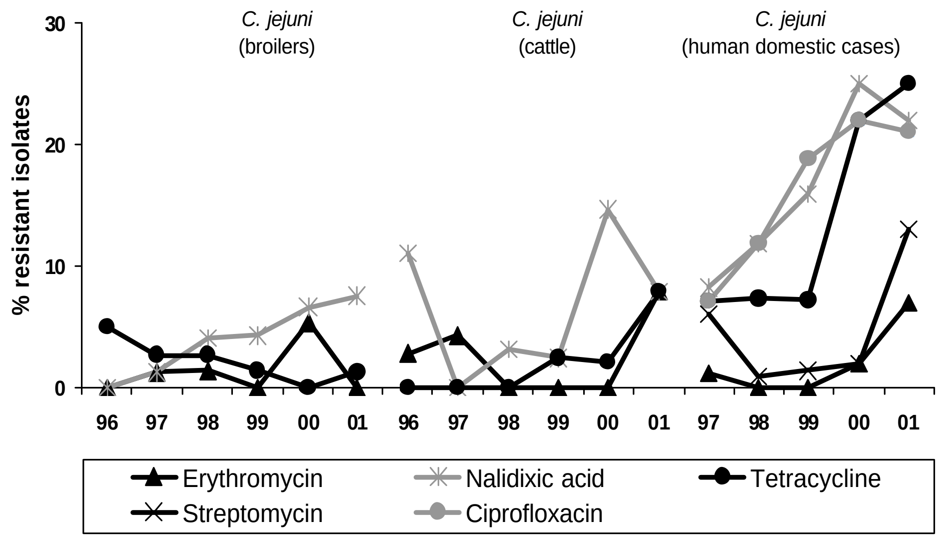


Figure 17. Trend in antimicrobial resistance to selected antimicrobial agents among Campylobacter jejuni *isolated from samples collected at slaughter from poultry and cattle, and from ill humans, Denmark.*

Danmap 2001

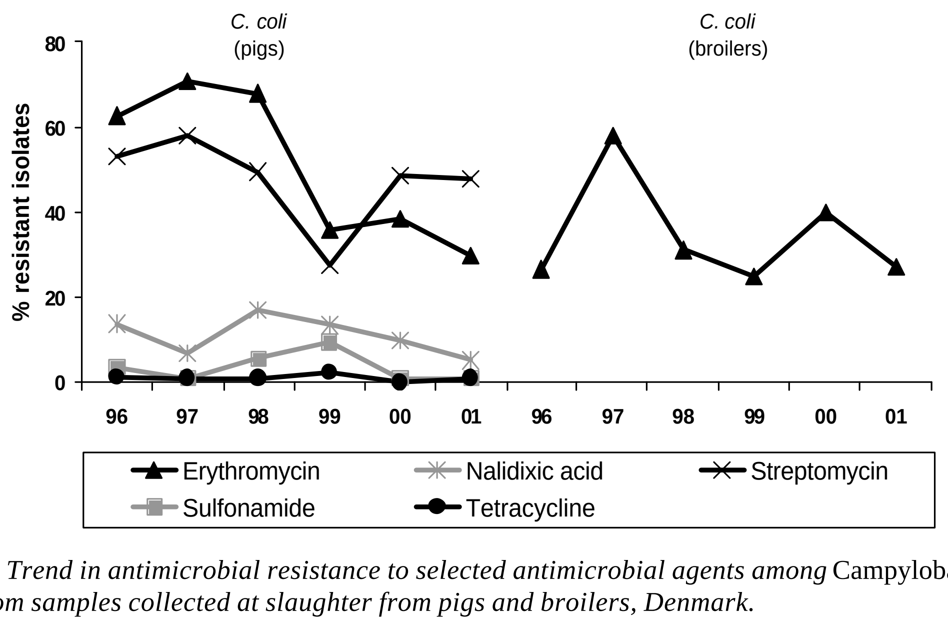


Figure 18. Trend in antimicrobial resistance to selected antimicrobial agents among Campylobacter coli *isolated from samples collected at slaughter from pigs and broilers, Denmark.*

The Statens Serum Institut conducted a small study of healthy human volunteers in 1996 (DANMAP, 1997). Stool specimens from the volunteers were cultured for enterococci, speciated and susceptibility tested for selected antimicrobial agents. Twenty-five *Enterococcus faecium* and 97 *E. faecalis* isolates were obtained. Under a new surveillance system in DANMAP entitled the 'Normal Flora Study (NORMAT)', stool specimens were also collected from healthy volunteers in 2002 and similarly tested. Participants in NORMAT are selected from the National Health Service register and are representative of the Denmark population in regards to gender and age distribution. The aim of NORMAT is to enrol 200 randomly selected persons each year in Denmark. Stool samples from 50 persons were tested in 2002; 19 samples yielded *E. faecium* and 27 yielded *E. faecalis* (Frimodt-Møller and Hammerum, 2002). The data from the two studies are presented in Tables 6 and 7.

Table 6. Antimicrobial resistance to selected antimicrobial agents among E. faecium *isolated from stool samples of healthy volunteers in 1996 and 2002, Denmark (Frimodt-Møller and Hammerum, 2002).*

	No. resistant/no. tested (% resistant)	
Antimicrobial	1996	2002
Avilamycin	0/15 (0%)	3/19 (16%)
Synercid	7/24 (29%)	0/19 (0%)
Erythromycin	2/25 (8%)	1/19 (5%)
Vancomycin	0/24 (0%)	0/19 (0%)

Table 7. Antimicrobial resistance to selected antimicrobial agents among E. faecalis *isolated from stool samples of healthy volunteers in 1996 and 2002, Denmark (Frimodt-Møller and Hammerum, 2002).*

	No. resistant/no. tested (% resistant)	
Antimicrobial	1996	2002
Flavomycin	1/49 (2%)	2/27 (7%)
Avilamycin	0/49 (0%)	0/27 (0%)
Erythromycin	8/97 (8%)	10/27 (37%)
Vancomycin	0/49 (0%)	0/27 (0%)

Interpretation

Food animals

When antimicrobial growth promoters were used in Denmark, antimicrobial resistance to most antimicrobial growth promoters was common in enterococci isolated from animals at slaughter. Since the discontinued use of antimicrobial growth promoters in Denmark, antimicrobial resistance to the antimicrobial growth promoters in enterococci has declined in the food animal reservoirs (broilers, cattle, pigs).

Among *Enterococcus faecium* isolates collected from broilers at slaughter, resistance to avilamycin, avoparcin, and streptogramins, declined from high (60-80%) levels when antimicrobial growth promoters were used in Denmark to lower (5-35%) levels following the discontinued use of these antimicrobial growth promoters. Among *Enterococcus faecium* isolates collected from pigs at slaughter, similar declines in resistance to erythromycin and streptogramins occurred following the discontinued use of antimicrobial growth promoters. Co-selection of avoparcin resistance by continued frequent use of tylosin (therapeutically) in pigs was probably an important factor in maintaining the approximately 15-20% levels of avoparcin-resistant *E. faecium* in swine despite the discontinued use of avoparcin as an antimicrobial growth promoter. When use of tylosin was reduced, levels of avoparcin-resistant *E. faecium* declined (Jensen *et al*., 2002; Aarestrup, 2002).

Among *Enterococcus faecalis* isolates collected from animals at slaughter, resistance to erythromycin declined following the discontinued use of antimicrobial growth promoters (Aarestrup, 2002). Resistance to avoparcin and avilamycin was rare among *E. faecalis* isolates (DANMAP, 2002).

Antimicrobial resistance among *Escherichia coli* isolates collected from broilers, or swine at slaughter, and isolates collected from poultry with septicemia, or pigs with diarrhea, did not appear to have been affected by the discontinued use of antimicrobial growth promoters (DANMAP, 2002). This is not unexpected as the antimicrobial growth promoters that were used had activity predominantly against Gram-positive bacteria rather than Gram-negative bacteria, such as *E. coli*.

Salmonella Enteritidis and *Salmonella* Typhimurium were the most frequently isolated serotypes of *Salmonella* from broilers and pigs, respectively. Antimicrobial resistance was rare in *Salmonella* Enteritidis. Among *Salmonella* Typhimurium isolates that were randomly selected from food animals for testing, there was an insufficient number from broilers (n=15 in 2001) to discern a trend in antimicrobial resistance associated with the discontinued use of antimicrobial growth promoters. Among *Salmonella*

Typhimurium isolates from pigs there was an increase in tetracycline resistance following the discontinued use of antimicrobial growth promoters, which likely resulted from the increased usage of tetracycline for therapeutic purposes in pigs during the period 1999-2001, although as already noted, no such increase in resistance was observed in *E. coli*, another Gram-negative organism from pigs. (DANMAP, 2002). This suggests that other factors may also have contributed to the increase in tetracycline resistance in *Salmonella* Typhimurium.

Among *Campylobacter jejuni* isolates collected from broilers at slaughter, no trend in antimicrobial resistance, including in macrolide resistance, is discernable following termination of antimicrobial growth promoters. Among *Campylobacter coli* isolates from pigs, there has been a decrease in erythromycin resistance following the discontinued use of antimicrobial growth promoters (DANMAP, 2002). Comparing results for isolates from broilers and from pigs it is clear that while quinolone resistance in campylobacter from broilers has increased, it has decreased in campylobacter from pigs. These changes appear to be independent of the withdrawal of antimicrobial growth promoters and only indirectly related to the changes seen in domestically-acquired infections in humans. A similar decline in resistance to nalidixic acid has been seen in *Salmonella* Typhimurium from pigs (DANMAP, 2002).

Tylosin, a member of the macrolide class, was the only drug used in pigs both as an antimicrobial growth promoter and a therapeutic agent, and it was used in both finishers and weaners. There are indications that tylosin use as an antimicrobial growth promoter had a greater impact on the prevalence of resistance to erythromycin (another macrolide) in enterococci isolated from pigs at slaughter than as a therapeutic agent, during either the weaner or finisher period. There is also some indication that use of tylosin as an antimicrobial growth promoter during the finisher period had a greater effect on erythromycin resistance than use of tylosin as an antimicrobial growth promoter in the weaner period. Although available data do not permit precise estimates, we believe that prior to termination of antimicrobial growth promoters most tylosin was used as an antimicrobial growth promoter in finishers. We base this on statements from the industry, on the >50 percent decline in tylosin use as an antimicrobial growth promoter after termination of use in finishers but before termination in weaners (there is some uncertainty here because some producers may have switched during this interval from tylosin to another antimicrobial growth promoter for weaners, e.g. olaquindox), and on the greater amount of feed consumed by finishers compared to weaners. Termination of antimicrobial growth promoters reduced the total amount of tylosin used in pigs by 89 percent from approximately 73,000 kg used in 1996 (68,350 kg for growth promotion plus approximately 5,000 kg for therapy) to 9,100 kg used for therapy in 2001. After termination, all tylosin was used as a therapeutic agent, and, in 2001 for example, roughly equal quantities (in kg active compound) were used in weaners and finishers for therapy (DANMAP, 2002). The prevalence of resistance to erythromycin in *Enterococcus faecium* isolated from swine at slaughter declined from 80 percent in 1997 just prior to the termination of tylosin as an antimicrobial growth promoter among finishers (1998) and weaners (1999), to less than 20 percent after termination, even though there was some increase in therapeutic treatments, especially among weaners.

Based on these observations, we believe that tylosin use as an antimicrobial growth promoter had a much greater impact on resistance to erythromycin among enterococci isolated from pigs at slaughter than tylosin use as a therapeutic agent. We also believe that tylosin use in finishers probably had a greater impact on this resistance than use in weaners, however further studies are needed to verify this conclusion. We consider it probable that reduced tylosin use in the finisher period compared with the weaner period may enable resistant bacteria to decline in numbers by the time the animals reach slaughter weight.

Food

The small number of enterococci isolated from food (i.e. pork and broiler chicken meat) make it difficult to discern trends in antimicrobial resistance associated with the discontinued use of antimicrobial growth promoters among enterococci isolated from food. The data that are available, however, suggest that resistance to avilamycin, avoparcin and virginiamycin among *Enterococcus faecium* isolates from broiler chicken meat declined following termination of antimicrobial growth promoters, and these results are statistically significant (Emborg *et al*., 2002a). Among *Enterococcus faecium* isolates from pork, there were no consistent trends in resistance to erythromycin and virginiamycin associated with termination of antimicrobial growth promoters, and isolates were not tested for resistance to avoparcin resistance prior to the termination of avoparcin use in 1995 (DANMAP2001; Boel and Andersen, 2002).

Humans

The small number of enterococci isolated from stool samples of healthy humans makes it difficult to discern trends in antimicrobial resistance associated with the discontinued use of antimicrobial growth promoters among enterococci isolated from healthy humans. Although the data are not robust and the representativeness of sampling is not clear, there may be a decline in the prevalence of virginiamycin resistance among *Enterococcus faecium* isolated from healthy humans following the discontinued use of antimicrobial growth promoters, including virginiamycin, in Denmark. There is also an indication that since the termination of antimicrobial growth promoters there may have been an increase in resistance among *E. faecalis* to the macrolide drug erythromycin, which may reflect an increase in the therapeutic use in pigs of tylosin (another macrolide). Avoparcin resistance appeared to be rare among enterococci isolated from stool samples of healthy humans in Denmark (Frimodt-Møller and Hammerum, 2002).

There are no data available on antimicrobial resistance among *Escherichia coli* isolated from stool samples of healthy humans in Denmark.

Among *Salmonella* Typhimurium isolates from ill humans with an unknown travel history or who report no history of travel abroad prior to illness onset, resistance to ampicillin, sulfonamide, tetracycline and chloramphenicol increased from 1996 to 1999. This is mainly explained by an increase in the proportion of *S.* Typhimurium DT104 and related phage types among *S*. Typhimurium isolates (DANMAP2001 p.26). Since 1999, the proportion of *S*. Typhimurium isolates decreased, and there was an increase in tetracycline and sulfonamide resistance in *S*. Typhimurium. The observed increase in tetracycline resistance in domestically acquired *S.* Typhimurium isolates from humans is likely to be associated with consumption of Danish pork (DANMAP, 2002), and may be associated with increased therapeutic tetracycline use in swine following the termination of antimicrobial growth promoter use. Although the increase in sulfonamide-resistant *S*. Typhimurium may also be associated with consumption of Danish pork, use of sulfonamides in pigs actually decreased from 1996 to 2000. The clinical consequence of increased tetracycline resistance is, however likely to be minimal for the therapy of *Salmonella* infections. This is because patients with gastroenteritis are unlikely to be treated empirically with tetracycline (and tetracycline is no longer used to treat persons with diagnosed *Salmonella* infections in Denmark). Increased tetracycline resistance among *Salmonella* is therefore not likely to result in ineffective treatment of *Salmonella* infections. Increased tetracycline resistance among *Salmonella* may result in additional human *Salmonella* infections, however, since persons who take tetracycline for other reasons are at increased risk of becoming infected with tetracycline-resistant *Salmonella*.

Among *Campylobacter jejuni* isolates from ill humans with an unknown travel history or who report no history of travel abroad prior to illness onset, there were small increases in erythromycin, quinolone, streptomycin, and tetracycline resistance following the discontinued use of antimicrobial growth promoters (DANMAP, 2002); the relationship between these increases, if any, with the discontinued use of antimicrobial growth promoters, is unknown. (DANMAP, 2002).

Conclusion

DANMAP is a unique and very useful program because it allowed the examination of antimicrobial resistance over time from 1996 to 2001. We believe that the DANMAP methods of collection of samples from animals at slaughter were very good. The methods for susceptibility testing, including selection of a single random isolate for examining the prevalence of antimicrobial resistance, were appropriate for trend ascertainment because the DANMAP methods have been consistent over this time period. Random selection of isolates is preferred to use of selective methods employing antimicrobial-containing culture media because a more accurate estimate of prevalence is possible. It will however underestimate the number of resistant bacteria that may be present at low concentration. On the other hand, DANMAP sampling of broiler meat, pork, and stool specimens from healthy humans was insufficient for our evaluation because the sample size appears to be too small and it is not clear that representative, probability-based sampling plans of the appropriate populations were used.

Extensive data were available that showed that the termination of antimicrobial growth promoters in Denmark has dramatically reduced the food animal reservoir of enterococci resistant to these growth promoters, and therefore reduced a reservoir of genetic determinants (resistance genes) that encode antimicrobial resistance to several clinically important antimicrobial agents in humans.

Data from healthy humans however are relatively sparse on which to assess the effect of the termination of antimicrobial growth promoters on the carriage of antimicrobial resistant bacteria. There is some indication that termination of antimicrobial growth promoters in Denmark may be associated with a decline in the prevalence of streptogramin resistance among *E. faecium* from humans. There is also an indication that the termination may be associated with an increase in resistance among *E. faecalis* to erythromycin (a macrolide), which may reflect in increase in the therapeutic use in pigs of tylosin (another macrolide). However, it should be noted that erythromycin is not a very important antimicrobial for the treatment of enterococcal infections in humans; preferred drugs include ampicillin, amoxycillin, vancomycin, streptogramins (for *E. faecium*), and linezolid. Further larger studies are needed to determine how much of an effect the discontinued use of antimicrobial growth promoters in Denmark will have on the carriage of antimicrobial resistance in the intestinal tract of humans in the community.

The antimicrobial growth promoters that were used in Denmark were active mainly against Gram-positive bacteria (with the exception of the quinoxalines). Therefore, direct effects of the termination of growth promoters on resistance in Gram-negative bacteria (e.g. *E. coli*, *Salmonella*) were neither expected nor observed. It is probable, however, that termination of antimicrobial growth promoters had an indirect effect on resistance to tetracycline resistance among *Salmonella* Typhimurium because of an increase in therapeutic tetracycline use in food animals. The clinical consequence of increased tetracycline resistance is, however likely to be minimal for the therapy of *Salmonella* infections. This is because patients with gastroenteritis are unlikely to be treated empirically with tetracycline (and tetracycline is no longer used to treat persons with diagnosed *Salmonella* infections in Denmark). Increased tetracycline resistance among *Salmonella* is therefore not likely to result in ineffective treatment of *Salmonella* infections. Increased tetracycline resistance among *Salmonella* may result in additional human *Salmonella* infections, however, since persons who take tetracycline for other reasons are at increased risk of becoming infected with tetracycline-resistant *Salmonella*.

Impact of the termination of antimicrobial growth promoters on human health (other than resistance)

Data

Foodborne Zoonotic Disease in Humans

Denmark conducts surveillance of human illness caused by a wide variety of diseases transmitted to humans primarily through eating contaminated food. Many of these foodborne diseases have food animal reservoirs and are therefore zoonoses (diseases transmitted from animals to humans). These foodborne diseases that are reportable to national authorities include human infections caused by *Salmonella* spp., *Campylobacter jejuni*, *Escherichia coli*, *Yersinia enterocolitica*, and *Listeria monocytogenes* (Annual report on Zoonoses in Denmark 2001). Human infections with *Salmonella* and *Campylobacter* are by far the most common bacterial foodborne diseases. Pigs and chickens are important reservoirs of *Salmonella* and *Campylobacter*.

The following two figures show the annual incidences of human *Salmonella* and *Campylobacter* infections (Figure 19 & 20).

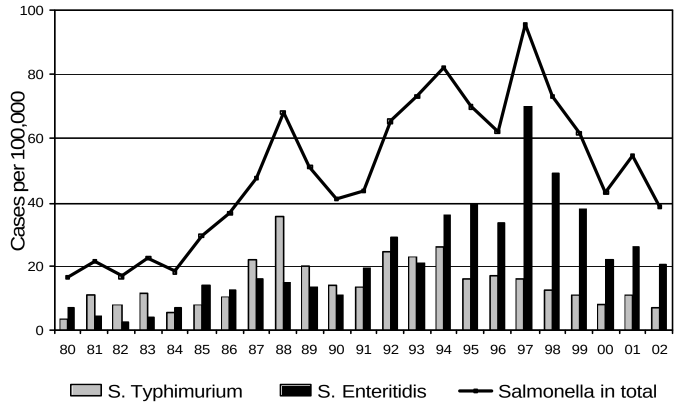


Figure 19. Registered cases of human salmonellosis in Denmark 1980-2002 (Annual Report on Zoonoses in Denmark 2002, Figure 8)

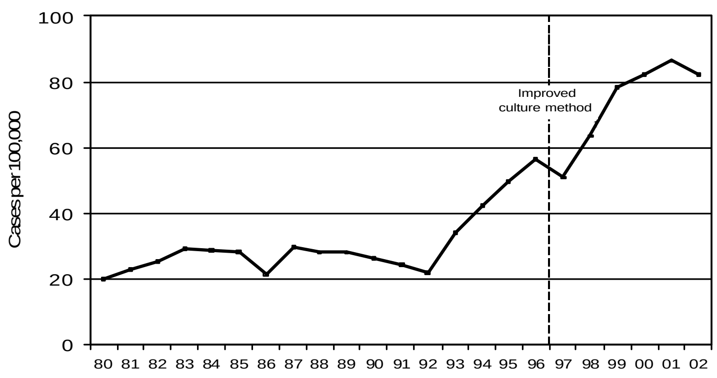


Figure 20. Incidence of campylobacteriosis in humans 1980-2002-(improved culture method was change from Skirrows medium to mCCDA) (Annual Report on Zoonoses in Denmark 2002, Figure 17)

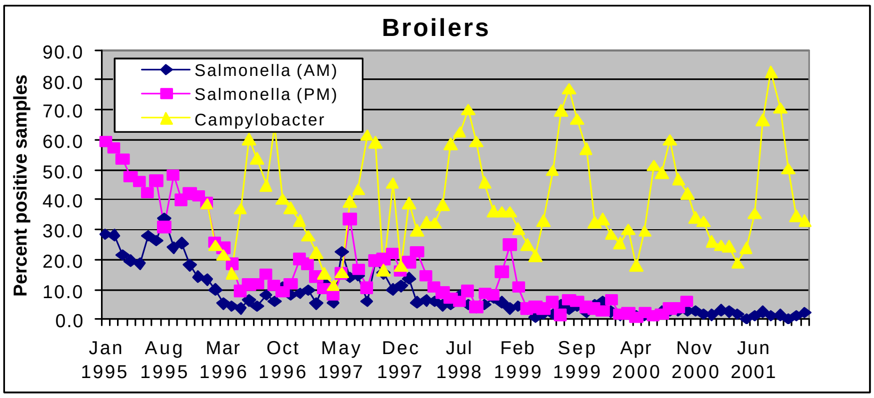
Monitoring of broiler chickens and pigs

Broilers have been routinely monitored for *Salmonella* since 1989 and *Campylobacter* since 1995. *Salmonella* monitoring in broilers was accomplished by collection of samples from each flock. Prior to June 2000, fecal samples for *Salmonella* monitoring were collected from selected broilers at slaughter. After 2000, fecal samples for *Salmonella* monitoring were collected via on-farm litter drag (sock). Prior to November 2000, selected carcasses were swabbed; after November 2000, pooled broiler parts were sampled. For *Campylobacter* monitoring in broilers, swabs of carcasses from each flock were taken at slaughter. Approximately 450,000 broiler samples are collected each year in Denmark (Figure 21).

Beginning in June 1995, all pig herds with more than 100 finishers slaughtered per year were monitored for the presence of *Salmonella* antibodies using a serological testing of meat 'juice' collected from pigs at slaughter. The number of meat samples taken at slaughter is dependent on herd size. In July 2001, sampling for *Salmonella* monitoring was restricted to pig herds with more than 200 finishers slaughtered per year. In addition to the serological testing, samples of pig meat from slaughterhouses were also collected monthly for *Salmonella* culture. Since January 2001, carcass swabs were used for the culturing for *Salmonella*. Approximately 830,000 pig samples were tested each year in Denmark (Figure 22).

Residues in food

The Danish Veterinary and Food Administration conducts antimicrobial residue monitoring of slaughter animals, milk and eggs (Table 8). Samples are collected using a stratified random sampling program and tested with the official EU reference microbiological test. From 1987-2001, samples were collected from approximately 0.1% of finisher pigs (1998-2001). In May 2001, the frequency of sampling was reduced because too few positives were identified in preceding years to justify continued intensive sampling (DANMAP, 2002).



Legend: AM=antemortem; PM=postmortem

Figure 21. Salmonella *and* Campylobacter *in broilers 1995-2001.*

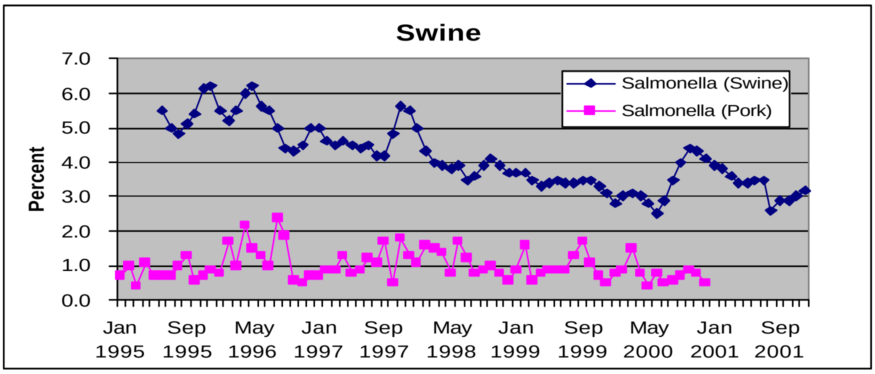


Figure 22. Salmonella *in swine (% seropositive herds) and pork (% culture positive meat samples) 1995-2001.*

Table 8. Frequency of antimicrobial residues in slaughter pigs, sows and poultry 1987-2001.

	92-96		1997		1998		1999		2000		2001	
Species	No. Tested	% +ve	No. Tested	% +ve	No. Tested	% +ve	No. Tested	% +ve	No. Tested	% +ve	No. Tested	% +ve
Pigs	96,482	0.02	19,483	0.03	20,509	0.01	21,154	0.02	20,474	0.01	21,914	0.005
Poultry	NA	-	NA	-	221	0	137	0	291	0	341	0

Interpretation

Human infection

The incidence of culture-confirmed human *Salmonella* infections increased from 1980 to 1997 to a peak incidence in 1997 (the year prior to the cessation of most antimicrobial growth promoters) of 95 culture-confirmed cases per 100,000 inhabitants (Figure 19). The incidence declined from 1997 to 2000 to 43 cases per 100,000 inhabitants. There was a modest increase from 2000 to 2001 to 54 cases per 100,000 inhabitants, however no increase in the prevalence of *Salmonella* in broiler or swine monitoring samples was observed during this period (Annual report on Zoonoses in Denmark 2001). Furthermore, the incidence in 2002 declined to 39 cases per 100,000 inhabitants. The steady decline in the prevalence of *Salmonella* in broiler or swine monitoring samples observed since 1995 continued during this period (Annual report on Zoonoses in Denmark 2001). Thus the incidence of human *Salmonella* infections declined following the termination of antimicrobial growth promoters. However, the peak in 1997 is largely due to *Salmonella enteritidis*, which in Denmark is believed to originate primarily from eggs (Annual Report on Zoonoses in Denmark 2001). Laying hens were not fed antimicrobial growth promoters, therefore we see no evidence that allows us to directly associate this fall to the termination of antimicrobial growth promoters in swine and poultry.

Since 1994, *Salmonella* serotype Enteritidis has been the most commonly isolated *Salmonella* serotype from ill humans, followed by *S*. Typhimurium. It is estimated that approximately 80% of human *Salmonella* infections in Denmark are domestically acquired (Annual Report on Zoonoses in Denmark 1997). In 1999-2001, approximately 4.8-15% of human culture-confirmed *Salmonella* infections in Denmark were judged to be associated with domestic pork and 0.8-4% from Danish broiler meat (Annual Report on Zoonoses in Denmark 1997, 2000 &2001).

It is estimated that approximately 80% of human *Campylobacter* infections in Denmark are domestically acquired, and a dominant source of human infections is eating chicken contaminated with *Campylobacter*, or eating other foods contaminated with *Campylobacter* originating from chicken (e.g., cross-contamination) (Annual Report on Zoonoses 2001). The incidence of human culture-confirmed *Campylobacter* infections has been steadily increasing since 1992, although it declined slightly in 2000 (Figure 20). There is no evidence that the termination of antimicrobial growth promoters in Denmark has influenced the incidence of human *Campylobacter* infections.

Yersinia enterocolitica infection in humans is believed to predominantly originate from pork. The incidence of yersiniosis has declined steadily from a high of 30 cases per 100,000 inhabitants in 1994 to 4.5 cases per 100,000 in 2002. There is no evidence that the termination of antimicrobial growth promoters in Denmark has influenced the incidence of human *Yersinia* infections.

Monitoring of animals

The prevalence of *Salmonella* in on-farm and slaughter broiler chicken samples decreased substantially since 1995 (Figure 21). Mean percentages of broiler flocks positive for *Salmonella* on both antemortem and postmortem testing were significantly higher (p<0.0001) before the withdrawal of antimicrobial growth promoters in 1998 than afterward. The prevalence of *Campylobacter* in broiler chicken samples was not significantly different before the termination of antimicrobial growth promoters and afterwards (Evans & Wegener, 2003).

There was a declining trend in the prevalence of seropositive pig herds 1995-2001(Figure 22). Based on the within-herd seroprevalence of *Salmonella*, herds were classified as level 1 (no or few seroreactors), level 2 (higher proportion of seroreactors) or level 3 (large proportion of seroreactors). The prevalence of herds classified as levels 2 or 3 was significantly (p<0.0001) greater before the termination of antimicrobial growth promoters in 1998 than afterward. The prevalence of *Salmonella* in fresh pork fell from 1.1% prior to antimicrobial growth promoter termination to 0.8% after termination, and this difference is statistically significant (p=0.0290) based on 18,510 pork samples in 1997 and 17,954 in 2000 (Evans & Wegener, 2002; Annual Report on Zoonoses in Denmark 1997; Annual Report on Zoonoses in Denmark 2000).

There is no evidence that termination of antimicrobial growth promoters affected the declining trends in prevalence of *Salmonella* in pigs and broilers from 1995 to 2001. While there are reports in the literature suggesting that antimicrobials fed to food animals can increase the prevalence or duration of fecal shedding with antimicrobial-sensitive *Salmonella* (the so-called ‘pathogen load’ effect), other studies have shown the opposite effect or no effect. Therefore, we believe it more likely that the extensive Danish pig and poultry *Salmonella* control programs were responsible for these trends.

Antimicrobial residues

Prevalences of antimicrobial residues in pork and poultry meat were consistently very low from 1987 to 2001 (<0.03% positive), and appear to have been unaffected by the termination of antimicrobial growth promoters (Table 8).

Conclusions

Overall, termination of antimicrobial growth promoters appears not to have affected the incidence of antimicrobial residues in foods or the incidence of human *Salmonella*, *Campylobacter*, or *Yersinia* infections in humans. These are the major zoonoses in Denmark that may be associated with consumption of pork and poultry. In an industry aggressively pursuing successful *Salmonella* reduction strategies, antimicrobial growth promoter termination appears not to have affected the prevalence of *Salmonella* in pig herds, pork, broiler flocks and poultry meat, or the prevalence of *Campylobacter* in poultry meat.

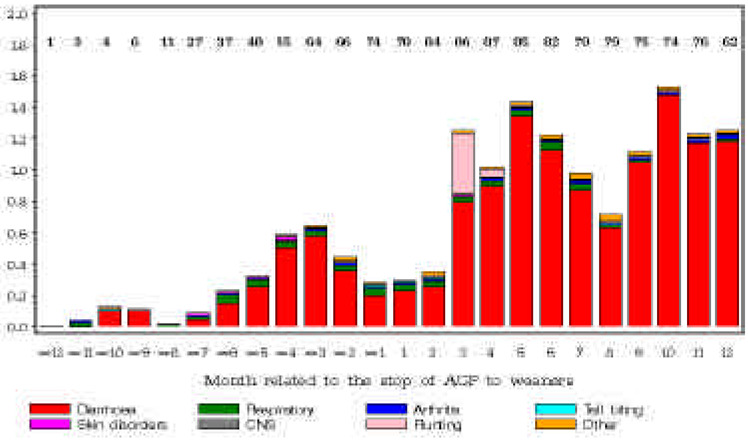


Figure 23. Average frequency of indications for antimicrobial treatment among weaners per pig-month at risk (number of farms contributing data per month listed at top).

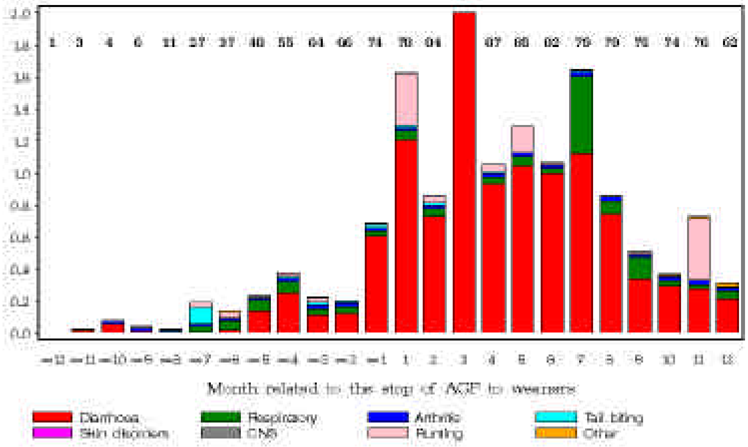


Figure 24. Average frequency of indications for antimicrobial treatment among grower/finishers per pig-month at risk (number of farms contributing data per month listed at top).

Impact of the termination of antimicrobial growth promoters on animal health (morbidity) and welfare[1]

Data

1. Research study on selected swine farms in Denmark

One hundred and fifty farrow-to-finish pig farms were identified by specialized swine veterinary practitioners and enrolled in a 1998-2000 longitudinal study of pig health and antimicrobial use (Larsen, 2002). In the absence of accurate clinical or laboratory diagnoses in all cases, farmers were asked to record their indications for antimicrobial treatment. To enable comparison over time and to summarize across farms, rates of farmer-recorded indications were expressed as treatment indications per pig-month (Figures 23 and 24).

[1] The impact of antimicrobial growth promoter termination on mortality in pigs and broilers is addressed under ‘Impact of the termination of antimicrobial growth promoters on animal production (swine and poultry)’ because only crude data (i.e. not cause-specific mortality data) were collected for the purposes of monitoring animal production. This section focuses on issues related to morbidity. The animal welfare issues addressed are confined to animal health issues (physical welfare).

2. *Broiler health data*

Broiler health information was provided by Danpo A/S, which slaughters and processes approximately 40% of broilers in Denmark. The data included flock-level occurrence of necrotic enteritis, need for therapeutic antimicrobials, and condemnation rates for diseased broilers at slaughter (Figure 25).

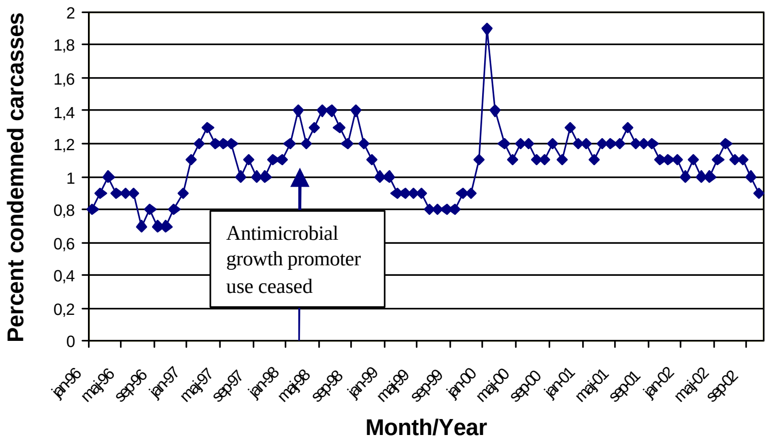


Figure 25. Per cent broilers condemned at slaughter 1997-2002. (A spike in condemnations unrelated to antimicrobial growth promoter termination occurred in March 2000. It was caused by an E. coli *infection that spread from a breeder flock to commercial flocks)*

3. *Laboratory submission data*

We were provided with the following graph showing the number of diagnostic submissions to the Danish Veterinary Institute, 1997-2000 (Figure 26).

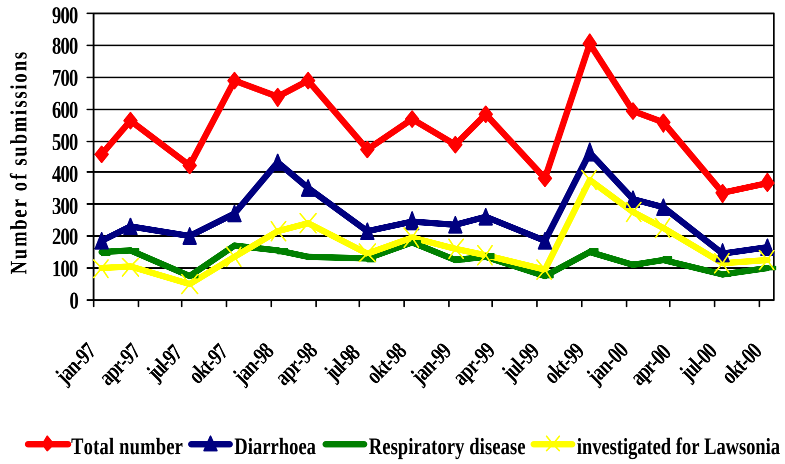


Figure 26. Submissions to DVI 1997-2000. Weaned piglets, growers and finishing pigs.

Interpretation

Swine

Data from the longitudinal study of farrow-to-finish farms (Larsen, 2002) suggest that most antimicrobial treatments in both weaners and finishers were administered for diarrhea. Among weaners, there was some increase in incidence of diarrhea treatment in the 6 months prior to antimicrobial growth promoter termination, but a much greater increase occurred after termination and continued for a year without decline. Many farmers and veterinarians reported difficulties, sometimes severe, controlling post-weaning diarrhea among weaners. The results of this study show an increase in treatments for diarrhea in the post-weaning period after the termination of antimicrobial growth promoters. The increase in diarrhea treatments was based on farmer reports. Since the occurrence of diarrhea was usually not confirmed by veterinary or laboratory diagnosis, it is likely that the incidence of diarrhea treatments was higher than the incidence of diarrhea. Therefore, while it is clear that some increase in incidence of diarrhea occurred, both the extent of the increase in diarrhea and the etiology of the diarrhea remain unclear. According to specimens sent to the Danish Veterinary Institute (DVI), many of these cases of diarrhea are caused by toxigenic *Escherichia coli* or *Lawsonia* (data not shown). Laboratory data from the Danish Veterinary Institute suggest that there were modest increases in diarrhea submissions from pigs in early 1998 and in late 1999 to mid-2000.

In 1999, when antimicrobial growth promoters were used only in weaners, 78% of antimicrobial growth promoters by weight were quinoxalines. Quinoxalines (carbadox and olaquindox, which were banned in 1999 by the EU due to concerns about toxicity to humans from occupational exposure) were the only antimicrobial growth promoters available with significant *in-vitro* activity against *E. coli* or useful for therapy of *Lawsonia* infections (Prescott, *et al*. 2001) (tylosin is reported to have activity against *Lawsonia*, but it was banned by the EU as a growth promoter in 1999). In the Larsen (2002) study, the post-weaning diarrhea problems leading to antimicrobial treatment increased from an average of approximately 0.4 treatments per pig-month in the six months prior to antimicrobial growth promoter termination in weaners, to approximately 1.0 treatments per pig-month in the six months after termination.

Among finisher pigs, there was also an increase in incidence of diarrhea treatment after antimicrobial growth promoter termination, however, incidence began to decline after 7 months, returning to pre-antimicrobial growth promoter termination incidence after one year. Problems with controlling *Lawsonia intracellularis* infections (diarrhea) were reported, and this infection is widespread in Danish pig herds (Jensen, 2002). Among finishers, some treatments may have been administered in reaction to fears of possible disease even if not actually present (Larsen, 2002).

We are unaware of any other animal health and welfare problems in swine following the termination of antimicrobial growth promoters. Although the issue of ear necrosis in swine was raised from the floor during the conference, there are no data on the extent of the problem or to support an association between the problem, if present, and termination of antimicrobial growth promoters.

Poultry

Prior to the termination of antimicrobial growth promoters, the industry anticipated some problems with necrotic enteritis (NE), a disease associated with *Clostridium perfringens* infection. A fund was established to compensate producers for losses should they occur, and producers were informed about the clinical signs of NE in their flocks to enhance early recognition. In the first year after termination, diagnoses were made in 25 of 1700 flocks compared with 1-2 per 1700 flocks annually prior to termination. Approximately 24 kg of amoxicillin was used to treat affected flocks. It is reasonable to assume that with this compensation fund available, a high proportion of flocks with NE would be identified, however, only 15% of the compensation fund was utilized.

There was some concern among veterinarians that there might be cumulative build-up of *Clostridium perfringens* in barns after multiple broiler flocks, eventually leading to outbreaks of NE or increased liver condemnations, however these problems did not materialize. The impact of NE has probably been considerably reduced by the continued use of ionophores in the first 18-20 days of life (Tornøe, 2002). Ionophores (e.g. monensin, narasin, salinomycin) are antimicrobials that are approved in Denmark and many other countries as coccidiostats (i.e. preventives of coccidiosis, a parasitic infection). Coccidiosis predisposes broilers to NE, and ionophores may also directly suppress *Clostridium perfringens* and therefore NE. Since antimicrobial growth promoter termination, Danish broiler producers believe that ionophores are the only effective means of NE prophylaxis, and continue to use them for this purpose. Experiments conducted in Denmark and elsewhere showed that severe NE outbreaks occurred when coccidiosis vaccines were used in place of ionophores (Tornoe, 2002).

For several months following antimicrobial growth promoter termination in early 1998, condemnation rates of broiler carcasses at slaughter increased by approximately 0.1%. The industry attributed the increase to a combination of factors, including antimicrobial growth promoter termination, occurrence of avian leucosis in some parent flocks, and disease secondary to vaccination of one rotation of broiler flocks for Gumboro disease (also called Infectious Bursal Disease, a viral infection). Subsequently, condemnation rates in broilers declined. A spike in condemnations unrelated to antimicrobial growth promoter termination occurred in March 2000. It was caused by an *E. coli* infection that spread from a breeder flock to commercial flocks.

We are unaware of any other animal health or welfare problems in poultry that can be clearly attributed to the termination of antimicrobial growth promoters. It has been suggested that there were increased footpad and skin problems in the broiler industry after the concomitant termination of the use of antimicrobial growth promoters and meat and bone meal in broiler rations. However, we have no information on the extent of these problems before the antimicrobial growth promoter termination, and there is no further documentation that exclusion of antimicrobial growth promoters and/or meat and bone meal caused these problems (Petersen, 2002). One study conducted after the termination showed that a significant reduction in skin and foot problems could be achieved without using antimicrobial growth promoters, by changing management practices, e.g. using wood shavings for litter instead of straw.

Conclusions

In swine, there was a significant increase in antimicrobial treatments for diarrhea in the post-weaning period after the termination of antimicrobial growth promoters. A less pronounced and transient increase in antimicrobial treatment for diarrhea was also observed in finishers. In broilers, necrotic enteritis was at most a minor broiler health problem following the termination of antimicrobial growth promoters, largely because producers continued to use ionophores for the prophylaxis of necrotic enteritis and coccidiosis.

Impact of the termination of antimicrobial growth promoters on the environment

Data

We are not aware of any Danish national monitoring programs or directed studies that specifically assessed the impact of antimicrobial growth promoter termination on the environment.

There are however some data available on nitrogen and phosphorus. In 1990/1991 the volume of nitrogen spread in the environment from animal manure was 244,000 tonnes. This has been reduced to 220,000 tons in 2001/2002 despite a significant increase in animal density in the same period (Figure 27) (The Danish Government 2002). The nitrogen content of manure has been reduced substantially since 1985 by reducing the protein content in the feed and by improved feed efficiency. The content of nitrogen in pig manure has been reduced by 39 percent from 1985 to 1999 (The Danish Gorvenrment 2002).

Interpretation

We believe that the possible environmental effects of antimicrobial growth promoter termination in the following areas deserve consideration: heavy metals (e.g. zinc, copper), soil nutients (e.g. nitrogen, phosphorus), bacteria and antimicrobial residues.

The accumulation of Cu or Zn in soils from the use of high levels of these minerals in pig diets is a concern. Inclusion of copper in post-weaning piglet rations to a maximum permitted concentration of 175 ppm reduces diarrhea and increases performance (Poulsen and Carlson, 2002).

Zinc oxide at 2,000-3,000 ppm in weaner pig rations has been shown to reduce the incidence and severity of diarrhea. However, ration concentrations exceeding 250 ppm are not permitted in Denmark for environmental reasons (Poulsen and Carlson, 2002). There appears to be no data describing the amount of zinc oxide actually used in pig diets in Denmark, or on any change in usage after termination of antimicrobial growth promoters.

The effects of antimicrobial growth promoter termination on total nitrogen and phosphorus output in animal manure appear to be negligible. Available national data indicate that surpluses of these nutrients from agriculture continued to decline following termination.

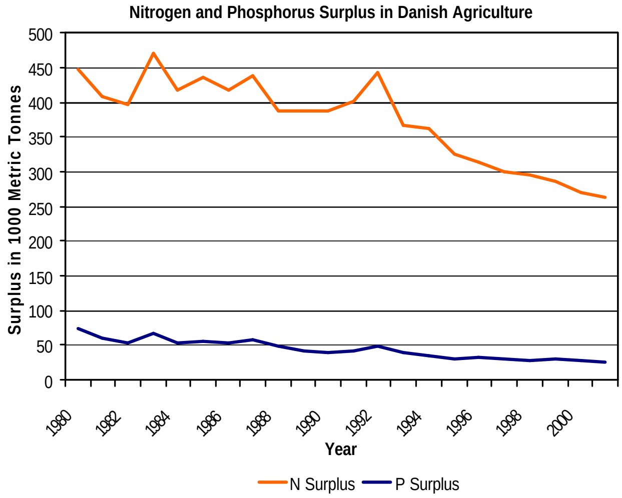


Figure 27 . Nitrogen and phosphorus surplus from agriculture in Denmark (Source: National Environmental Research Institute).

Reductions in total antimicrobial use and resistance in enteric bacteria of food animals associated with termination of antimicrobial growth promoters may have environmental benefits, however, no specific data were presented on ground water or soil contamination with resistant organisms or antimicrobial residues.

Conclusions

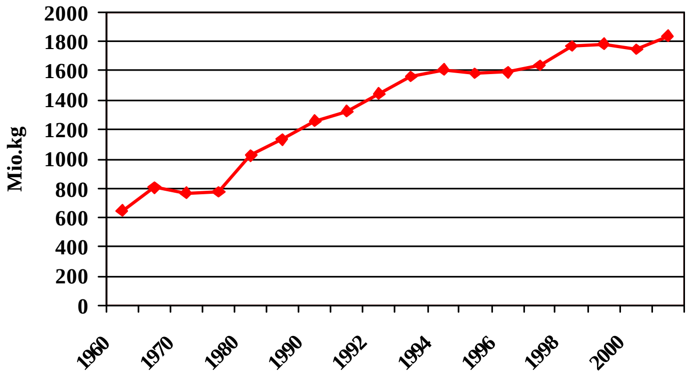
There was no evidence of any adverse environmental effects due to the termination of antimicrobial growth promoters, although there is very little data available with which to make an assessment. The effects of antimicrobial growth promoter termination on total nitrogen and phosphorus output in animal manure appear to be negligible. Available national data indicate that surpluses of these nutrients from agriculture continued to decline following termination.

Impact of the termination of antimicrobial growth promoters on animal production (swine and poultry)

Data

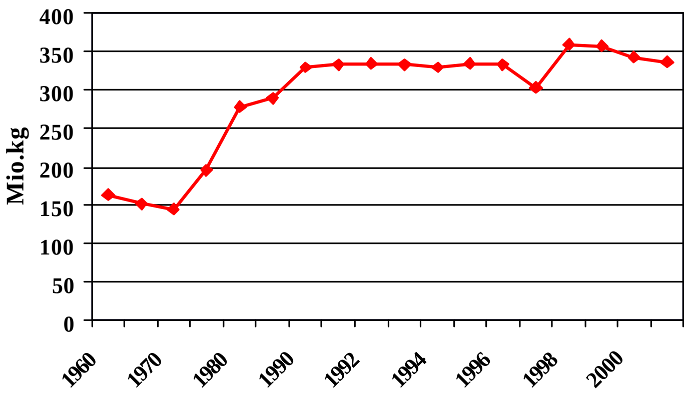
Swine Production

The amount of pig meat produced in Denmark and the amount consumed domestically are shown in Figures 28 and 29, by year since 1960 (Landbrug, 2001). Figure 30 shows the number of pig producers in Denmark 1972-2001.



Source: Landbrug 2001, Table 12.24

Figure 28. Total production of pork in Denmark, 1960-2001 (Landbrug, 2001).



Source: Landbrug 2001, Table 12.27

Figure 29. Domestic consumption of pork in Denmark, 1960-2001 (Landbrug, 2001).

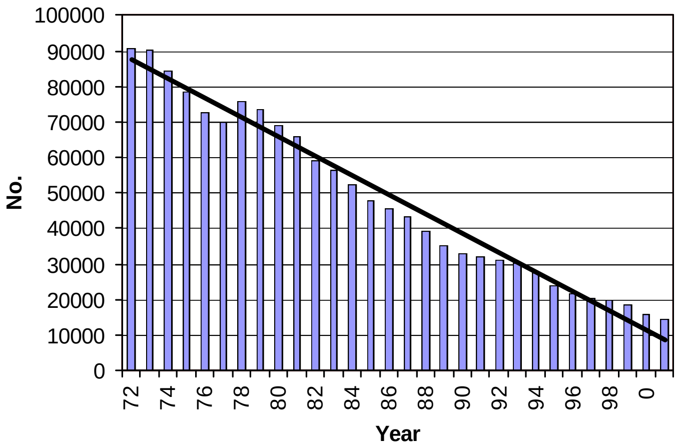


Figure 30. Number of pig producers in Denmark 1972-2001.

The National Committee for Pig Production operates a swine production records system (efficiency control program), to which pig producers submit data monthly. Of approximately 13,500 pig producers in Denmark, about 1,500 (11%) participate in this program. The following two graphs (Figures 31 and 32) show the growth rate and % mortality of finishing pigs and weaner pigs in Denmark during the last several years, as estimated by this records system (Callesen, 2002). Table 9 shows feed efficiency data for weaners and finishers 1996-2002.

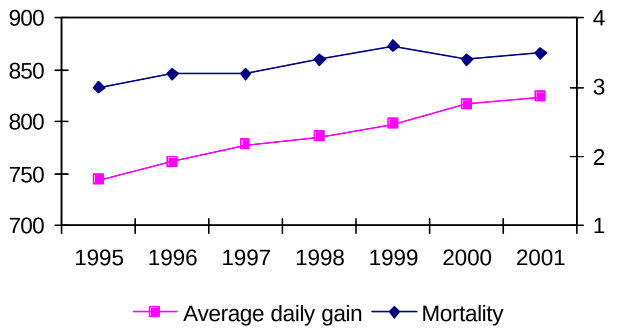


Figure 31. Productivity in Finishers: Danish Pork Board (Callesen, 2002).

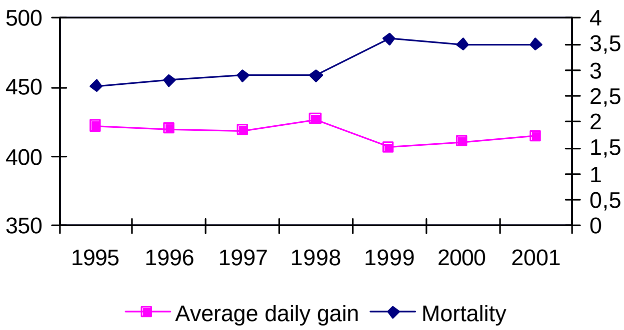


Figure 32. Productivity in Weaners: Danish Pork Board (Callesen, 2002).

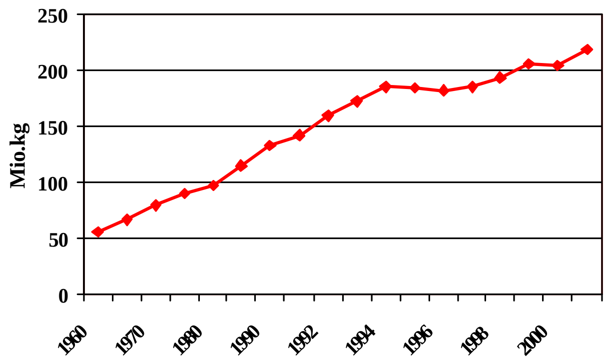
Table 9. Feed efficiency in weaners and finishers 1996-2002.*

	Feed Efficiency	
	Weaners (0-30 kg)	Finishers (30-100 kg)
Year	Feed Units / produced Pig**	Feed Units / Kg gain
1995	97.9	2.94
1996	97.6	2.93
1997	97.1	2.89
1998	99.4	2.91
1999	99.2	2.89
2000	99.3	2.89
2001	99.3	2.89

*Performance figures from herds with efficiency control
**Feed for sows (but not gilts) included
Source: The National Committee for Pig Production, Danske Slagterier. Annual Reports 1995-2002.

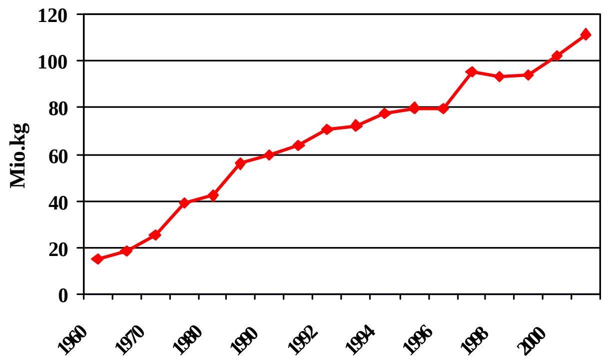
Broiler Production

The amount of poultry meat produced in Denmark and the amount consumed domestically are shown below in Figures 33 and 34, by year since 1960 (Landbrug, 2001).



Source: Landbrug 2001, Table 12.24

Figure 33. Total production of poultry in Denmark, 1960-2001



Source: Landbrug 2001, Table 12.27

Figure 34. Total Poultry Meat Available for Consumption, 1960-2001

Data on broiler productivity collected by the Danish Poultry Council are shown in the Figures 35, 36 & 37. The records were of several performance and descriptive variables of individual flocks. A first dataset included 6,815 flocks from 237 farms and 575 houses, covering the period before and after the termination of antimicrobial growth promoters, from November 1995 to May 1999. A second dataset included 6,179 flocks slaughtered between June 1999 and June 2002 (Emborg *et al.*, 2002b).

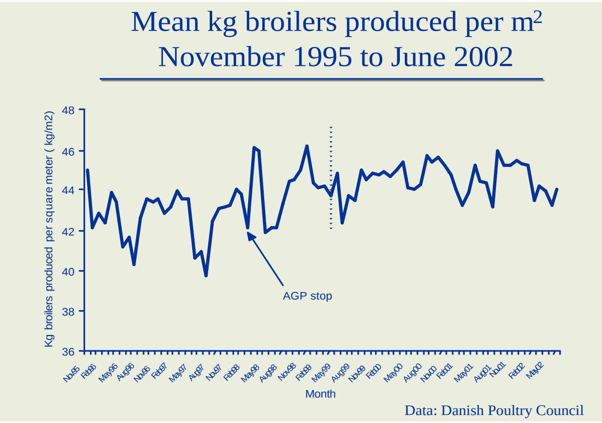


Figure 35. Mean monthly kilogram broilers produced per square metre.

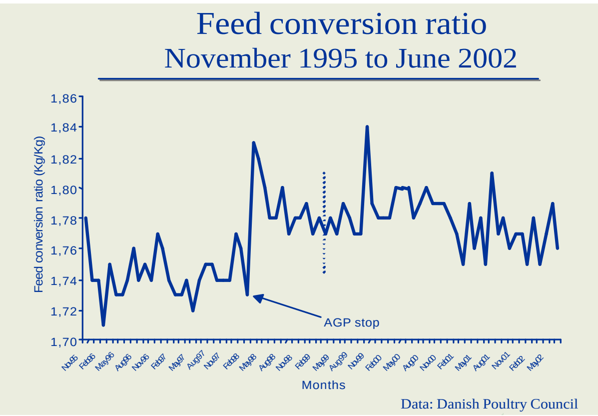


Figure 36. Mean monthly feed conversion ratio.

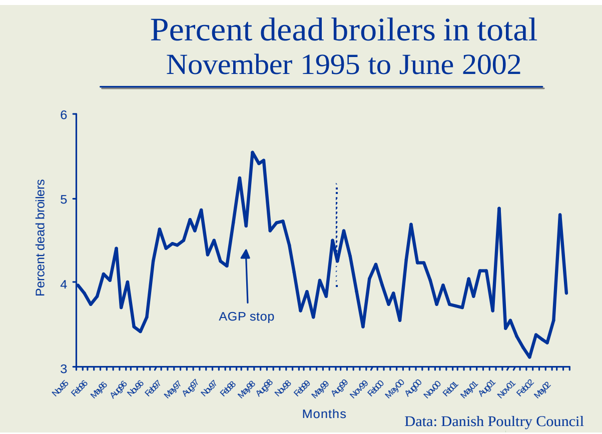


Figure 37. Mean monthly percent dead broilers.

Interpretation

This section reviews information on the impact of antimicrobial growth promoter termination on pig and poultry production. The next section (Economic impacts of the termination of antimicrobial growth promoters in Denmark) addresses the financial impact of termination on industry and the national economy.

Swine Production

There has been a steady increase in total pork production in Denmark since 1990 despite a steady decrease in the number of pig producers. These changes reflect the dynamic nature of the industry and its adaptability, and are likely to have been driven largely by macroeconomic factors, national policy, and other factors. These changes were not obviously affected by the termination of antimicrobial growth promoters in 1998-1999.

Based on production records, the number of days to 100 kg body weight (birth to approximate slaughter date) decreased by 2.4 days from 173.9 in 1997 to 171.5 in 2001 (i.e. an improvement of 1.4%). However, a trend line extrapolated from previous years' data suggests that improvements in genetics and production technology would likely have resulted in a reduction in the age to reach 100 kg to 169.9 days in 2001, without the termination of antimicrobial growth promoters (Calleson, 2002). That suggests a true cost of termination of antimicrobial growth promoters may have been an increase of 1.6 days (171.5 – 169.9) to reach 100 kg (i.e. a loss of 0.9%).

There was an increase in average mortality in weaners from 2.9% (1995-1998) to 3.5% (1999-2001) after the termination of antimicrobial growth promoters. This increased mortality has persisted in the two years following the termination (Callesen, 2002). There was a decrease of 2.6% in average growth rate of weaners, from 422gm/day (1995-1998) to 411gm/day (1999-2001), after termination of antimicrobial growth promoters. After the decrease in daily gain to 407gm/day in 1999, the average growth rate increased to 415gm/day in 2001. The average age of pigs at 30kg has increased from 82.7 days (1995-1998) to 85.4 days (1999-2001), an increase of 2.7 days.

It was estimated that it took 2.7 additional days to reach 30 kg but only 1.6 additional days to reach 100 kg. Considering the assumptions required for estimation of these two numbers and therefore the errors of estimation, these values (2.7 days and 1.6 days) may actually be two estimates of the same number. If so, it appears then that nearly all of the effect of antimicrobial growth promoter termination on the age required to reach 100 kg occurred before the pigs reached 30 kg body weight (i.e. the weaner period), with little or no effect in the later growth stages. Alternatively, the estimate of an increase in days due to termination of antimicrobial growth promoters to 100kg for pigs of 1.6 days compared to 2.7 days to 30 kg may be due to compensatory growth after 30 days. There was no clear effect of the termination on feed efficiency during finishing, but there was an increase of 1-2% in feed units required per weaner produced following the termination of antimicrobial growth promoters. There may be multiple factors that contributed to this increase, including increased incidence of diarrhea, additional days to reach 30 kg, and perhaps other effects beyond disease prevention (e.g. effects on nutrition, physiology, commensal intestinal microbial flora) (SOU, 1997).

The 2.6% reduction in growth rate of weaners stands in contrast to five recent controlled experiments of the Danish National Committee on Pig Production that show an average 10.8% increase in growth rate in response to antimicrobial growth promoters (Kjeldsen, 2002). This is somewhat surprising because we would expect that responses to these antimicrobials would be greater where health is poorer, and we would also expect that pigs on research farms would be healthier than pigs on commercial farms. However, the latter is not always true and we have no details about the health status of the pigs used in these experiments. In many fields of science the magnitude of results obtained under experimental conditions is different than that obtained in the field situation for a whole variety of reasons, and it is possible that under field conditions in Denmark, antimicrobial growth promoters did not have a very substantial effect on growth. Alternatively, the smaller change over time than was predicted from the controlled experiments may have occurred because something in addition to just stopping the use of antimicrobial growth promoters also occurred during this period. One possibility was that Danish pig producers reacted to the termination of antimicrobial growth promoters by making other management changes to improve pig health. It is clear that one response was an increase in therapeutic use of antimicrobials in weaners. It is likely that many producers adopted non-antimicrobial production enhancers and/or they altered production systems with such changes as adoption of other feed ingredients, tightening biosecurity, improving sanitation, increasing weaning weights, adopting all-in-all-out pig flow, reducing stocking density, or others. Such changes in production systems would be especially important to producers because many of the changes would require capital investment that in some cases could be substantial. Unfortunately, no studies were done to specifically determine whether, and to what degree, and at what cost, termination of antimicrobial growth promoters influenced producers in Denmark to adopt non-antimicrobial production enhancers and/or altered production systems. National experts in industry reported that all-in-all-out management was adopted for a variety of reasons, and that there has not been a reduction in stocking density in the industry overall. We think it is important to point out that at the same time that antimicrobial growth promoters were terminated, the industry was adapting to other programs affecting management, including *Salmonella* control and animal welfare regulations. We believe that termination of antimicrobial growth promoters was one factor among several that may have led to changes in production systems, and with the available data we cannot identify the individual effects on overall production of these different interventions, nor their associated costs.

There has been no major effect of the antimicrobial growth promoter termination on productivity in finishers. The average percent mortality of finishers increased from 3.1% (1995-1997) to 3.5% (1998-2001), after the termination of antimicrobial growth promoters. However, this slight increase in mortality rate appears to be a continuation of the trend observed since at least 1992. The average growth rate of finishers increased 6% after the termination of antimicrobial growth promoters, from 761gm/day (1995-1997) to 806 gm/day (1998-2001). However this change also appears to be a continuation of the trend observed since at least 1995 (Calleson, 2002).

There is no clear evidence that the increases in mortality and weight gain of finishing pigs are associated with the termination of antimicrobial growth promoters. It is our interpretation that if there is an effect on mortality and weight gain in finishers associated with the termination of antimicrobial growth promoters, it appears to be very small and therefore not detected in the available data.

Conclusions - Swine Production

The termination of antimicrobial growth promoters resulted in some loss of productivity, primarily in weaners. There was no major effect of the antimicrobial growth promoter termination on productivity in finishers. The economic effects of the antimicrobial growth promoter termination on the pig producer (discussed in more detail later in the report) would have been variable and presumably may have included some or all of the following: costs associated with modifications of the production systems to increase pig health, decreased feed efficiency, reduced growth rate and increased mortality in weaners, increased use of therapeutic antimicrobials and costs associated with purchasing alternatives to antimicrobial growth promoters. Some of these costs (e.g. increased therapeutic antimicrobials, reduced growth rate) have been measured and were not large, but others, especially some costs associated with modifications of the production systems, are difficult to measure and were not included in this report, although they may have been substantial for some producers. These costs would have been at least partially offset with savings associated with not purchasing antimicrobial growth promoters. Overall, total volume of pork production in Denmark continued to increase in the period following the termination of antimicrobial growth promoters.

Poultry Production

There has been an increase in total poultry meat production in Denmark since 1990. This increase is not obviously affected by the termination of antimicrobial growth promoters in 1998, and perhaps is driven by major market forces.

There was no detrimental effect of the termination of antimicrobial growth promoters on either mortality or weight gain in broilers. There was however a decrease in feed efficiency. The amount of feed required to gain 1 kg of broiler weight (feed efficiency), increased from 1.74 kg/kg (1995-1997) to 1.78 kg/kg (1998-2000), an increase of 0.04 or 2.3%. A statistical analysis of data from the 6,815 flocks in the first dataset described above, adjusting for several factors, produced an estimate of the decrease in feed efficiency of 0.016 kg/kg or 0.9% (Emborg *et al*., 2002b). Calculations suggested that the savings associated with not purchasing antimicrobial growth promoters almost exactly offset the cost of the smaller (i.e. 0.016 kg/kg) estimate of reduction in feed efficiency.

The average mortality in poultry was 4.1% (1995-1997) before and 4.0% (1998-2000) following antimicrobial growth promoter termination. Mortality increased to 4.5% in 1998 but then declined to 3.8% in 1999 and 2000 (Emborg *et al.*, 2002b).

The average weight of broilers at 42 days of age increased from 1,959gm (1995-1997) while antimicrobial growth promoters were being used to 2,012gm (1998-2000) after the termination. This increase in weight gain appears to be a continuation of the trend observed since at least 1995.

Some costs associated with modifications to the production systems are difficult to measure and were not included in the report, although they may have been substantial for some producers.

Conclusions – Poultry Production

Based on available data, the effects of antimicrobial growth promoter termination on poultry production appear to be small and limited to decreased feed efficiency (-2.3%) that is offset, in part, by savings in the cost of antimicrobial growth promoters. There were no changes in weight gain or mortality that appeared to be related to the termination of antimicrobial growth promoters.

Economic impacts of the termination of antimicrobial growth promoters in Denmark

Data

Finn K Udesen (Jacobsen and Jensen, 2003[1]) from the National Committee for Pigs, has estimated that the productivity losses outlined above incurred by removing antimicrobial growth promoters in the production of pigs has cost approximately 7.75 DKK (1.04 €) per pig produced. A breakdown of these costs is shown in Table 10 below.

Table 10. Productivity reductions and cost per produced pig incurred by removing AGP.

	Units	Unit cost	DKK per pig produced
Excess mortality	0.6%	425 DKK/pig (20 kg)	2.55
Excess feeding days	1.6 days	1.10 DKK/day	1.75
Increased medication	25,500 kg	53 mill. DKK	2.25
Increased workload	30 sec./pig	145 DKK/hour	1.20
Total cost			7.75

Source: Estimates made by Finn K. Udesen from the National Committee for Pigs

In addition, there is evidence from the Danish Bacon and Meat Council (personal communication, 2003) that pig producers spent nearly 1 DKK per pig extra on organic acids in feed. However, this additional cost was offset by an estimated 1 DKK per pig saved by not using antimicrobial growth promoters.

In the case of poultry, evidence presented in the production section above suggested that the cost associated with the reduction in feed efficiency due to antimicrobial growth promoter termination was almost exactly offset by savings associated with not purchasing antimicrobial growth promoters. Thus the overall impact on the cost of poultry production is assumed to be zero (Emborg *et. al*. 2002b).

Jacobsen and Jensen (2003) estimate the impact on the Danish economy of termination of antimicrobial growth promoters using a general equilibrium economic model of the agricultural sector in Denmark. The model estimates the effect of antimicrobial growth promoter termination on pig and poultry production, the agricultural sector and the Danish economy more widely. The model uses a baseline scenario which projects the likely development of the Danish economy to 2010. As part of this baseline scenario, pig production is projected to increase by 30.5% over the 1995-2010 (an average 1.8% per year). The estimated increase in pig production costs of 7.75 DKK per pig translates into an increase in pig production costs of just over 1% (see Table 11 below), with an assumed 0.0% change in poultry production costs.

Table 11. Estimated total cost increase for pig keeping in Denmark, percent.

	1997/98	Sensitivity analysis	
		-25%	+25%
Produced pigs per sow	20.0	20.0	20.0
Extra production cost per pig produced DKK..	7.75	5.81	9.69
Extra production cost per sow DKK	138	103	172
Total pig keeping cost per sow DKK	14832	14832	14832
Percentage increase in costs	1.05	0.78	1.31

Source: Economics of Agricultural Enterprises, Serie B. Economics of Agricultural Enterprises. Danish Research Institute of Food Economics and own calculation

1. This reference is a revised version of the paper presented at the conference in Foulum. In response to queries from the Panel, some of the estimated production costs were updated, the economic analyses were recalculated and some of the text was revised.

For purposes of analysis, two additional cost scenarios were also considered, where pig production costs are assumed to increase by 25% more or 25% less than the Udesen estimate of 7.75 DKK. These alternative scenarios are shown in Table 11.

These estimates were input into the economic model to calculate the economy wide effects of removing antimicrobial growth promoters from feedstuffs in Denmark. The results of running the model (see Table 12) show a relatively small reduction in pig production of around 1.4% per annum as a result of antimicrobial growth promoter termination (giving a forecast growth of pig production of 28.7% from 1995-2010 compared to the 30.5% of the baseline scenario), and an increase of 0.4% in poultry production. The latter result is because poultry production is a competitor to pig production both for inputs and consumption and so indirectly benefits from lower pig production. Exports of processed pig meat are forecast to be 1.7% lower than they would be in the absence of antimicrobial growth promoter termination, and export volume of poultry meat increases by 0.5%.

The 25% sensitivity analysis results (which allow for some uncertainty as to the impact on production costs of withdrawal of antimicrobial growth promoters) show a range of 1%-1.7% reduction in pig production and 0.27% to 0.45% increase in poultry production.

Table 12. Consequences of withdrawal of antimicrobial growth promoters, percentage changes.

	Production	Export
Agriculture:		
Cereal	-0.1	0.1
Oilseed	0.2	0.1
Potatoes	0.1	0.1
Sugar beet	0.0	
Roughage	0.0	
Cattle, live animals	0.0	
Milk	0.0	
Pig, live animals	-1.4	
Poultry and eggs	0.4	
Fur farming	0.1	
Horticulture	0.1	0.1
Manure	-0.6	
Processing:		
Cattle meat	0.0	0.1
Pig meat	-1.4	-1.7
Poultry meat	0.4	0.5
Dairy	0.0	0.1

Taking into account ‘knock-on’ effects within the agricultural sector and the Danish economy more generally, the overall estimated impact for the Danish economy of antimicrobial growth promoter termination is a reduction of 0.03% (363 million DKK (48 million €) by 2010 at 1995 prices) in real Gross Domestic Product (GDP). The 25% sensitivity analysis results show a range of a reduction of 270 million DKK to 452 million DKK in GDP for the Danish economy. The analysis assumes that antimicrobial growth promoter termination does not affect domestic consumer preferences or export markets.

Interpretation

There are two main limitations to the preceding analyses of the economic impact of antimicrobial growth promoter termination in Denmark.

The first is that the above estimates of the effect of antimicrobial growth promoter withdrawal on production costs may be subject to error. Although data records and information on pig and poultry production in Denmark are very good, estimates of the impact of individual changes in production systems, such as termination of antimicrobial growth promoters, are very difficult to make given the multitude of factors that may be changing over the same time period being considered. The effect of antimicrobial growth promoter termination on pig production costs is likely to have been variable and will have included some or all of the following: decreased feed efficiency, reduced growth rate and increased mortality in weaners, increased use of therapeutic antimicrobials and purchase of alternatives to antimicrobial growth promoters, and costs associated with modifications of the production systems to increase pig health. Some of these costs (e.g. increased therapeutic antimicrobials, reduced growth rate) have been measured and were not large, but others, especially some costs associated with modifications of the production systems, are difficult to measure and were not included in this report, although they may have been substantial for some producers. It is possible that some of these difficult to measure costs might be addressed in future studies designed and carried out to specifically and accurately measure these costs on representative farms. Representatives of the Danish Bacon and Meat Council (personal communication, 2003) believed that changes to pig production systems other than those accounted for in the economic analysis presented above were driven by other factors and were not the result of withdrawal of antimicrobial growth promoters.

Second, the above analyses do not take into account the possible positive impact that withdrawal of antimicrobial growth promoters might have had (or may have in the future) on consumer demand, both in the domestic market and exports (for both Danish pig and poultry products). Indeed, the macroeconomic model of Jacobsen and Jensen (2002) explicitly assumes that consumer perceptions of pig and poultry meat do not change as a result of antimicrobial growth promoter termination. In Denmark, the pork industry is very important, representing almost half of agricultural export and 6% of all exports. Denmark is the largest exporter of pork in the world, and approximately 85% of production is sold abroad. The most important export markets are Germany, UK and Japan. Price and quality are considered to be the most important factors for sales, followed by food safety considerations, including use of antimicrobial growth promoters. The Danish pig industry is therefore sensitive to possible consumer, food manufacturer or food retailer concerns, either now or in the future. It would be expected that termination of antimicrobial growth promoters would add to consumer confidence in Danish pig meat, give Danish producers some competitive advantage and help to increase or, at least, maintain consumer demand and retain access to some valuable markets or product segments (see Lauritsen, 2001). Evidence that this has happened is difficult to find due to the many factors influencing the demand for pig meat and pig meat prices. Thus, this likely benefit to the pig and poultry industries remains unaccounted for.

It is clear that the actual total production of pig meat and poultry meat have not been noticeably affected by antimicrobial growth promoter termination (Lauritsen 2001, Landbrug, 2001). Pig prices have increased by around 19% per annum from 1999 to 2001 and largely as a result gross margins (value of output less variable costs) in pig production have increased substantially (by 145% from 1999 to 2000 and by a further 39% from 2000 to 2001 for slaughter pigs, see Table 13). This is likely to have more to do with the price fluctuations of the pig cycle (i.e. the historically-observed cyclical fluctuation in pig prices over time) than due to antimicrobial growth promoter termination in 1998 or other adjustments to pig production systems. (Similarly, the price of meat for consumers has varied greatly between 1992 and 2001. The price for ham has changed from 45.0 DKK/kg to 65.7 DKK/kg with no obvious relationship to the termination of antimicrobial growth promoters.)

This relatively favourable economic climate for pig producers over the period following antimicrobial growth promoter withdrawal may have aided the Danish pig industry in adapting to the change without undue pressure on profitability in the short-run.

Conclusion

The net costs associated with productivity losses incurred by removing antimicrobial growth promoters from pig and poultry production were estimated at 7.75 DKK (1.04 €) per pig produced and no net cost for poultry. This translates into an increase in pig production costs of just over 1%. Some of these costs (e.g. increased therapeutic antimicrobials, reduced growth rate) have been measured and were not large, but others, especially some costs associated with modifications of the production systems, are difficult to measure and were not included in this report, although they may have been substantial for some producers. Results from using a general equilibrium model of the Danish economy suggest that, as a result of this change

Table 13. Average pig prices and gross margins for Danish pig producers 1992-2001.

	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001
Average Pig prices/kg (DKK)	12.40	9.69	10.15	10.39	11,37	11,68	8,24	7,92	9,46	11,26
Gross margin weaners (DKK)	210[a]	180[a]	141	183	220	230	109	103	195	250
Gross margin slaughter pigs (DKK)	135[a]	115[a]	76	107	135	138	51	51	125	164

Data source: DS statistics 1992-2001
a: Estimated figures

in costs, pig production would be around 1.4% per annum lower than might be expected and poultry production 0.4% per annum higher due to termination of antimicrobial growth promoters. The latter result is because poultry production is a competitor to pig production both for inputs and consumption and so indirectly benefits from lower pig production. The overall estimated impact for the Danish economy of antimicrobial growth promoter termination is a reduction of 0.03% (363 million DKK (48 million €) by 2010 at 1995 prices) in real Gross Domestic Product (GDP).

Any additional cost to production and the national economy may be, at least partially, offset by the benefits of increased consumer confidence in, and demand for, Danish pig and poultry meat produced without antimicrobial growth promoters. Also to be set against the cost are the likely human health benefits to society of antimicrobial growth promoter termination.

Attempts to manage effects of termination of antimicrobial growth promoters

Many of the direct attempts to manage possible animal health effects of antimicrobial growth promoter termination were discussed in preceding sections (e.g. antimicrobial therapy, financial compensation for necrotic enteritis losses in poultry). Some attempts were also made to mitigate expected losses in production efficiency. For example, poultry feed companies made various changes to feeds to optimise efficiency and whole wheat and feeding enzymes were extensively used in rations (Emborg *et al*., 2002b), however, we do not know if these practices were effective.

In anticipation of antimicrobial growth promoter termination, Denmark invested in considerable research towards efficient production of healthy pigs and broilers without antimicrobial growth promoters. Animal health research focused on the following strategies: to prevent introduction of infectious disease onto farms (e.g. enhanced biosecurity); to enhance natural disease resistance by selective breeding; to control spread and severity of disease within farms; to develop rations that protect against enteric infection; and to efficiently identify sick animals for treatment (Bækbo, 2002; Baadsgaard, 2002; Madsen and Pedersen, 2002; Henryon and Berg, 2002; Juul-Madsen *et al*., 2002). Among management methods that can be used for enhanced biosecurity, specific-pathogen-free (SPF), all-in-all-out (AIAO), and wean-to-finish housing have been explored. AIAO management in the post-weaning phase shows considerable potential for controlling enteric disease (e.g. *Lawsonia intracellularis*), especially with clean-up of facilities between batches (Baekbo, 2002). We do not know how extensively these technologies and management changes were adopted as a consequence of antimicrobial growth promoter termination, and acknowledge that they often require capital investments or other costs (Kjeldsen, 2002). National experts in industry explained to us that some changes (e.g. AIAO management) were adopted and for a number of reasons, not only termination of antimicrobial growth promoters, and that these changes had occurred over a number of years.

Vaccines are used in Danish swine production to prevent respiratory tract infections, systemic infections and neonatal diarrhoea, however, no vaccines are currently available for the prevention of enteric infections in weaned pigs. The *L. intracellularis* vaccine currently available in the U.S. has not been marketed in Europe, but a newly developed, live attenuated vaccine for this pathogen is under evaluation in Denmark. There is also ongoing Danish research on antigens of *L. intracellularis* in pigs and *E. coli* in pigs and poultry, but successful candidates for effective killed vaccines are not anticipated in the near future. While development of cost-effective vaccines to prevent post-weaning enteric diseases in pigs is a high research priority, these vaccines are viewed as long-term solutions.

Danish researchers have conducted many studies in search of feeding strategies that improve health status and at the same time improve growth performance, although we do not know the extent to which they have been adopted in the industry. In pigs, organic acids and fermented liquid feeds showed some promise, although results from studies of enzymes, probiotics, oligosaccharides and plant extracts were less encouraging (Canibe *et al*, 2002; Kjeldsen, 2002). Use of coarsely ground feed tended to reduce risk of infection with *Salmonella* and some *E coli*, however, growth performance appeared to suffer (Jensen *et al*., 2002). Somewhat similar results were obtained in broiler studies of various feed additives, with positive effects from organic acids, whole wheat and non-starch polysaccharide-degrading enzymes (e.g. xylanose) and little effect from probiotics and oligosaccharides (Engberg, 2002).

We conclude that Danish farmers, veterinarians, feed companies and researchers have been successful in managing many of the effects of antimicrobial growth promoter termination. More efforts are needed, however, to completely overcome problems with diarrhea in the post-weaning phase of weaner pig production. Furthermore, broiler and pig production would benefit from the further development of non-antimicrobial strategies, including addition of feed additives, that improve production efficiency without harm to animals, humans or the environment.

Conclusions and Recommendations

Internationally, there has been considerable speculation about the effects of antimicrobial growth promoter termination on efficiency of food animal production, animal health, food safety and consumer prices. These issues have been addressed in the 'Danish experiment', and there have been no serious negative effects. We conclude that under conditions similar to those found in Denmark, the use of antimicrobials for the sole purpose of growth promotion can be discontinued. Denmark's program to discontinue use of antimicrobial growth promoters has been very beneficial in reducing the total quantity of antimicrobials administered to food animals. This reduction corresponds to a substantial decrease in the overall proportion of individual animals given antimicrobials, and in the duration of exposure among animals given antimicrobials. This represents a general change in Denmark from continuous use of antimicrobials for growth promotion to exclusive use of targeted treatment of specific animals for therapy under veterinary prescription. The program has also been very beneficial in reducing antimicrobial resistance in important food animal reservoirs. This reduces the threat of resistance to public health. From a precautionary point of view, Denmark's program of antimicrobial growth promoter termination appears to have achieved its desired public health goal.

The phasing out of antimicrobial growth promoters was done without major consequences. Under Danish conditions, the negative impacts of antimicrobial growth promoter termination are largely attributable to their disease prophylaxis (i.e. disease prevention) properties, with no effect on growth in broilers and only a small effect on growth in pigs. In pigs, where most antimicrobials were used in Denmark, antimicrobial growth promoter termination was associated with a reduction in growth rate and an increase in mortality and diarrhoea in weaners, but these changes were not detectable in finishers. Many of these effects were probably due to termination of olaquindox and carbadox. Even if the pig industry had not decided to voluntarily cease antimicrobial growth promoter use in 1998/99, olaquindox and carbadox would still have been withdrawn in 1999 by EU regulation over concerns about potential toxicity to humans from occupational exposure. The other antimicrobial growth promoters have little or no activity against the Gram-negative bacterial infections believed to be most important in post-weaning diarrhea of pigs (tylosin may have activity against *Lawsonia*, but it was banned as an antimicrobial growth promoter by the EU in 1999). Therefore, even if there had been no voluntary discontinuation of antimicrobial growth promoter use, other solutions to the problem of increased post-weaning diarrhea would have been needed. In finisher pigs, antimicrobials did not appear to have these disease prophylaxis benefits and discontinued antimicrobial growth promoter use was not associated with a sustained increase in morbidity or mortality. In broilers, antimicrobial growth promoter termination was not associated with increases in morbidity and mortality, however, ionophores (a drug class not used in humans) were used routinely in feed to prevent the parasitic disease coccidiosis, and this probably also provided some protection against the bacterial disease necrotic enteritis. Savings in antimicrobial growth promoter costs largely offset losses in feed efficiency in broilers.

Therefore, when terminating antimicrobial growth promoters, advance planning should be conducted and steps should be taken to minimize disease in vulnerable classes of animals, especially weaner pigs. In addition to antimicrobial treatment of diseased animals, this may include the use of in-feed antimicrobial agents for the purpose of prophylaxis for defined periods in selected herds found to be at risk. However, antimicrobials that are used for therapy in either humans or animals or select for resistance to these drugs should be avoided.

Overall, the likely impact of withdrawal of antimicrobial growth promoters on pig and broiler production, and for the Danish economy, is a relatively small but negative effect. Some of these costs (e.g. increased therapeutic antimicrobials, reduced growth rate) have been measured and were not large, but others, especially some costs associated with modifications of the production systems, are difficult to measure and were not included in this report, although they may have been substantial for some producers. The small negative effect may be, at least partially, offset by the benefits of increased consumer confidence in, and demand for, Danish pig and poultry meat produced without antimicrobial growth promoters. Any net cost needs to be set against the likely human health benefits to society following antimicrobial growth promoter termination, as it would be expected in some circumstances to result in the lowering of the antimicrobial resistance rate in bacteria that are ingested by people via the food chain.

Applicability to WHO Global Principles

We believe that Denmark's program for termination of antimicrobial growth promoters in pigs and broilers is consistent with the WHO Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food (WHO, 2000). These principles are reflected in Danish national policies and regulations, industry initiatives, national surveillance programs, and research initiatives. WHO Global Principles call on governments to adopt a proactive approach to reduce the need for antimicrobials in animals and ensure their prudent use. The Danish government and food animal industries were proactive in withdrawing antimicrobial growth promoters, both as a public health preventive measure (i.e. banning of avoparcin and virginiamycin), and to ensure consumer confidence (i.e. animal industry's voluntary termination of remaining antimicrobial growth promoters). Extensive surveillance of antimicrobial resistance and antimicrobial use were undertaken, focusing on classes of drugs important in human medicine. The methods and data are publicly available. Epidemiological studies were conducted to identify risk factors for resistance increases above levels of concern. Therapeutic antimicrobials are available by prescription only. Guidelines on prudent use of antimicrobials are available and readily accessible. These actions are all consistent with the Global Principles.

The review shows that the benefits of antimicrobial growth promoters were largely confined to weaner pigs and were largely attributable to disease prophylaxis. This underscores the importance of the Global Principles concerning prophylactic use of antimicrobials (WHO):

- Use of antimicrobials for prevention of disease can only be justified where it can be shown that a particular disease is present on the premises or is likely to occur. The routine prophylactic use of antimicrobials should never be a substitute for good animal health management;

- Prophylactic use of antimicrobials in control programmes should be regularly assessed for effectiveness and whether use can be reduced or stopped. Efforts to prevent disease should continuously be in place aimed at reducing the need for the prophylactic use of antimicrobials.

Applicability to other countries

Denmark's experience with antimicrobial growth promoter termination was very similar to Sweden's experiences after termination of growth promoter use in 1986 (Wierup, 2002). This strengthens our belief that Danish experiences may be generally applicable to other countries with similar animal production conditions. Many of the observations and lessons learned should also be applicable to other countries, however there are some qualifications. Danish pork and broiler industries are intensive, with closed housing, good biosecurity and relatively high health status compared to many other countries. The consequences of an antimicrobial growth promoter ban in countries with lower health status in pigs and broilers might be different and this should be taken into account. It is also important to consider diet, climate and availability of veterinary services. In addition, the effects of termination on disease and productivity may vary depending on the type of antimicrobials (e.g. pharmacological properties, spectrum of activity against bacteria) that are currently used in a country. The economic effects will depend upon several factors including the effects on performance levels, the cost of any technologies adopted to compensate for the termination of antimicrobial growth promoters, and these costs may be offset by the benefits of increased consumer confidence and public health.

Furthermore, Denmark enjoys a high level of infrastructure that does not exist in all countries, especially developing countries, and each country will need to adapt plans to their own circumstances. For example, Denmark's capability to monitor antimicrobial use, antimicrobial resistance and animal production is quite advanced. The pig industry is organized into a governing cooperative and farmers are co-owners of slaughterhouses. For this and perhaps other reasons, Denmark may be one of the few countries whose agricultural industry could implement a nation-wide voluntary action on antimicrobial growth promoters of this magnitude. Other countries may need a longer period for full implementation perhaps supported by regulatory action in order to implement a similar program.

The antimicrobial growth promoters that were used in Denmark were active against both Gram-positive and Gram-negative bacteria. Those used against Gram negative bacteria (olaquindox, carbadox and salinomycin) are not used in human antimicrobial therapy. In some other countries, however, a variety of broad-spectrum antimicrobial growth promoters are used, including drugs used in human therapy, such as tetracyclines and sulfonamides. It is likely that these broad-spectrum antimicrobial growth promoters would exert antimicrobial resistance selection pressure on Gram-negative bacteria, including important foodborne pathogens, such as *Salmonella*.

Other countries should re-examine their policies concerning antimicrobial use for disease prophylaxis in light of Denmark's experience. In Europe, use of antimicrobial growth promoters for disease prophylaxis or therapy is not legally permitted. The experience in Denmark shows that biology is not always changed by a legal definition, i.e., a law stating that they should not be used for prophylaxis does not stop the drugs from actually performing that function when they are used legally for another indication. Clearly, in some instances, antimicrobial growth promoters used in Denmark had disease prophylactic effects, especially for weaner diarrhea. Ionophores used as coccidiostats in broilers were also believed to be beneficial in preventing necrotic enteritis.

It should be noted that termination of antimicrobial growth promoters in other countries with different industry structures, perhaps different production systems and economic conditions than those existing in Denmark at the time of antimicrobial growth promoter withdrawal, may experience different effects on production costs and different macroeconomic impacts.

In view of the limited effects of antimicrobial growth promoter termination on efficiency of food animal production, it is unlikely that similar action in developing countries would decrease the total meat production in these countries.

Recommendations to Denmark

Denmark is a world leader in monitoring of antimicrobial use, resistance, zoonotic disease, and food animal production. Nevertheless, this review shows that some improvements to an already impressive program should be considered. Acquisition of substantially more antimicrobial susceptibility data on bacteria from the food chain (e.g. meat) and healthy humans (including fecal carriage), either through monitoring or targeted population-based studies, is recommended. The problem of post-weaning diarrhea of pigs is critically important and more efforts are needed to identify its cause(s) and methods of safe, effective and efficient control. More emphasis and research should be placed on non-antimicrobial disease control methods (improved management systems, vaccines, organic acids, etc.). It is important to maintain the excellent quality of on-farm research and to expand experimental research on methods for efficient non-antimicrobial production.

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Glossary

All-in-all-out management
Management practice in which all livestock in a room or barn, that are usually of uniform age, are handled in batches. They are introduced, raised and then removed together, allowing the facility to be emptied, cleaned, and prepared for the next group of animals. It is used to reduce transmission of infection between groups of animals.

Antimicrobial Growth Promoter
In Denmark (and rest of the EU) an antimicrobial authorized as a feed additive to be used in food animals to improve rate of gain or feed efficiency.

Antimicrobial Residues (in food)
Antimicrobials or their metabolites remaining in edible tissues from animals at harvest or slaughter following treatment. Withdrawal periods after use normally ensure their absence in food at unsafe levels.

Broad-spectrum antimicrobial
An antimicrobial effective against both gram-positive and negative bacteria.

Broilers
Broiler chickens that are typically slaughtered at approximately 5-6 weeks of age (2 kg)

Farrow-to-finish
Pig farms that have sows and raise pigs from birth to slaughter.

Finishers
Pigs from the end of the weaner phase at 10-12 weeks of age (approximately 30kg) to slaughter at 5-6 months of age (approximately 100kg). In this report we use the term 'finishers' to refer to both the grower and finisher phase. For the purposes of terminating antimicrobial growth promoters, the Danish pig industry used 35kg as the approximate beginning of the finisher phase.

Gross margin
Value of output less variable costs

Narrow-spectrum antimicrobial
An antimicrobial effective against a limited number of bacteria; often applied to an antimicrobial active against either gram-positive or negative bacteria.

Pathogenic bacteria (pathogens)
Bacteria that cause infections. These can either be primary (causing disease alone) or opportunistic (only causing disease following damage).

Pig cycle
The process by which pig farmers increase production until prices fall and production consequently decreases, following which prices rise and the cycle is repeated.

Poultry
Chickens or turkeys. Sometimes refers to meat from these birds.

Prophylaxis
The use of an antimicrobial to prevent infection (or clinical expression of disease) that is anticipated to challenge the host during the treatment period.

Surveillance
In this document, it comprises continuous, intensive, targeted or non-random collection of data on the incidence, prevalence and spread of bacteria.

Therapeutic use
The use of an antimicrobial for the purpose of inhibiting a pathogen that already infects the host (i.e. treating a disease condition).

Weaners
Pigs in the period from removal from the sow at 3-4 weeks of age (approximately 7kg) to entering the finisher period at 10-12 weeks of age (approximately 30kg). For the purposes of terminating antimicrobial growth promoters, the Danish pig industry used 35kg as the approximate end of the weaner phase.

Zoonotic bacteria
Bacteria that are pathogenic to humans and are transferred to humans by contact with animals, animal excreta, or animal products (including food).

Annex 1. Symposium Programme

Wednesday 6 November 2002

Opening ceremony

09:00 *Chairmens adress*

09:05 *Welcoming address* **-** *Danish strategies to contain antimicrobial resistance in agriculture*

Mariann Fischer-Boel - *Minister of Food Agriculture and Fisheries*

09:15 *WHO welcome and introduction to WHO global strategy for the containment of resistance*

Peter Braam - *WHO-HQ, CDS/CSR/EPH*

09:30 *EU strategies on antimicrobial resistance*

Representative of the EU Commission

09:45 *Danish Institute of Agricultural Sciences' welcome*

Arne Jensen - *Director of the Danish Institute of Agricultural Sciences*

09:50 *Danish Veterinary Institute's welcome*

Knud Børge Pedersen - *Director of the Danish Veterinary Institute*

Effects of the termination of AGP use on bacterial resistance to antimicrobials

10:00 *Effects of the termination of AGP use on antimicrobial resistance in food animals*

Frank M. Aarestrup - *Danish Veterinary Institute*

10:20 *Effects of the termination of AGP use on antimicrobial resistance in bacteria from foods*

Jeppe Boel - *Danish Veterinary and Food Administration*

10:40 *Effects of the termination of AGP use on antimicrobial resistance in humans*

Niels Frimodt Møller - *Statens Serum Institut*

11:00-11:20 Coffee break

11:20 *Effects of the termination of AGP use on antimicrobial resistance in pig farms*

Håkan Vigre - *Danish Veterinary Institute*

11:40 *Occurrence and persistence of vancomycin resistant enterococci (VRE) in Danish broiler production after the avoparcin ban*

Ole Eske Heuer - *Danish Veterinary Institute*

12:00 *Effects of the termination of AGP use on presence of resistance genes in bacterial isolates from production animals*

Lars Bogø Jensen - *Danish Veterinary Institute*

Effects of the termination of AGP use on animal welfare and productivity

12:20 *Effects of termination of AGP use on broiler health and productivity*

Hanne-Dorthe Emborg - *Danish Veterinary Institute*

12:40 *Effects of termination of AGP use on pig welfare and productivity*

Jes Callesen - *Danish Bacon and Meat Council*

13:00-14:00 Lunch

Consequences of termination of AGP use for animal health and the use of antimicrobials in food animals for therapy and prophylaxis

14:00 *Surveillance experiences from DANMAP and VETSTAT*

Flemming Bager - *Danish Veterinary Institute*

14:20 *Consequences of termination of AGP use for pig health and usage of antimicrobials for therapy and prophylaxis*

Per Bundgaard Larsen - *Danish Veterinary Institute*

14:40 *Consequences of termination of AGP use for broiler health and usage of antimicrobials for therapy and prophylaxis*

Niels Tornøe - *Danpo A/S*

Effect of the termination of AGP use on foodprices and the competitiveness of agricultural industries

15:00 *Sector and Economy wide effects of terminating the use of AGP in Denmark*

Søren E. Frandsen - *Danish Research Institute of Food Economics*

15:20 *Consequences of terminating the use of AGPs for competitiveness in the international market place*

Henrik B. Lauritsen - *Danish Bacon and Meat Council*

15:40-16:10 Coffee break

Consequences of termination of AGP use for the environment

16:10 *Environmental effects of the termination of AGP use in Denmark*

Hanne Damgaard Poulsen - *Danish Institute of Agricultural Sciences*

International speakers

16:30 *Antimicrobial use in food-producing animals in the United Kingdom*

David Taylor - *Glasgow University Veterinary School*

16:50 *Use of AGPs in the USA – patterns of use and public health concerns*

Fred Angulo - *Centers for Disease Control and Prevention*

17:20 *Use of AGPs – does it play a role in combating malnutrition in the developing world?*

Peter Collignon - *The Canberra Hospital*

17:40 *Discontinuing the use of AGPs – the Swedish experience*

Martin Wierup - *Swedish Animal Health Service*

18:00 Dinner at the Danish Institute of Agricultural Sciences

Thursday 7 November 2002

Alternatives to the use of antimicrobial growth promoters

Management and hygiene

09:00 *Animal health as affected by management procedures in commercial pig production*

Poul Bækbo - *Danish Bacon and Meat Council*

09:20 *Animal welfare and health as affected by management procedures in commercial broiler flocks*

Jette Søholm Pedersen - *Danish Agricultural Advisory Centre*

Feed and feed additives

09:40 *Organic acids and fermented liquid feed as alternatives to AGPs in pig production*

Nuria Canibe - *Danish Institute of Agricultural Sciences*

10:00 *Improved feed composition and feed processing as alternatives to AGPs in pig production*

Bent Borg Jensen - *Danish Institute of Agricultural Sciences*

10:20-10:40 Coffee break

10:40 *Effects of the termination of AGP use on outbreaks of Lawsonia intracellularis in pigs*

Tim K. Jensen - *Danish Veterinary Institute*

11:00 *Alternatives to AGPs in broiler production*

Ricarda G. Engberg - Danish Institute of Agricultural Sciences

11:20 *Alternatives to AGPs in pig production – practical experience*

Niels Jørgen Kjeldsen - *National Committee for Pig Production*

Disease management

11:40 *Reducing the use of antimicrobials in pig herds by improving data on disease treatment and disease*

Niels Peter Baadsgaard - *Danish Institute of Agricultural Sciences*

12:00 *Automatic data as early disease indicators in pig production*

Thomas Nejsum Madsen - *National Committee for Pig Production*

12:20 *Breeding pigs for resistance to clinical and sub-clinical diseases*

Mark Henryon - *Danish Institute of Agricultural Sciences*

12:40 *Natural resistance as an alternative to AGP in poultry*

Helle Juhl Madsen - *Danish Institute of Agricultural Sciences*

13:00-14:00 Lunch

International speakers

14:00 *Use of alternatives to AGPs in animal food production in China*

Defa Li - *China Agricultural University*

14:20 *Use of alternatives to AGPs in animal food production in the USA*

James E. Pettigrew - *University of Illinois*

14:40 *The EU Commission's research strategy and plans for antimicrobial resistance research in the Sixth Framework Programme*

Anna Lönnroth – *European Commission*

General discussion and closing of symposium

Annex 2. List of Participants in WHO Expert Review

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