Combating the risk of antimicrobial resistance in animals for the benefit of human health in Denmark

A case study of emerging risks related to AMR for the
International Risk Governance Council (IRGC)

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Contents

Abbreviations

AGP	Antimicrobial growth promoter
AM	Antimicrobial
AMR	Antimicrobial resistant/resistance
CF	Contributing factor from the IRGC
CIA	Critically Important Antimicrobial
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Program
DK	Denmark
DKK	Danish kroner
ECDC	European Centre for Disease Prevention and Control
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
IRGC	International Risk Governance Council
OIE	World Organisation for Animal Health
UK	United Kingdom
US	United states of America
VRE	Vancomycin-resistant *Enterococcus* bacteria
WHO	World Health Organization

Part1: The risk of animal antimicrobial use for human medicine

This paper articulates the foodborne AMR risk and through a case study, highlights effective risk management options for consideration in other countries or for other novel AMR risks[1,2]. The case study focuses on the experience in Denmark, and from there sparsely attempts to make statements on international level.

All use of antimicrobials, in humans, animals (incl. fish) and the environment may result in the generation of bacterial strains that are resistant to antimicrobials. Therefore, also any use of antimicrobials in animal production may lead to accumulation AMR bacteria which can cause untreatable infections in humans. There is a global trend showing antibiotic resistance (AMR) is on the rise (Danmap, 2010; ECDC, 2010; ECDC, 2009; UN 2005; UN, 2001). Especially dangerous in this context are the findings of more multidrug resistant (MDR) infections which are almost untreatable and increases in resistance to antimicrobials considered critically important in human medicine. Given the large number of animals produced for food production and the large amount of antibiotics used in this industry, many in the same classes as for use in people, this is also the largest reservoir for generating AMR bacteria. For instance in Denmark, with a population of about 6 million people, the antibiotic consumption by humans is 50.7 tonnes compared with 126.9 tonnes in food-animals which mainly includes about 117.6 million broiler chickens and 28.5 million pigs (DANMAP, 2010).

Antibiotics and the two sides of the coin

In the process of raising animals to produce food or using other animal-derived products, such as milk or eggs, a small fraction of the animal's bacteria is present on the end product. Through eating improperly prepared or stored animal products contaminated with bacteria, many people get infected each year, which most of the time results in diarrhoea or sometimes in more severe disease. Though the level of contamination is usually close to zero, because of the high frequency of meat consumption and accidental high levels of contamination, the total number of cases in a population may become substantial and therefore food safety and working towards low or non-contaminated food is important.

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[1] In this case study we will use both the words antimicrobials and antibiotics interchangeably, although these words are not technically fully. An antimicrobial is a substance that kills or inhibits the growth of microorganisms such as bacteria, fungi, or protozoans. Antimicrobial drugs either kill microbes or prevent the growth of microbes. It includes disinfectants, which are substances used on non-living objects or outside the body. An antibacterial is a compound or substance that kills or slows down the growth of bacteria. The term is often used synonymously with the term antibiotic; today, however, with increased knowledge of the causative agents of various infectious diseases, antibiotics has come to denote a broader range of antimicrobial compounds, including antifungal and other compounds.

[2] It does not concern the effect of residues of antimicrobial use, which were bellow or near the physical limit of detection as tested in pig and chicken samples (see UN, 2003).

Using good food manufacturing procedures, pasteurization and other methods, producers and the food industry try to keep the fraction of bacteria in food for sale as low as possible. Antibiotics in animal production have been used to both increase animal health and thus decrease the risk of producing food contaminated with bacteria. In the short term, this approach worked for many years, and it still does. In the long term, however, it has been found that there is a flip side to the antimicrobial coin, as prolonged use of antibiotics leads to the appearance of AMR bacteria. Now resistant, these bacteria cause an even greater risk for food safety and animal health. On the short and long term, the use of antibiotics may thus have both beneficial as well as harmful effects on food safety. To bring the short and long term goals in line with each other, one has to balance the benefits and risks of using antibiotics in food-animal production.

Resistance

AMR is not new and the prolonged use of antibiotics in general will lead to the occurrence of resistant bacteria, simply through survival of the fittest. Given the many trillions of bacteria in the animal- and human flora, the use of antimicrobials will almost always lead to the occurrence of AMR bacteria.

There are many classes of antibiotics, each with a different mode of action and to some degree different target organism. Some antibiotics interfere with the bacterial protein production, *e.g.* glycopeptides, and others interfere with the bacterial cell wall *e.g.* penicillin. A fast escape route to treat an antibiotic- resistant bacterial infection is to use a different class of antibiotics than the one to which resistance was expressed to. For instance, it is possible to use an antibiotic which targets bacterial glycopeptides glycopeptide when bacteria are penicillin resistant. This works, however, only for some time since resistance may develop to the second drug, resulting which may in turn result in multi-resistant bacteria (= bacteria resistant to three or more antimicrobials).

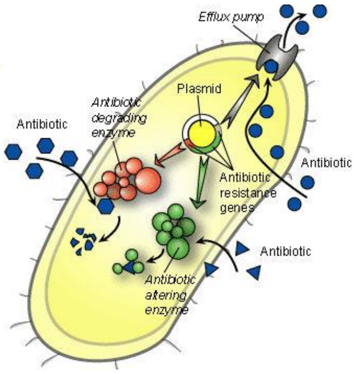

*Figure1***.** Schematic representation of a bacterial cell showing several AMR mechanisms (UN, 2005).

Resistance can be acquired by different genetic events such as i) mutations in the chromosomal or other genetic elements, altering the antibiotic target or amplifying rescuing mechanisms and ii) by genetic (*e.g.* DNA) transfer of resistance genes between bacteria. In the latter case, the transferred genetic elements (*e.g.* plasmids) may hold an array of different resistance genes making bacteria multiresistant in one go. There are four principal mechanisms of resistance known which are depicted in figure 1, being: 1) the antibiotic target is structurally altered, 2) the antibiotic is inactivated, 3) entry cell entry is blocked or 4) the antibiotic is pumped out of the cell.

Transmission routes

Through food, direct contact, and via the environment the human and the animal bacterial flora interact and bacteria from animals end up in people and vice-versa. Figure 2 sketches some of the transmission routes of bacteria. Via these routes bacteria from food- animals may enter the human reservoir and *vice versa*.

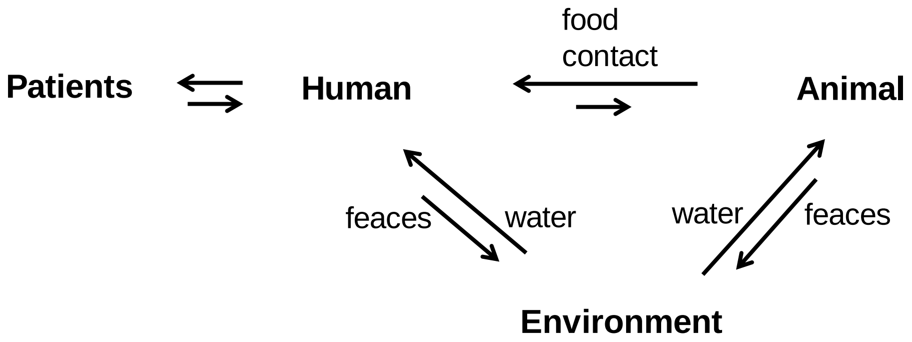

Figure 2. *Several important transmission routes via which the human- and animal flora are in contact with each other.*

Because most bacteria are non-pathogenic commensals (part of the natural flora) and also because many bacteria are host specific and do not survive in different hosts, much of this exchange goes un-noticed. However, in particular, the exchange of zoonotic[3] micro-organisms capable of living in both humans and animals, and AMR micro-organisms may cause problems. Either directly because of their pathogenic nature, or they may develop into opportunistic harmful infections during human antibiotic treatments, and will cause threats to the most vulnerable segment of societies *i.e.* the young, the elderly, the immune-compromised and recovering patients .

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[3] Zoonotic bacteria are pathogenic bacteria (in one or more species) that are naturally transmissible from vertebrate animals to humans and vice-versa.

How did the emerging risk of AMR from the animal reservoir develop?

In the early 1940s antibiotics were first introduced to control bacterial infections in humans. The success in humans led to their introduction in veterinary medicine in the 1950s, where they were used in food- and companion-animals. Antibiotics, nowadays, have also found their way into intensive fish farming and some are used to control diseases in plants. Their use is thus wide-spread.

Antibiotics in animals are used essentially in three different ways, for therapy of individual cases, for disease prevention (prophylaxis) treating groups of animals and as antibiotic growth promoters (AGP). Since the 1950s, AGP has been intensively applied to food-animals, regardless of the animals' health status or the risk of bacterial infection. For AGP use, antibiotics are added to animal feed at sub-therapeutic concentrations to improve growth. The mechanism by which this works was (and still is) unclear, nevertheless, this use of antibiotics led to a steep increase in antibiotics use in animals. Between 1951 – 1978 the use in the United States alone went from 110 to 5580 tons (UN, 2011). During the same period many bacterial strains that were previously susceptible to antibiotics became resistant. For example, in England the prevalence of tetracycline-resistant *Escherichia coli* in poultry increased from about 4% to about 65% after four years (1957–1960) of antibiotic's use in poultry (Sojka,1961).

Though there was not much solid evidence in the early seventies, concern about AGP use causing AMR and the possible adverse effects on human health started to build. The main reasons for concern were 1) that the same classes of antibiotics were used in humans and animals, 2) there was a steep increase in the animal antibiotic use which in animal producing countries exceeded the human consumption and 3) because many different types of antibiotic were used as an AGP. In Great Britain this led to the appointment of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine, chaired by M.M. Swann (Swann, 1969). In 1969 they recommended that antibiotics should not be used as AGPs if they were used as therapeutic agents in human or animal medicine, or when they were associated with the development of cross-resistance to antibiotics used in people. This led to a ban of all use of AGP in food-animals if these antimicrobials were also important for therapeutic use in humans in the UK and subsequently in the EU. The action was enforced on individual antimicrobials and did not consider analogues of these drugs. Therefore the use of AGP in effect continued for most types of antibiotics with these analogues and this allowed for the selection of cross-resistance to human therapeutic drugs. In addition, the rest of the world did not follow the European path.

As a preventive measure, Sweden banned all use of antibiotics for AGP in 1986. In other countries the use of AGP went on although concerns grew bigger as researchers started finding evidence showing that the overuse of chemical analogues of human therapeutic antibiotics in food-animals led to increased levels of AMR bacteria that are considered a risk for human health (AMR zoonotic bacteria). Next to Sweden, in particular Denmark, being a large pig- and chicken-producer, was concerned and as a result Denmark started investigating the relation between AGP and the occurrence of AMR bacteria in animals, and whether this could result in increased risk for human health. The Danish concern over the continued use of antibiotics in animals and the risk for human health can be best illustrated with the avoparcin case.

The Danish avoparcin case

The avoparcin case started in the '90 as a build-up of knowledge coming from different independent studies on the presence of AMR bacteria in (food-) animals that received avoparcin as AGP (Hammerun 2007; Aarestrup, 2010; Danmap, 1996). Avoparcin is a so-called glycopeptide and chemical analogue of vancomycin, which is a last resort drug for human use.

Avoparcin was first introduced in 1988 for use in animals. In Denmark avoparcin was broadly used as AGP both in pigs and chickens. The first evidence, that showed that this use of avoparcin led to AMR, was a survey in 1995, in which researchers found vancomycin-resistant *Enterococcus* bacteria (VRE) in 80% of the chickens from conventional producing (avoparcin using) farms whereas none were found in chickens from organic farms. This indicated that the use of avoparcin as AGP caused the high VRE occurrence in chickens and might be causing VRE problems seen in humans. In humans a similar increase in VRE bacteria was seen, which could either be due to vancomycin use in humans, or might be caused by human consumption of contaminated meat (Aarestrup, 1995; Aarestrup, 1996; Wegener, 1997).

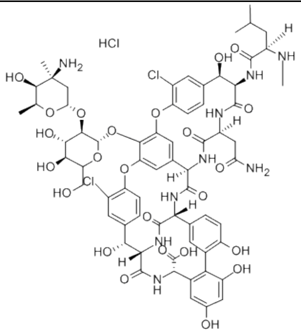	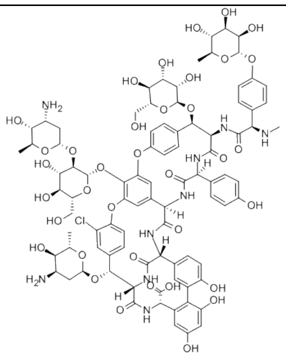
Human last resort drug vancomycin.	Veterinarian analogue: avoparcin

Figure 3. *The use of human analogues antibiotics in animals may select for AMR bacteria that are untreatable in people with human antibiotics. The example above shows the high similarity between the chemical structures of vancomycin and avoparcin, a human and veterinarian glycopeptide, respectively*

This situation of rising numbers of VRE bacteria was not only seen in Denmark, it was a general problem in all countries using avoparcin as AGP (Woodford, 1998). These early findings were picked up in different studies of which some were published. However, due to the complexity of the transmission routes underlying the transmission of bacteria between species (animal to human) and within species (human to human; see figure 2), it was hard to say how serious the risk of zoonotic, animal to human, transmission of AMR bacteria was.

In Denmark both the authorities and the farmers recognized this lack of knowledge about the transmission to humans, but they were also shocked by the steep increase in AMR caused by the use of AGPs in food food-animals. Therefore, the Danish farmer organizations agreed to voluntary withdrawal of the use of avoparcin in chickens. In addition, the Minister of Food and Agriculture and Ministry of Health initiated an integrated surveillance approach, called DANMAP [4] (explained further on) to fill knowledge gaps. This approach helped to answer important questions about the rise of AMR bacteria and the risk for human health and cleared the way for evidence-based and broadly supported legislation. One of the first acts of the government was new legislation saying veterinarians were no longer allowed to make a profit from selling– prescription antibiotics, and– a ban on all avoparcin use as an AGP. This led to a strong reduction of glycopeptide resistance in bacteria from animals as shown in Figure 4.

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[4] DANMAP is the acronym of Danish Integrated Antimicrobial Resistance Monitoring and Research Program.

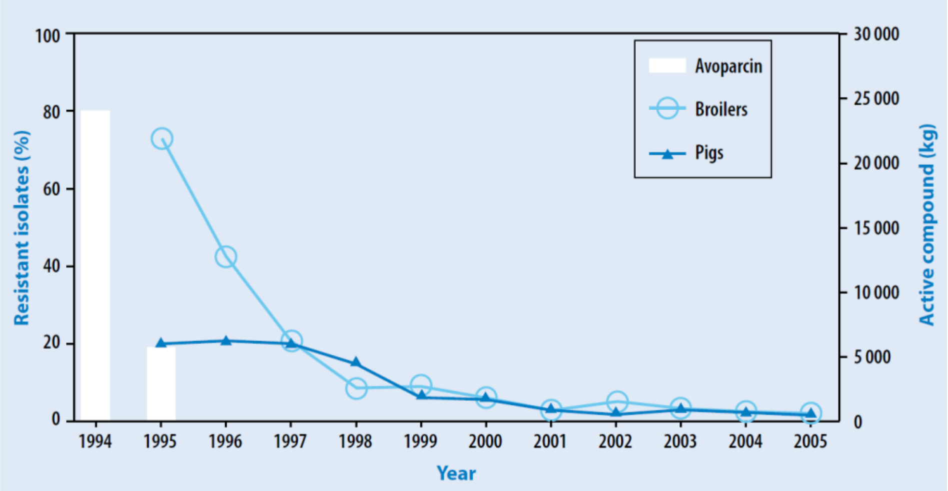

Figure 4. The effect of the stop of avoparcin use as AGP. The occurrence of VRE isolates in faecal samples from pigs and broiler chickens is shown on the left-hand axis. The yearly consumption of avoparcin in chickens and pigs is in Denmark is shown on the right-hand axis (UN, 2011).

Who was affected by the emerging risk of AMR in Denmark

One may distinguish stakeholders in the AMR debate , those at (high) human health risk (consumers), the farmers, 'the producers' of the AMR bacteria, groups that had a profit from the situation (industry, veterinarians and potentially the farmers), the group documenting and monitoring the risk (scientists) and the group deciding on action (the government).

Through eating food contaminated with AMR bacteria (meat, milk, eggs etc.), the occurrence of AMR in animals affected the whole population. However, those that would be most harmed by AMR infections are the most vulnerable section in society: the young children, the elderly, the immuno-compromised people, the chronically diseased people and recovering patients. For these groups failure of antibiotic therapy would be most dramatic because of their inferior health condition or young and/or inefficient immune system.

The centre of debate quickly focused on the farmers, they stood both as the source of the AMR risk and as the most important actor considered part of the solution that could reduce this risk. The overuse of antibiotics by the farmers was the immediate cause of the emergence of some of the AMR risk coming from animal use. At this level veterinarians were also involved, by their prescription of and advice on the use of antibiotics for AGP and animal therapy. Later, with the ban on AGPs the farmers (now informed on the risk) again took a central role and directly cooperated in cutting back the use of antibiotics for AGP. Farmers literally paid the price of antibiotic use and the change in antibiotic use in animals were seen to (through their union) react immediately on the evidence showing use of antibiotics leading to increased risk for human health.

The pharmaceutical industry (incl. the AGP feed preparing industry), through their campaigns promoted the inappropriate and (over-)use of antibiotics in animals. The situation concerning the veterinarians warrant further explanation. Before 1995 practicing veterinarians were playing a dual role, on the one hand guarding prudent antibiotic use in animals, but on the other hand it was also in their interest to use as much antibiotics as possible, because they made a very significant part of their profit (for many around 1/3) on their own prescribed antibiotics. In retrospect it may be said that this situation was not providing the right incentives for the prudent use of antibiotics in animals.

Food-, veterinarian- and human health experts from universities and public health institutes, aided by hospitals and food inspection labs, were part of the group that identified the risk and communicated this to society in general and especially to the farmers organizations and the government. In fact significant parts of the unique surveillance effort on antimicrobial (AM) use and the occurrence of AMR across both animal and human use was devised in collaboration between scientists, government and agricultural organizations. Importantly, through the subsequent research and monitoring work, effects of control measures could also be evaluated and emerging AMR risks identified, as the basis for continued prudent action.

At the government level the Ministry of Health and the Ministry of Food, Agriculture and Fishery have been collaborating and have been responsible for implementing control measures. These Ministries together with the Ministry of Science, Technology and Innovation continue financially supporting the required surveillance and research activities related to antimicrobial use and the occurrence AMR in Denmark.

Factors that contributed to the occurrence of AMR in animals in Denmark

Several other factors may have contributed to the situation where AMR in animals rose to extremely high levels and caused a risks to human health. In this section, we would like to name some of the factors and relate them to 12 generic contributing factors (CF) which the International Risk Governance Group (IRGC) has identified: 1) scientific unknowns, 2) loss of safety margins, 3) positive feedback, 4) varying susceptibility to risk, 5) conflicts about interests, values and science, 6) social dynamics, 7) technological advances, 8) temporal complications, 9) communication, 10) information asymmetries, 11) perverse incentives, 12) malicious motives and acts (IRGC, 2010).

Complexity of the problem

Scientific unknowns (CF1), varying susceptibility to risk (CF4) and conflicts about interests, values and science (CF5) played part in the emergence of AMR. Technological advances (CF7) and temporal complications such as the complexity of the source of the problem (see figure 2) (CF8), contribute to the identification of the AMR risk. In retrospect, it may be concluded that much of the risks developed during the period of uncontrolled antibiotic use, was the result of several unclear situations (CF1/5). The lack of evidence on transmission routes, the different stakeholders and the economic incentives involved, and the debate about the mechanisms by AGPs might or might not work, led to the increased and uncontrolled use of antibiotics and also resulted in a situation where governments did not know how best to act, or indeed whether to act at all.

The answer to the question if antibiotic use in food-animals led to increased risks of AMR for humans, is difficult because of the complexity of the transmission routes between species (human-human), intra-species (human-animal) and crossing regional borders (CF1). This complexity is part of, but certainly not the full reason for, why it has taken almost 30 years (from about 1969 to 1995) to establishing the risk in some scientifically valid way. Scientific and technological advances (CF7) in microbiology (such as more harmonized ways to determine AMR and the advances made in bacterial genotyping) and also the first steps towards cross-sectoral work were also needed to establish the risk. In fact, DANMAP provides the earliest truly cross-sectoral, science-based management systems in Denmark, and maybe in the world.

- Despite accumulating evidence showing that part of the AMR bacteria from farms are linked to resistance bacteria in humans, the impact of agricultural antibiotic use was, and still is under debate (Wegener, 1999; Bronten, 2001; Phillips, 2003; Jensen 2004; Hammerum, 2010). In retrospect, however, the difference in use of glycopeptides between Europe and the US shed some light (Bronten, 2001, Smith 2005). In the 70's the US and several European countries adopted different policies on avoparcin use in animals and vancomycin in humans. In Europe avoparcin was approved for AGP and in the US it was not. In addition, in Europe the use of vancomycin in hospitals was low compared to the heavy use in American hospitals. Surveillance in the 90's showed a high level of VRE bacteria both in US and European hospitals, however, in the general population the VRE prevalence in the US was much lower than that in Europe. Suggesting that the VRE strains did not leave the hospitals, while in Europe VRE strains from the animal reservoir entered the human community and hospitals. Also in retrospect, Wegener et al. (1999)

found that almost 20% of the normal *Enterococcus* flora in non-vegetarians were of the VRE-type, while VREs were not detected in vegetarians.

The mechanism by which AGP should work was not clear and this use of antibiotics was (and still is) therefore under debate (CF1 and CF4). This unclear situation and the distracting discussions may have been a contributing factor to a situation where the problem was recognized relatively late, only after 80% the chickens were found VRE positive.

- The use of AGP was promoted by different stakeholders as it was said to stimulate animal growth and it could prevent some of the mild infections mainly in young animals that led to mainly diarrhoea. As the number of animals on a farm is substantial, such mild problems formed a difficult problem that could potentially be solved by use of an AGP, by simply mixing antibiotics into the food to passively medicate all animals. The assumption that AGP lead to a real growth promotion is, nowadays, still under debate and there are studies showing some slight increases in growth rate but also studies finding no clear beneficial effect of AGP on growth rate (Aarestrup, 2010; Lee, 2012; UN, 2003).

The complexity of the problem and the conflicts about interests, values and science (CF5), with different ministries (health and agriculture) and stakeholders (human and veterinary doctors, pharmaceutical- industry and traders, farmers, food-safety- industry and experts) involved made this a complex problem to elucidate through an agreed objective framework, even to the point where establishing the risk was contentious, not to mention reaching agreement on specific solutions for the problem.

Economic incentives

One of the so-called perverse incentives (CF11) that contribute to the high levels of AMR bacteria in (food) animals may have been the personal economic incentive for veterinarians to (over-)subscribe antibiotics. Up to 1995 veterinarians could prescribe and also sell antibiotics themselves and thus could make a direct profit from this. It is believed that this has promoted the antibiotic consumption, and it would seem that the discontinuation of this practice was one of the major reasons for a subsequent drop in antimicrobial use in animals of up to 20-30%. In addition, there were other incentives from pharmacies and the pharmaceutical industry which encouraged veterinarians to inappropriately and (over-)use antibiotics. One was that veterinarians could sell antibiotics for a higher price than pharmacies and industry. After 1995, legislation was put into action to de-stimulate antibiotic overuse by veterinarians. Through this law the pharmacies could divide larger batches of antimicrobials into single packages in order to sell smaller quantities of antimicrobials, and they could do this at the same price as the veterinarians. Next, the law prohibited pharmacies and the pharmaceutical industry from offering economic incentives to veterinarians for the purpose of increasing product sales. In addition, detailed treatment guidelines for veterinarian antimicrobial use were developed, and have been updated annually.

Industrialization

Though scientific and technological advances (CF7) helped to identify the AMR risk in animals, technological advances and new ways of animal producing were also a contributing factor for 1) the introduction of antibiotics in animals in the first place and 2) the high levels (approaching a 100% of affected animals) to which AMR resistance from food-animals could rise. Industrialization and high concentrations of animals have contributed to the emerging risk of AMR. Denmark is a large and industrialized producer (and exporter) of food-animals. To give an indication, on a population of 5 million people, Denmark produced about 117.6 million broiler chickens and 28.5 million pigs, 1.1 million cows and 1.2 million turkeys annually (DANMAP, 2010). The veterinary antibiotic consumption, and the associated risk of AMR, is therefore relatively large when compared to the human consumption of antibiotics. In addition, the social dynamics and the economic importance of the animal industry (CF6) may have led to the large scale introduction of AGP, as at the time it was thought to be the only way to achieve an economical and constant high production of healthy animals. Industrialization of animal production meant that farms house many animals and there is a lot of transport of young and grown-up animals, to and from farms and slaughterhouses. This may both have resulted in amplification of disease problems as one sick animal may infect many others, within relatively close confinement. The associated large volumes of animal transport may have caused the wider spread of disease, from farm to farm or to the environment. At the same time, however, because of the importance of the industry for Denmark and the large scale of the AMR problem/risk this also attracted enough attention to start a public debate and put the human health threat caused by AGP use, on top of the government's agenda.

Identification of the emerging risk of AMR and political agenda setting in Denmark

The situation around the use of avoparcin as AGP was not only seen in Denmark, it was a general problem observed in countries using avoparcin as AGP. Already in 1993 researchers in the UK found increases in VRE in nonhuman reservoirs and in 1995 VRE had been found in animals, humans and sewage in Germany (Bates, 1993; Woodford, 1998). These studies, however, did not lead to direct actions. The Danish survey (1995) that showed the dramatically high level of 80% VRE in chickens from conventional production versus 0% from organic production, did however result in direct actions from both the farmers and the government. A few days after the Danish scientists had discovered the high prevalence VRE among the broiler chickens, the industry was informed about the findings. The Danish farmer organizations agreed to voluntarily stop the use of avoparcin in chicken. While such early decisions by agricultural actors in the face of new scientific findings is certainly not the rule, Danish agriculture has a tradition of using and respecting science. A number of the solutions chosen by Danish farmers, leading to a Danish agricultural system continuously able to compete globally and actually recently becoming the largest exporter of pork globally, stem from early application of relevant science. It should also be noted that the Danish agricultural system is based on a co-operative system where the farms basically own the full production system, including up to the slaughterhouse and major production industry. All this contributed to a situation where scientific data, if considered valid, would actually also be acted upon by agricultural organizations. The organizations at the time expected government action, no matter what, and therefore wanted to act quickly in order to maintain influence on management decisions. To what degree this played a part is difficult to estimate. Later that same year, the Minister of Food and Agriculture did ban the use of avoparcin as growth promoter in all animals, so in effect the projection of government action turned out to be true.

The Danish ban of avoparcin was not in line with the EU legislation and did not seem acceptable for the drug industry at that stage. Some of the major arguments against the ban were related to the uncertainty as to what the real effect of such drastic measures would be. The theoretical outcome scenarios included especially a significant (negative) effect on animal health and a significant (negative) gross economic effect . At the same time there were real questions as to the potential effect of mitigation actions as per the future level of antimicrobial use and antimicrobial resistance. Therefore, in a collaborative effort of all stakeholders, the DANMAP surveillance program was initiated in 1995, in order to get a better understanding of the effects of the use and the discontinued use of antibiotics. The groups working together in DANMAP monitor both the consumption of antimicrobials and the occurrence of AMR in animals, humans and food. Concerning the avoparcin case, the initiation of DANMAP enabled the Danish scientists to document the effects of the ban on avoparcin, which over a period of 3-4 years led to a steep reduction of VRE in animals (Figure 4). With the start of DANMAP, and the work performed in the following years, several important things were done (and are still being done) to assess the risk of AMR for human health:

- putting emerging health risks related to AMR on the governmental-, agricultural- and public health sector agendas,
- producing evidence-based legislation to reduce the risk of AMR,
- convincing stakeholders to use antimicrobials more wisely.

The data flowing from DANMAP was used specifically by the then Minister for Food and Agriculture, Henrik Dam Christensen, to make the argument that an AGP ban was needed at the EU level. While drug industry argued against such ban, and in the end actually took the issue to the European court, they did not prevail. It is estimated that the perceived validity of the Danish data in this area contributed significantly to this outcome, together with a significant number of scientific papers from other parts of the world.,

Part 2: AMR risk assessment and risk management through DANMAP: the integrated approach taken by Denmark.

As outlined above, because of the complexity of the problem and the limited amount of solid data available, it was hard for the Danish government (and other governments around the globe) to draw clear conclusions on risks for human health caused directly by the use of AGP and animals antibiotics in general. A simple ban on antibiotic use in animals could have taken away animals as a reservoir for AMR bacteria, however, it could as well have devastating effects on animal production and thus on the economy.

Denmark was one of the first countries to recognize there was knowledge gap, and to develop a strategy to try to fill this gab. This was done by setting up a knowledge and collaboration platform for AMR: the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP). DANMAP was established in 1995 by both the Danish Ministry of Food, Agriculture and Fisheries and the Danish Ministry of Health and is jointly funded by the Ministry of Health and the Ministry of Science, Technology and Innovation. Figure 5 shows how DANMAP is organised.

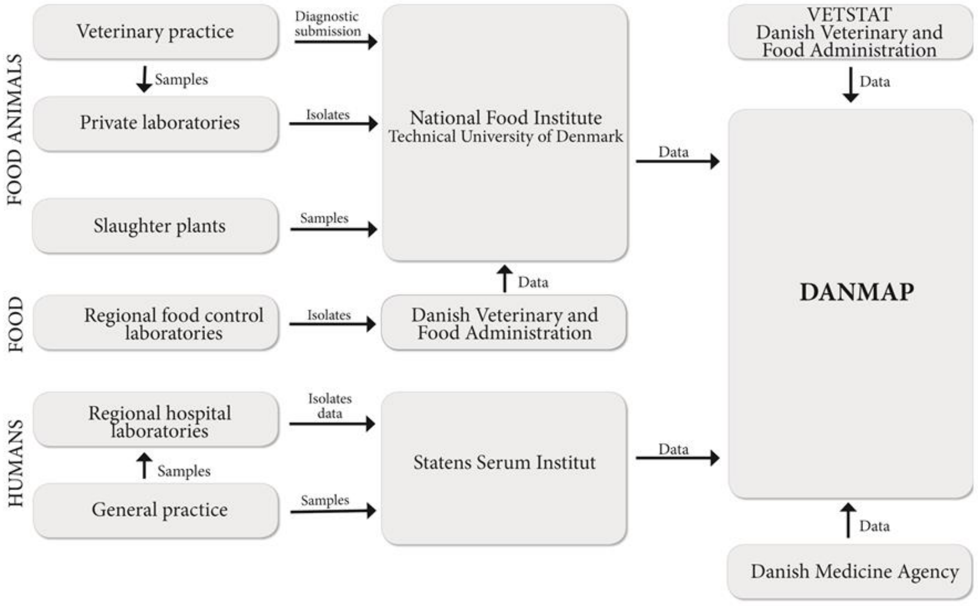

Figure 5. Organisation of DANMAP showing how the different institutes and agencies work together and how the information on AMR in humans, animals and food is brought together in DANMAP.

The current objectives of the DANMAP program are:

- To monitor the consumption of antimicrobial agents for food-animals and humans,

  - As part of DANMAP, the database VetStat was initiated in 2002 to monitor the veterinarian use of antimicrobials, related all the way down to single farm level. This online system collates detailed information on antimicrobial use on every farm in Denmark. Most of the information is automatically transferred to the database via the billing systems.
- To monitor the occurrence of AMR in bacteria isolated from food-animals, food of animal origin and humans,
  - incl. three categories: human and animal pathogens, zoonotic bacteria, and indicator bacteria (to monitor the overall exchange).
- To study associations between antimicrobial consumption and antimicrobial resistance.
- To identify routes of transmission and areas for further research studies.

Since 1997, the results covering the three reservoirs food, food-animals and humans have been published in annual reports. More detailed technical studies are published in international scientific literature and present on scientific or agenda setting meetings as those of the WHO, FAO, OIE and EU.

Achievement of the DANMAP supported evidence based risk management

The strength of the integrated approach of DANMAP was that it both integrated and separated different factors in the process of risk management. In addition, it made evidence based decision making possible which helped to bring together and convince all relevant stakeholders and ministries.

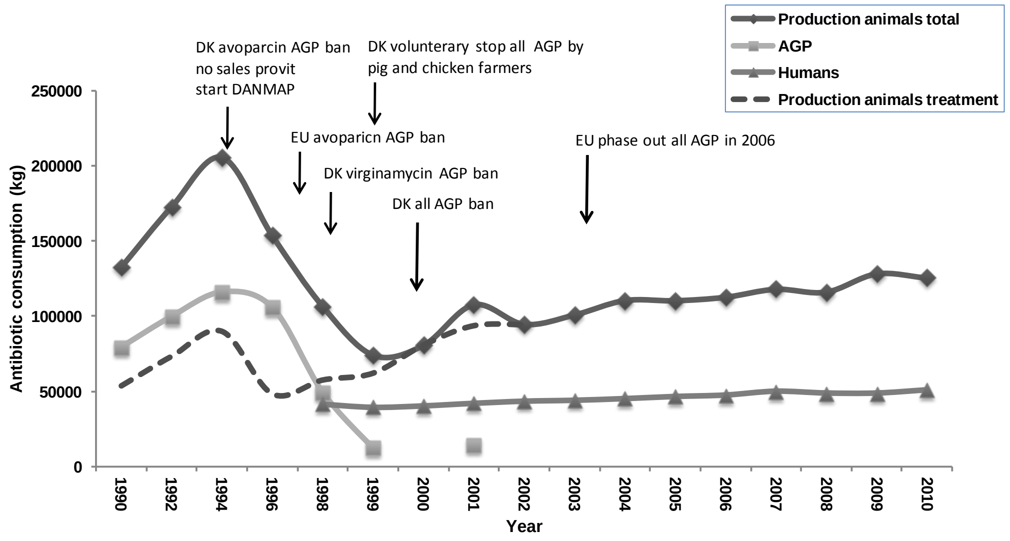

Figure 6. *Consumption of antimicrobials in humans and animals and the different actions by Denmark (DK) and the EU. (Data from DANMAP 2001, 2002, 2010; Aarestrup et al. (2010))*

DANMAP integrated a national cross-sector surveillance programs to asses the risk of AMR.

- The collaboration between microbiologists, physicians, veterinarians and epidemiologists offers a broad range of expertise and professionals.
- Also, all relevant stakeholders have access to all relevant data and samples collected from animals, food, and humans and can thus redo experiments or re-analyse data. This helped to get a broader support.

DANMAP separated the risk management from the risk assessment.

- Scientists are assessing the risk while the authorities, such as the Danish Veterinary and Food Administration and the National Board of Health are conducting the risk management.

DANMAP facilitated decision-making by bringing transparency to the evidence. Through the integrated approach in DANMAP a broad audience was reached including all relevant private and public stakeholders. With the reports publicly available on the internet everyone had access to the information. This made the situation around the use of veterinarian antibiotic and the risk for human AMR more transparent, helping to cover the gap in knowledge. This made implementation of risk management interventions easier and more broadly accepted.

Back to the avoparcin case, based on the data from DANMAP, Danish authorities, in partnership with agricultural producers, initiated major mitigation efforts and reduce the risk of AMR for human health. This specific case then became the model for handling subsequent cases in Denmark, in the end leading to a national ban of the use of AGP, and later leading to an EU-wide ban.

Figure 6 shows the human and veterinarian antibiotic use and some of the major actions that were taken to reduce the risk of foodborne AMR in humans. In 1995 there was the voluntarily stop of avoparcin use for AGP by chicken farmers, and later that year the Danish government banned the use of all avoparcin as an AGP. This was followed by a ban for all use of avoparcin in the EU in 1996. The Danish government banned the use of virginiamycin as an AGP in food-animals in 1998. This was followed by an overall ban of virginiamycin, bacitracin, tylosin, and spiramycin by the EU in 1998. In

2003, the EU made the decision to phase out all use of AGPs by the beginning of 2006. However, the Danish chicken industry decided to stop all use of AGPs in 1998 and the swine industry did so in 2000.

Management methods to control AMR in animals in Denmark

Danish legislation and guidelines

To manage the risk of AMR both direct methods to manage AMR risks on farms, guidance on more prudent use of antimicrobials on farms (incl. detailed treatment legislation and guidelines for veterinarians) have been developed. Since the introduction, these are being updated annually. This legislation and these guidelines have been developed in collaboration with the relevant government authorities, practicing veterinarians, and experts employed by universities and they provide recommendations on the appropriate antimicrobials for the treatment of common diseases in food-animal, so to reduce the development of new AMR emerging risk.

Some of the most important legislation following the avoparcin case comprised several components: 1) restrictions to the use of medical feed treating flocks when medicinal products could be used for a specific therapeutic indication; 2) limitations to prescribe antimicrobials longer than 5 days for most cases; 3) allow pharmacies to sell single packages of antimicrobials (to slow down the sold quantities) at the same price as veterinarians; and 4) prohibit pharmacies and industry from offering economic incentives to increasing product sales.

Direct methods to manage possible animal health effects of AGP termination that are used in Denmark are:

1. controlled antimicrobial therapy of sick animals,
2. financial compensation for losses (*e.g.* necrotic enteritis) in poultry,
3. feed companies made changes to feeds to optimise feed efficiency *e.g.* whole wheat and feeding enzymes were used (Emborg, 2002).

In 2010 a new tool to reduce antimicrobial use was introduced. Based on the information from VetStat the Danish Veterinary and Food Authority (DVFA) were able to introduce “The Yellow Card Initiative” (DVFA, 2012). Like in a football match, individual farmers and veterinarians that have the highest antimicrobial use get a yellow card and only by reducing the antibiotic use (for instance by adopting methods from low users) they can lose it. This does not only work as a stick, it also gives the users a sense of how well they are doing compared to their colleagues. It is interesting to note that in the European Union several countries now have started to collect similar data to compare antibiotic use at country level (EMA, 2011).

Research for alternatives

Furthermore, Denmark invested in research towards efficient production of healthy pigs and broilers chickens without AGP. Animal health research focused on the following strategies:

- enhanced bio-security to prevent and control the introduction, spread as well as the severity of infectious disease on and between farms,
- enhance natural disease resistance by selective breeding,
- develop feed that causes less enteric infections (*e.g.* better digestible feed),
- efficiently identify individual sick animals for treatment instead of preventive flock treatment,
- vaccination of animals to prevent disease.

For enhanced bio-security several methods have been proposed, which could be practically implemented on farms, including, the use of specific-pathogen-free (SPF) animals and feed, all-in-all-out (AIAO) strategies and wean[5]-to-finish housing. Especially AIAO management with clean-up of facilities between batches in the post-weaning phase has been considered very effective for controlling enteric diseases which increased after the termination of AGP (Baekbo, 2002). Drawback of these risk management methods is that they require substantial capital investments and knowledge. It is not known how extensive these technologies have been adopted but experts from the Danish food-animal industry say that some changes (*e.g.* AIAO management) have been adopted not only because of the ban on AGP but for other reasons as well.

Finally a major change in veterinarian practises in major animal production farms has been instituted through different initiatives, away from a focus on (antimicrobial) treatment and more towards sensible prevention of disease through change in management of animal production.

The cost of AMR risk management strategies in Denmark

The economic and production cost of the ban on AGP in Denmark have been studied for the pig and poultry industry (Emborg, 2002; Jacobsen and Jensen, 2003; UN, 2003). The net costs associated with productivity losses incurred by removing AGP from pig and poultry production were estimated at 1.04 € per pig produced and no net cost for poultry. The Danish Bacon and Meat Council calculated that pig producers spent nearly 1 DKK (0.133 €) per pig extra on organic acids as food preservative

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[5] weaner is used for a young/child pig

but this was offset by an estimated 1 DKK per pig saved by not using AGP. Together, this translated into an increase in pig production costs of about 1%. These costs were mainly due to the increased use of therapeutic antimicrobials and a reduced pig growth rate. The overall estimated impact for the Danish economy of was a reduction of 0.03% (48 million €) by 2010 (in 1995 prices) in real Gross Domestic Product (GDP). The efficiency of pig production has, however, increased significantly over the last 10 years to an overall level higher that before the AGP ban. Investigations including such recent developments have not yet been published yet, but it suggest that a constant high level of production can be achieved without use of AGP.

Some costs and benefits were too complex to measure and have not been accounted for in these evaluations. This included mainly the cost associated with modifications/modernisations of production systems, such as, modifications that increased bio-security to prevent larger outbreaks within and between farms. These cost may, however, have been offset with several benefits such as 1) the increased consumer confidence in Danish meat, 2) the associated increased demand (export) for Danish meat and 3) the decreased human health costs and benefits (*e.g.* lower number of untreatable infections).

Part 3: Conclusions and recommendations for controlling the risk associated with antibiotic use in animals

One of the take home messages of the DANMAP approach is, that the combination of major knowledge gaps and the existence of different stakeholders' opinions makes it necessary to support any AMR control efforts with scientific evidence. In addition, it is of primary importance to have cross-sectoral investigations of the relationships between AMR bacteria and the consumption/sale of antimicrobial agents. It was data from such investigations which were published and open to anyone interested, which formed the basis to enforce a stricter policy towards the use of antibiotics. This relates to the following IRGC contributing factors (CF): open communication (CF9) and taking away information asymmetries (CF10). It should be noted that there was a political involvement at the highest level (Head of State) in ensuring cross-sectoral collaboration between the agricultural and the human health sector. One of the outcomes of such involvement was the creation of the Ministry for Food, Agriculture and Fisheries in 1996with a responsibility for managing the Farm-to-Table chain in collaboration with the Ministry of Health.

The functioning of DANMAP and the changes in legislation for antibiotic use in humans and animals have been reviewed in different studies, and in particularly by WHO (UN, 2003), and has been very complete. It was concluded that, the overall change in Denmark, from the continuous use of antimicrobials to the exclusive use for treatment of specific animals, has been very successful. In addition it was concluded, that the Danish program has been beneficial in reducing antimicrobial resistance in important animal reservoirs, and thereby Denmark has reduced the threat of resistance to human health.

WHO has generated a lists of Critically Important Antimicrobials (CIAs) for human health, with the most important critical classes being:

- the quinolones (used for serious *Salmonella* infections),
- the cephalosporins (used for serious *Salmonella* infections, especially children),
- the macrolides (used for serious *Campylobacter* infections).

In Denmark, the animal use of these three groups has been restricted through legislation and on a voluntary ban.

Next, it was also concluded that the only benefits of AGP noted were confined to weaner pigs and was attributable to disease prophylaxis. WHO has developed Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food (WHO, 2000):

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

In retrospect it can be said, that the actions taken through DANMAP have been consistent with these WHO Global Principles underscoring the importance of them.

The Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food have been supplemented with, 1) guidance on the prudent use of antibiotics from the Codex Alimentarius Commission[6], and 2) six priority recommendations from WHO to reduce the overuse/misuse of antibiotics in food-animals for the protection of human health (UN, 2001):

1. Require obligatory prescriptions for all antibiotics used for disease control in food-animals.
2. In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antibiotics for growth promotion if they are also used for treatment of humans.
3. Create national systems to monitor antibiotic use in food-animals.
4. Introduce pre-licensing safety evaluation of antibiotics [intended for use in food-animals] with consideration of potential resistance to human drugs.
5. Monitor resistance to identify emerging health problems and take timely corrective actions to protect human health.
6. Develop guidelines for veterinarians to reduce overuse and misuse of antibiotics in food-animals.

Next to scientific research and surveillance, a key to the success behind the successful Danish approach was the trust and willingness to collaborate that exists between the many stakeholders:

- The veterinarians accepted to forgo (a significant) profit from selling antibiotics.
- The agricultural sector has over the years imposed a voluntary ban on growth promoters but also restricted the use of new antimicrobials to protect efficient human use.

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[6] a WHO/FAO collaboration

- Farmers have accepted reductions in the amount of antimicrobials they could store, making it less likely to grab some antibiotics (*e.g.* to counteract the "if you have plenty of it why not use it?").
- The agricultural sector accepted (reluctantly) to reduce antimicrobial use in farms with high use (relative to average farms).

An important improvement to DANMAP was the implementation of the automated VetStat system for surveillance of the veterinary use of drugs for food-animals. Groups aiming at monitoring AMR are advised to set-up a similar monitoring program to know how much antibiotics are used and for which purpose.

General suggestions for dealing with emerging AMR risks flowing from the DANMAP approach

How to deal with early warnings and complexity

In the process of identifying AMR risks and finding possible solutions it has been challenging to know which information was relevant for analysing and characterizing the AMR risk. The avoparcin case shows that one way was to “follow the money”.. When there are financial incentives for antibiotic use this may (in the long run) lead to excessive use situations. By having a monitoring program, (e.g. one similar to VetStat), to map the consumption of antibiotics or related parameters one may obtain relevant early warning signals.

The decisions, following the avoparcin case, show that the decision making was done as fast as possible but also one step at a time, with the effect of each decision monitored. Within the complex relations of stakeholders the farmers stood central. Through their union, they were the stakeholders that were first addressed and also the ones that made the problem their own. The farmers, literately had to pay the price for using antibiotics and the consequences of the ban, but they could also benefit from the ban through possible savings. It is, therefore, important to involve the farmers in the whole process of monitoring and decision making and inform them on the benefits and risk of using antibiotics.

In addition, following general principles as given by international organisation such as WHO/FAO/OIE may help reduce the complexity and facilitate decision making. It is not given that for specific countries/cases, each of these recommendations needs to be implemented fully. Given the specifics of the problem, some may be not necessary or should be adapted in accordance with the specific situation at hand, however, these principles are a good start for getting useful solutions.

How to communicate clearly and effectively and make people and organisations accountable

The use of DANMAP showed that it was worthwhile to make information publicly available *e.g*. by use of internet and in annual reports, and to use language that is understood by all stakeholders and the interested public. For reliability the information should be from independent research institutes, and it should make clear statement about results as well as about uncertainties.

The avoparcin case showed, that one should confront the people that create the risk (farmers followed by veterinarians and pharmaceutical industry) with the evidence that shows their activities lead to risk is essential, as well as include these stakeholders in defining and setting up the systems to monitor and characterize the problem. For this, the public opinion is also important, and it should be made clear that public opinion may turn against the risk producers when their activity continues to create said risk. And *vice versa*, by abandoning the risk causing activity, the public opinion will turn such that more, in this case, Danish meat is consumed. In short, this means that one should supply farmers with adequate information about the potential effect antibiotic use, especially in situations where there is a continuous belief that AGP is highly profitable and risk free.

How to resolve the trade-off between risk aversion and risk taking

With AGP, precaution was maybe one of the first reasons for stopping the use and to think about ways to stop or reduce the use of other antibiotics in animal production. The process of generating new legislation was done in a stepwise fashion and in collaboration with the main stakeholders. Moreover, the steps were taken in a controlled manner by monitoring the effects of discontinuing the use of antibiotics.

Transferability to other countries

Based on the experiences in DANMAP, many other countries have set up surveillance systems to monitor and detect possible emerging AMR related risks. For instance, since 2009, the EU countries report their findings to ECDC for analysis and reporting on annual basis, enabling early detection of cross-border AMR risks (ECDC, 2010). Countries that are considering to set-up a DANMAP-like programs, or that are considering an AGP ban or changes in their policies on antimicrobial prophylaxis use, may evaluate the consequences in light of Denmark’s experience.

Danish pork and chicken industries are intensive, with closed housing, good bio-security and a relatively high animal health status which may have buffered possible benefits that AGP may have under different conditions. The consequences of an AGP ban in countries with lower health status might be different. 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 in a country.

Denmark enjoys a high level of well-functioning infrastructure, including advanced capabilities to monitor antimicrobial use, antimicrobial resistance and animal production. The pig industry is organized in a cooperative fashion and farmers are co-owners of slaughterhouses. For this, and perhaps other reasons, Denmark could readily implement a nation-wide voluntary action on veterinary antimicrobial use. Countries, especially developing countries, that lack one or more of these infrastructures may need a longer period for full implementation perhaps supported by regulatory actions.

Countries with different industry structures, production systems and economic conditions than Denmark may experience different effects on production costs and macroeconomic impacts.

The economic effects will depend upon several factors, including the effects on performance levels and the cost of technologies to compensate the termination of AGPs. However, in view of the limited effects of AGP termination on efficiency of food-animal production and the merely 1% increase in production cost for the pig farmers, it is unlikely that similar action in less advanced countries would severely harm their overall meat production. Therefore, it may be accepted that the drawback and benefits are likely to be similar as those experienced in Denmark.

In general, food exporting countries would be well advised to continue to follow the international debate in relation to food safety risks, as well as successful risk management options. Historical evidence would seem to show that the avoidance of foodborne risk in some countries will at some stage result in similar avoidance in other countries. Therefore, most likely in some future scenario most if not all countries will actually ban the use of AGP. The countries adopting such ban late run the risk of using market share because of (in this case valid) consumer concerns.

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