Food and Agriculture Organization of the United Nations

Ministry of Environment and Food of Denmark
Danish Veterinary and Food Administration

TACKLING ANTIMICROBIAL USE AND RESISTANCE IN PIG PRODUCTION
LESSONS LEARNED IN DENMARK

TACKLING ANTIMICROBIAL USE AND RESISTANCE IN PIG PRODUCTION
LESSONS LEARNED IN DENMARK

Published by
the Food and Agriculture Organization of the United Nations
and
the Ministry of Environment and Food of Denmark

Rome, 2019

Required citation:
FAO and Denmark Ministry of Environment and Food – Danish Veterinary and Food Administration. 2019. *Tackling antimicrobial use and resistance in pig production: lessons learned from Denmark*. Rome. 52 pp.
Licence: CC BY-NC-SA 3.0 IGO.

ISBN 978-92-5-131221-6

CONTENTS

FIGURES

CONTRIBUTORS

PIA JUL, ELISABETH OKHOLM NIELSEN

Ministry of Environment and Food of Denmark,
Danish Veterinary and Food Administration

UTE WOLF SÖNKSEN

Statens Serum Institut

FLEMMING BAGER, KARL PEDERSEN

Technical University of Denmark

CARSTEN JENSEN, KEN STEEN PEDERSEN, VIBE PEDERSEN LUND

Danish Veterinary Association

JAN DAHL, TRINE VIG

Danish Agriculture and Food Council

NICOLAI ROSAGER WEBER

SEGES Danish Pig Research Centre

FOREWORD

This report describes an arduous campaign to limit the use of antimicrobials – specifically antibiotics – in the Danish swine-producing sector. Readers may interpret the conclusion as a promotion of the swine industry in Denmark. This is not the case; rather it is an example of one country's experience addressing antimicrobial resistance (AMR) in the swine sector. It is a testimony of the collaboration between the regulatory sector within the Ministry of Environment and Food (and its agriculture-focused precursors), private veterinary practitioners and swine producers (large and small), to tackle the unsustainable overuse of antibiotics in the industry. The report is a retrospective tribute to all those who had the foresight to make significant changes to ensure consumer protection – improving hygiene at primary sites of swine production, developing options for intervention through a system of surveillance and collation of data from feed mills to veterinary practitioner prescriptions, identifying sites for intervention, setting targets, restructuring the relationship between the veterinary services and farmers, and implementing changes in behaviour for greatest impact. Denmark in many ways laid out a plan before there was any known roadmap to follow; every step was based on continuous analysis and feedback to the operators – private and public – for ongoing monitoring and accountability as a driver for change.

In 1998, a ban on antibiotics as growth promoters came into effect. In addition, thanks to Denmark's policy of investing in strategies for infection prevention – for example, improving hygiene and nutrition, and introducing improved housing facilities – the overall use of antibiotics in the swine sector continues to decrease, and a reduction of 25 percent has been achieved since 2009. Throughout this period, profitability has been maintained.

The "story" is far from ended. As new information becomes available, such as findings concerning livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA), the Danish swine industry is once again leading the way in determining how to curb its occurrence through science, risk assessments for policymaking, public discourse and stakeholder engagement. Solutions are born of a shared goal for safe and sustainable food production.

Meeting the challenge of antimicrobial resistance involves learning from one another. It is hoped that this historical guide may serve other countries, food producers, regulators, veterinarians and those responsible for veterinary structures, as well as academia, to help identify ways forward to limit the emergence and spread of antimicrobial resistance that threatens public health, animal health and safe food production worldwide and in their own environment.

Juan Lubroth
Chief Veterinary Officer and
Antimicrobial Resistance Focal Point,
Animal Health Service,
Food and Agriculture Organization
of the United Nations

©DVFA

PREFACE

Antimicrobial resistance (AMR) is of growing global concern. AMR in human pathogens is forecast to cause an increasing number of deaths accompanied by rising costs in healthcare. Usage of antimicrobials in humans and animals leads to selection for resistance; furthermore, from a One Health perspective, the close connection between animals, food, people and the environment requires urgent action across sectors for reduced and more prudent use in both humans and animals (FAO, 2016a).

Denmark has a long history of production and export of food and food-producing animals. Despite the size of the country, the level of production of animals, especially pigs, is high: the last two decades have seen production increasing to 32 million pigs per year. The production increase was accompanied by a rise in antimicrobial use, which came increasingly under the spotlight with growing awareness at the national level. The authorities have worked in close collaboration with stakeholders to mitigate the risk of AMR under a One Health approach. In 2017, Denmark used approximately 100 tonnes of antimicrobials for all food-producing animals, which is a low rate of usage compared with other European countries (EMA, 2017a). The present report aims to communicate some of the lessons learned with a focus on pig production.

Key to the success of Danish agricultural export has been the formation of strong farmers' organizations and cooperatives for feed mills, abattoirs and dairies. The last few decades have seen the consolidation of farmer-owned cooperatives; as of 2018, one large meat processor cooperative accounts for most of the exports of these products within and outside the European Union (EU).

National public awareness about the use of antimicrobials and AMR in the Danish pig industry increased in the early 1990s. The Danish approach to tackling AMR has been established with close collaboration between the authorities, industry and scientists; indeed, favoured solutions at the national level have broad support – politically, scientifically and in the industry. New initiatives or legislation are discussed among stakeholders and often adjusted to ensure better compliance and effect. This approach has been pivotal for the successes achieved in Denmark and could serve as inspiration for others.

ABBREVIATIONS

ADD	Animal daily dose
AGISAR	Advisory Group on Integrated Surveillance of Antimicrobial Resistance
AGP	Antimicrobial growth promoter
AMR	Antimicrobial resistance
ASF	African swine fever
CHR	Central Husbandry Register
CSF	Classical swine fever
DADD	Defined animal daily dose
DAFC	Danish Agriculture and Food Council
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DAPD	Defined animal daily dose per 1 000 animals per day
DFVF	Danish Institute for Food and Veterinary Research
DMH	Danish Ministry of Health
DTU FOOD	National Food Institute
DTU VET	National Veterinary Institute
DVA	Danish Veterinary Association
DVFA	Danish Veterinary and Food Administration
EMA	European Medicines Agency
EPA	Environmental Protection Agency
ESBL	Extended-spectrum beta-lactamase
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FMD	Foot-and-mouth disease
LA-MRSA	Livestock-associated methicillin-resistant *Staphylococcus aureus*
MEFD	Ministry of Environment and Food of Denmark
OIE	World Organisation for Animal Health
PCV2	Porcine circovirus type 2
PED	Porcine epidemic diarrhoea
PMWS	Post-weaning multisystemic wasting syndrome
PRRS	Porcine reproductive and respiratory syndrome
SD	Swine dysentery
SPC	Summary of Product Characteristics
SPF	Specific Pathogen Free
SSI	Statens Serum Institut
SVS	Statens Veterinære Serumlaboratorium
TGE	Transmissible gastroenteritis of swine

VASC	Veterinary Advisory Service Contract
VF	Veterinær- og Fødevaredirektoratet
VRE	Vancomycin-resistant enterococci
WHO	World Health Organization

©DVFA

1. THE DANISH PIG SECTOR THEN AND NOW

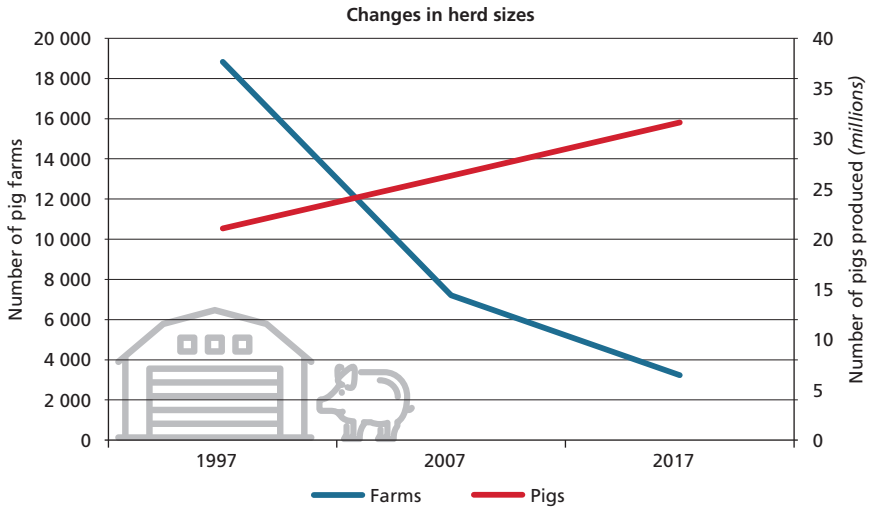
During the last 40 years, the Danish pig industry has undergone extensive development – from small family-run farms to large professional farms. While most pig farms are still family owned, increased mechanization and specialization have led to their consolidation into a smaller number of large farms (Figure 1).

The last 20 years have also seen a significant increase in knowledge and awareness about antimicrobials.[1] Just 20 years ago, Danish pig farmers were using antimicrobials for growth promotion. New research and knowledge has led to a ban on antimicrobial growth promoters (AGPs) and a focus on prudent use. In Denmark, use of antimicrobials in the pig industry is declining each year despite increasing production of pigs (Figure 2).

IN DENMARK, USE OF ANTIMICROBIALS IN THE PIG INDUSTRY IS DECLINING EACH YEAR DESPITE INCREASING PRODUCTION OF PIGS

In 2017, Danish production reached over 32 million pigs, of which close to 18 million were slaughtered in Denmark, while 14 million piglets were exported to mainly Germany and Poland for further fattening (DAFC, 2018a). The export of growing pigs began in 2004 and the demand for Danish weaners has increased every year (Figure 2).

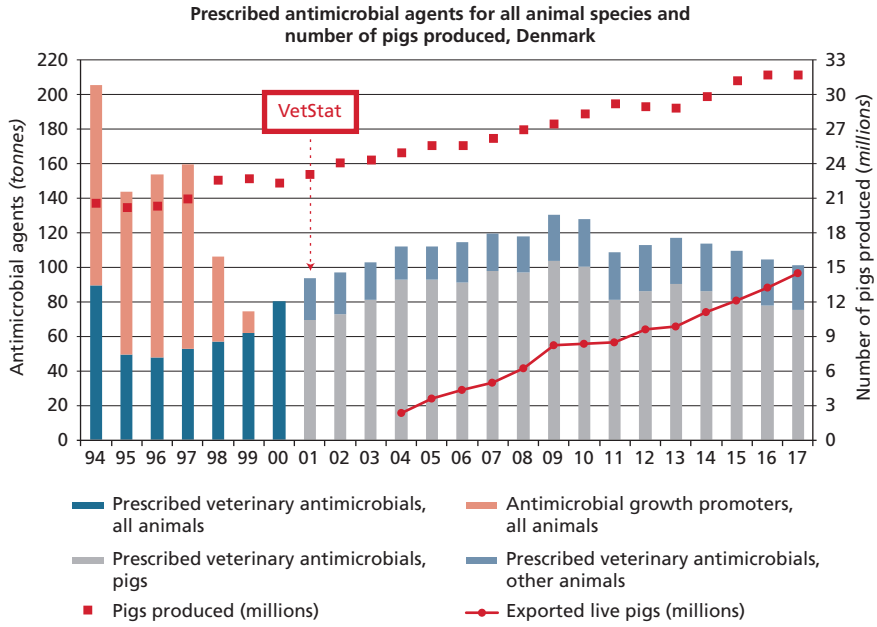
FIGURE 1. Relationship between number of pig farms and number of pigs produced in Denmark, 1997, 2007 and 2017



Source: Statistics Denmark.

[1] Antimicrobials is a collective term for antiviral, antibacterial, antifungal and antiprotozoal agents.

FIGURE 2. Use of antimicrobials in relation to total pig production, including export, 1994–2017



Note: 1994–2000 data reflect antimicrobial use for all animals. 2001–2017 data are from VetStat and divided into use for pigs and use for all other animals.
Source: DANMAP and Statistics Denmark.

The pig industry plays an important role in the Danish economy. More than 90 percent of production is exported to over 120 markets around the world, accounting for over 19 percent of the total food products exported (DAFC, 2018b). Given its high export share, the industry depends on access to a large number of markets in the world. This is one of the key drivers for continuously improving and maintaining high standards of animal health and food safety.

COOPERATION BETWEEN AUTHORITIES, PIG FARMERS AND VETERINARIANS – THE KEY TO LOW ANTIMICROBIAL USE

During the last three decades, the farm structure has undergone significant change (Figure 1). Most farms used to be operated as integrated production units with pigs raised on the same farm from birth to slaughter; today's farms have more specialized herd structures. Only one-third of farms are currently operated as integrated farms and the remaining herds are divided into sow herds and specialized weaner and finisher farms. This development is a result of strict environmental legislation, regulating the allowance of animals per hectare (MEFD–EPA, 2017). It is also due to the need for farmers to specialize in production of sows, weaners or finishing pigs in order to increase efficiency.

The Danish industry is based on a cooperative structure, where pig breeding, pig production, abattoirs and food-processing companies are owned by

the farmers. The industry cooperatives have allowed Danish farmers to build up an integrated structure owned and controlled by them.

Veterinarians, on the other hand, belong to the Danish Veterinary Association (DVA). The DVA represents not only veterinarians in private practice, public office and large companies, but also students and retired veterinarians. Both the large cooperatives in the industry and the DVA represent their members when new legislation is discussed with the authorities. In addition, the Danish Veterinary and Food Administration (DVFA) holds regular informal meetings ad hoc with the above-mentioned stakeholders in the pig sector to discuss views and problems connected to animal health, welfare and use of antimicrobials for food-producing animals.

The whole farm-to-fork chain is managed by the Ministry of Environment and Food of Denmark (MEFD). This makes it easier to move initiatives and decisions through the governmental system. The Ministry itself does not perform any research. However, in addition to research carried out by the industry, the Ministry can ask researchers at the Danish universities to help answer scientific questions that are relevant in the decision process. The universities are given a yearly fee to provide this service in addition to supplying research projects.

Privately funded investments in research and development over many years have enabled the industry to play a role in the production of safe food while remaining a competitive supplier to many international markets. Most research initiatives are funded by the production levy paid by all pig producers for each pig slaughtered or each piglet exported and by royalties from the commercial sale of genetic material. The pig industry has centralized its research programmes, and research is carried out in close partnership with universities, the authorities, supply industries and trade associations, at both the national and the international level. Most of this research takes place on commercial farms, with over 200 pig farms currently participating in trials. The farmer organizations communicate the results to fellow members.

©DVFA

The unique organizational structure of the pig industry has made dissemination of research results and best practices easier than in countries where there are a greater number of stakeholders and partners. This structure, where most pig farmers are members of one of the main organizations, has also enabled effective voluntary bans on the use of antimicrobials. The industry plays an important role in the national residue surveillance programme. Today, the programme includes analysis of around 3 000 samples annually in accordance with Directive 96/23/EC (European Union Law, 1996; European Commission, 2018). Furthermore, slaughterhouses analyse around 10 000 samples annually as part of their own control programme. The programme rarely detects antimicrobial residues in pig meat, indicating that the mandatory withdrawal periods are observed by all farmers. These results are made public in the yearly report of the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) (DANMAP, 2018).

©DVFA

The next challenge for the Danish pig industry will be an upcoming restriction on therapeutic use of zinc oxide. Zinc oxide is given during the first two weeks after weaning to minimize diarrhoea in piglets. There is concern that the ban will lead to increased use of antimicrobials for diarrhoea treatment. Given the potentially negative impact of zinc oxide on the environment, the European Union (EU) is withdrawing the marketing authorizations for veterinary medicines containing zinc oxide in 2022, thereby effectively banning its use (EMA, 2017b). The authorities and pig farmer organizations are working on projects to help farmers phase out the use of therapeutic zinc oxide without replacing it with antimicrobial use. The research set in motion following the EU referral has yet to be concluded, and it is therefore still uncertain what effect the ban will have. Should an increase in antimicrobial use be observed, the authorities will call the relevant stakeholders for meetings to discuss the best way to mitigate the new issue. At present, the focus is on improving pig health by preventing diarrhoea at weaning, thus reducing the need for therapeutic antimicrobials.

DEVELOPMENTS IN PIG HEALTH

Surrounded by water and with very few land borders, Denmark is in a unique situation in terms of controlling incoming biological material and thus diseases affecting pig health. Denmark has never experienced an outbreak of African swine fever (ASF), porcine epidemic diarrhoea (PED) or transmissible gastroenteritis of swine (TGE), and has been free from classical swine fever (CSF) since 1933, foot-and-mouth disease (FMD) since 1983 and Aujeszky's disease since 1991 (MEFD, 2017a). Denmark is recognized by the World Organisation for Animal Health (OIE) as free from FMD and CSF (OIE, 2018a and 2018b).

Continuous efforts are made to prevent the introduction of infectious diseases into Denmark: strict industry-driven control of washing and disinfection of lorries transporting animals across the border, limited import of animals, and industry rules for quarantine of imports have successfully kept Denmark free from these diseases for many years.

SPF system: improved disease control on pig farms

In 1971, the Danish Specific Pathogen Free system (SPF system) was established by the industry in collaboration with university specialists and it remains an important tool for the control and improvement of animal health on pig farms. SPF pigs are free from a range of swine pathogens. The SPF system is based on a set of stringent rules concerning biosecurity, health control and transportation of pigs between herds (DAFC, 2018c). The overall objective is to avoid the introduction of new pathogens into herds. The SPF system includes important pig diseases such as mycoplasmosis, pleuropneumonia, swine dysentery (SD), mange, lice, porcine reproductive and respiratory

syndrome (PRRS), and atrophic rhinitis of pigs. Today, approximately 75 percent of Danish pigs are born in the SPF system (DAFC, 2018c). The health status of each herd is publicly available and is used daily for the trade of pigs between herds. The herd status is also essential information when veterinarians and other visitors plan visits between farms. The SPF system has had a deep impact on the way pigs are produced in Denmark and a profound effect on the need for treatment of infectious diseases.

Herd structure and disease control

Multisite production has become common and pigs are often moved between herds at specific ages, for example, at weaning and when they reach 30 kg, facilitating control of some of the classic production diseases. However, closed production systems require specific care when introducing new breeding stock, such as separate quarantine sections with stricter biosecurity measures.

A high level of external biosecurity is achieved in Denmark, not only through the SPF system (Filippitzi *et al.*, 2017; Postma *et al.*, 2016), but also thanks to the so-called "Danish entry". The Danish entry entails a room divided into a clean area and a dirty area. When entering the room through the dirty area, the person washes their hands and changes their clothes and boots before moving to the clean area and into the pig facility (Pig Research Centre, 2018).

Intestinal infections are a major problem and account for a large proportion of total antimicrobial consumption in Danish pigs. Viral infections – such as swine influenza, PRRS and porcine circovirus type 2 (PCV2) – also increase antimicrobial consumption as they are associated with secondary bacterial infections. Given that many of these diseases can be handled with vaccinations and good management, further reduction in antimicrobial use is possible without compromising animal welfare. The sales of vaccines for pigs increased from 28 million doses in 2009 to 55 million doses in 2017 (DVFA figures).

The central role of the herd veterinarian is enhanced by the SPF system, and collaboration between the farmer and the veterinarian is key to ensuring the success of long-term herd health strategies. Disease prevention is crucial: diseases are controlled by biosecurity measures, targeted use of vaccines and diagnostic tests adapted to the herd. Regular mandatory herd health visits with written reports are essential to ensure the effectiveness of these measures.

COLLABORATION BETWEEN THE FARMER AND THE VETERINARIAN IS KEY TO ENSURING THE SUCCESS OF LONG-TERM HERD HEALTH STRATEGIES

THE ROLE OF HERD VETERINARIANS

The veterinary profession in Denmark underwent substantial change in 1995, as new regulations meant that veterinarians were no longer allowed to sell veterinary prescription medicines to farmers to make a profit (a change known as "decoupling"). A veterinarian can supply medicine to enable the farmer to initiate treatment, but is only allowed to charge the set price for the medicine with no extra fees. Medicine for further treatment is provided on prescription

©FAO/Giulio Napolitano

by pharmacies. There are enough pharmacies to ensure that farmers can obtain sufficient supplies. The change to the law was politically driven by concern that veterinarians could have an economic incentive for prescribing medicines. Parallel legislation was adopted to establish new Veterinary Advisory Service Contracts (VASCs) between farmers and veterinarians.

Structural changes in the pig sector led to the institution of the above-mentioned VASCs. The fact that educated farmers were managing large specialized productions resulted in an increased demand for preventive pig healthcare. Farmers with a VASC are allowed to stock medicines and give anti-microbial treatments between monthly veterinarian visits; farmers treating new disease cases follow the veterinarian's written instructions laid down in the herd health plan. Between 1995 and 2010, VASCs were voluntary; in 2010, they became mandatory for all large pig herds and today more than 95 percent of pigs in Denmark are covered by VASC agreements (DVFA figures).

The amendments in legislation meant that veterinarians had to change their business model almost overnight; no longer able to earn their primary income through sales of prescription medicines, they increased the fees charged for veterinary advice. Given that 12 herd health visits per year are mandatory under VASC, an increasing number chose to specialize as Danish pig herd veterinarians. What is more, the regular herd health visits paved the way for herd veterinarians to become highly trained experts and the primary advisors to farmers with regard to herd health management, animal welfare and disease prevention. The legislation was supported by both the pig industry and the DVA.

The continued focus on reduction in antimicrobial usage and the sustained efforts to ensure competitiveness of the Danish pig sector have provided Danish pig herd veterinarians with unique expertise in preventive medicine. Mixed veterinary practices still exist in Denmark, but specialization has meant that in 2018 there are fewer than ten specialized pig practices providing veterinary advisory services to virtually all pig farmers in Denmark. In recent years, these specialized pig herd veterinarians have also started to provide herd health advice to farmers in other European countries.

Today, pig herd veterinarians participate in the strategic work of the management boards of pig farms. Farmers and advisors collaborate on structural changes, and agricultural, economic and financial matters, resulting in a holistic view of the farm and visions for the future. In the future, it will be possible to collect and process even more detailed data on individual farms; the pig herd veterinarian will have to become even more specialized, acquiring new competencies.

©DAFC

2. MONITORING ANTIMICROBIAL USE

DANMAP – MAKING DATA ON ANTIMICROBIAL USE AND RESISTANCE IN BOTH ANIMALS AND HUMANS PUBLICALLY AVAILABLE

DANMAP – the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme – was established through a collaboration between the veterinary, food and human sectors in the mid-1990s in response to concerns raised about how antimicrobials were used in food-producing animals in Denmark. One of the primary drivers behind the collaboration was the observation that the use of AGPs could cause antimicrobial resistance (AMR) which posed a health hazard to humans (Klare *et al.*, 1995). Plus antimicrobial use in pig production had increased since the mid-1980s (SVS, VF and SSI, 1998).

Over the past 20 years AMR has been monitored in zoonotic enteric pathogens isolated from food animals, meat and humans, as well as in commensal bacteria from the intestinal tract of food animals and from meat samples (SSI, DTU Vet and DTU Food, 2018). Where possible, the results from the monitoring programmes are interpreted in a One Health context[2] in the annual DANMAP report (DANMAP, 2018). One example is the monitoring of extended-spectrum beta-lactamase (ESBL) *Escherichia coli* in cattle, pigs, poultry, beef, pork, chicken meat and human disease cases using whole genome sequencing. Data analysis has demonstrated that under the condition of very low use of third- and fourth-generation cephalosporins, the overlap between the above-mentioned reservoirs is small in Denmark.

THE RESULTS FROM THE MONITORING PROGRAMMES ARE INTERPRETED IN A ONE HEALTH CONTEXT

VETSTAT DATABASE FOR MONITORING ANTIMICROBIAL USE

The monitoring of antimicrobial use is based on detailed sales information reported to the VetStat database (for veterinary medicines) and the Medstat database (for human medicines). Reporting antimicrobial consumption in animals initially posed a number of challenges. In 1995, data on the sales of antimicrobials in the veterinary field were mainly available from the general

[2] One Health represents a holistic vision to address complex challenges that threaten human and animal health, food security, poverty and the environments where diseases flourish (FAO, 2011).

©DVFA

Danish medical statistics, based on reporting from wholesalers (Figure 2). The detailed resolution of the data was poor, as information about the target species of antimicrobial use was not available. Nevertheless, it was clear that the use of therapeutics in pig production had increased sharply during the second half of the 1980s and the early 1990s, to the extent that the national pig producers' association became concerned. A governmental report from May 1997 documented that use of therapeutic antimicrobials in pigs increased by 33 percent between 1986 and 1994, while use of AGPs for all farm animals increased by 73 percent in the same period (Ministeriet for Fødevarer, Landbrug og Fiskeri, 1997). The increase was attributed in particular to oral medication, mainly tetracycline, and the report concluded that the increase largely represented overuse not justified by disease patterns or increased production.

While the national data on antimicrobial use in animals in the mid-1990s allowed a general overview of the situation, it lacked sufficient detail for targeted intervention. For example, information about target species was based on expert opinion or best guesses and information about use at herd level was lacking.

The VetStat database was launched on 1 August 2000 with the objective of providing close to real-time data on all sales of prescribed medicines for production animals, at both the farm and the species level (cattle, small ruminants, pigs, poultry, aquaculture, fur animals and other). VetStat was designed to work together with the Central Husbandry Register (CHR), which contains data on all farms in Denmark, including animal species present and their numbers (or a surrogate measure, such as the average number of animals at

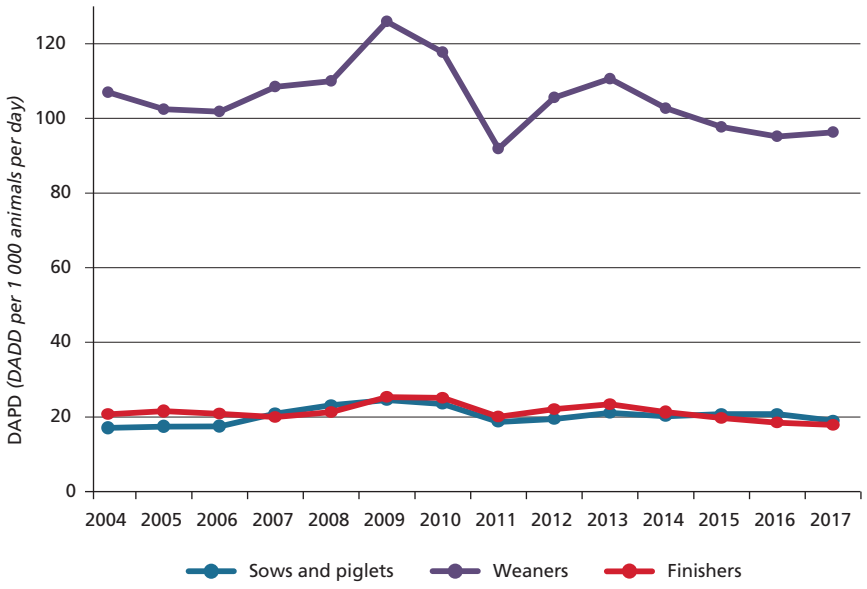
a given time). The CHR provides denominator information (animal population) for reporting of veterinary antimicrobials relative to herd size. VetStat records the age of the target group and the reason for prescribing antimicrobials.

Data on antimicrobial sales for the pig sector are predominantly entered into VetStat from the prescription information submitted by pharmacies at the point of sale of the product to the pig producer. In addition, medicines used or sold by veterinarians are recorded in VetStat by each individual veterinarian or veterinary practice. However, data collection did not have an easy start: it soon emerged that good quality data require continuous validation. When discrepancies arose or there were delays in reporting, the relevant pharmacy and veterinarian were contacted; continuous communication led to improvement in the system and in the data quality. The amounts of prescribed and sold antimicrobials are converted into a technical unit – animal daily dose (ADD). ADD parallels the defined animal daily dose (DADD) used in DANMAP.

By incorporating information contained in the CHR about herd size, age group and antimicrobials prescribed in technical doses, VetStat can monitor total antimicrobial use measured in ADD at farm level, enabling the comparison of usage between farms and over time on individual farms. It is thus possible to identify which part of the animal production phase is associated with a particularly high use of antimicrobials – for example, the number of treatments in weaner pigs is higher than in other age groups (e.g. finisher pigs). Figure 3 shows the consumption of all antimicrobials in Danish pig production. DAPD (defined animal daily dose per 1 000 animals per day)

IT IS POSSIBLE TO IDENTIFY WHICH PART OF THE ANIMAL PRODUCTION PHASE IS ASSOCIATED WITH A PARTICULARLY HIGH USE OF ANTIMICROBIALS

FIGURE 3. Antimicrobial consumption in Danish pigs by age group, 2004–2017



Source: DANMAP.

is a measure of treatment intensity: 100 DAPD means that on a given day, 10 percent of the respective population is treated with antimicrobials (see Box 1 for full explanation of DAPD and DADD).

Since the launch of VetStat in 2000, experience has shown that all phar-

BOX 1. ADD, DADD, DAPD – Metrics of antimicrobial consumption in animals

Over time and between animal populations wide variability may occur in selection between antimicrobial classes, and in active compounds selected within an antimicrobial class. The dosages of different antimicrobial medicines administered may vary considerably depending on factors such as potency, pharmacokinetic characteristics, formulation and disease targeted. Accordingly, shifts in choice of drugs (without change in disease occurrence and treatment frequency) may be misinterpreted as a change in total consumption when measured in kg active compound at group level. To facilitate analysis of changes in use patterns, standardized metrics are utilized.

The **animal daily dose (ADD)** is defined as the assumed average maintenance dose of a given product per day per kg body weight (ADDkg) multiplied by a defined standard animal body weight. The "standard" body weights used to calculate ADD from the ADDkg are set as the assumed average weight at treatment for each age group within each species.

As an example, if the ADDkg of a selected medicine is 5 mg/kg and the selected standard weight of the target animal (e.g. piglet) at time of treatment is 10 kg, then the ADD value would be 50. The number of ADDs used in a population is the total amount of antimicrobial agent consumed divided by the ADD value.

The **defined animal daily dose (DADD)** is similar to the ADD but instead of defining at product level, the standard maintenance dose is defined according to antimicrobial active substance. The DADD has been specifically defined for use in DANMAP and therefore does not always match the "prescribed daily dose" or the recommended dosage in the authorized Summary of Product Characteristics (SPC) of individual products.

The **defined animal daily dose per 1 000 animals per day (DAPD)** is the DADD per 1 000 animals per day and is used as a measurement of **treatment intensity**. For example, a count of 100 DAPD in weaners means that on a given day, 100 out of 1 000 (10%) of the weaner pigs were treated.

More information on metrics can be found here:

https://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP2017/DADD%20for%20pigs%202017.ashx

https://www.danmap.org/~/media/Projekt%20sites/Danmap/DANMAP%20reports/Danmap_2009.ashx

maceutical products must have the same ADD assigned if they contain the same active antimicrobial component at equivalent concentration and are administered by the same route. This permits the implementation of a benchmark system. Initially, ADDs were based on the recommended dose regimens for each pharmaceutical product. In 2014, products containing the same active substance were aligned, applying ADD values. It should be noted that ADD is a technical unit applied to data for the purposes of monitoring; it does not alter the actual administered dose regimens of veterinary medicinal products, which are administered in accordance with their authorized Summary of Product Characteristics (SPC).

Since its inception, data from VetStat have formed the basis for various interventions by stakeholders (primarily the relevant authorities, but also animal industry associations). Interventions include the voluntary cessation of use of third- and fourth-generation cephalosporins and the Yellow Card Initiative (see section: The Yellow Card Initiative on Antibiotics in the 2010s).

©DVFA

3. ORGANIZATIONAL AND GOVERNMENTAL INITIATIVES

IT IS CRUCIAL THAT EFFORTS TO MITIGATE AMR FOLLOW A ONE HEALTH APPROACH

AMR bacteria and resistant determinants are regarded as zoonotic, with the potential for transmission within and between humans, animals, food and the environment. Therefore, it is crucial that efforts to mitigate AMR follow a One Health approach. The early efforts outlined in this report were driven by and focused on the veterinary sector. To promote a One Health approach, Denmark established the Danish National Antimicrobial Council in 2010 with very broad representation from governmental authorities, universities, hospitals and various stakeholder organizations such as the Danish Veterinary Association. The objective of the Council is to discuss and contribute to the solution of specific tasks in the field of antimicrobials and offer guidance to national and international initiatives on antimicrobial use and resistance. Similarly, an Advisory Committee on Veterinary Medicines was set up in 2018 to help make evidence-based professional decisions in relation to the use of veterinary medicine and to predict and tackle issues proactively.

In the 1990s, action plans for reducing levels of *Salmonellae* in beef, pork, eggs and poultry meat were formulated with the overall aim of reducing the number of human *Salmonella* infections attributed to these sources; these have since been integrated in current legislation (MEFD, 2017b,c,d,e,f). Thanks to the strong focus on increasing biosecurity, the plans have been a success resulting in a significant reduction in *Salmonella* contamination in pork meat.

In 2017, the Ministry of Environment and Food together with the Ministry of Health launched a One Health strategy against AMR (DMH and MEFD, 2017) to implement the global action plans of the Food and Agriculture Organization of the United Nations (FAO, 2016b) and the World Health Organization (WHO, 2015) at the national level. Denmark's action plans were directed against AMR in both human and veterinary medicine (DMH, 2017; DVFA, 2017a).

In order to support veterinarians in the appropriate prescription of antimicrobials, the authorities – together with research institutes and the pig industry – have issued prescription guidelines providing advice on how to achieve the optimum clinical effect of treatment (DVFA, 2018a). The guidelines are based on knowledge of resistance patterns for individual bacteria. Given

©FAO/Giulio Napolitano

PROPHYLACTIC USE OF ANTIMICROBIALS IS NOT ALLOWED UNDER DANISH LAW

the increasing awareness of the importance of the human health aspects of resistance development, recommendations take into account which antimicrobial preparations are likely to have the best therapeutic effect in the animal population under treatment, while also minimizing the risk of developing resistance to antimicrobials considered critically important in human health.

The primary mission of the Danish Veterinary and Food Administration is to promote safety, health and quality from farm to fork. The DVFA covers the entire food chain from the pigs on the farm to the meal on your plate. The DVFA assumed its current structure around 2000; responsibility for food quality and for AMR in zoonotic bacteria were merged with the veterinary administration to give a more coherent organization.

The DVFA conducts supervision, guidance and control of veterinarians and pig farmers with respect to regulatory compliance. Following the substantial changes in the 1990s in the legislation regarding antimicrobials and the work of veterinarians, inspections during 2000–2010 focused on the supervision of veterinarians with the intention of raising awareness about how to correctly prescribe and provide instructions to farmers. As of 2010, the DVFA continues to review veterinarians' work during basic inspections, but the focus area changes each year.

All veterinary antimicrobials are administered under a prescription dispensed by a veterinarian. Prophylactic use of antimicrobials is not allowed under Danish law. Use of antimicrobials must be therapeutic or metaphylactic; all antimicrobials must be administered under the supervision of the herd veterinarian within the incubation period of any infection known to have occurred. During 2000–2010, veterinarians were audited and their prescribing habits were benchmarked against other veterinarians. When an audit highlighted any inconsistencies or a lack of appropriate prescribing, a dialogue subsequently took place between auditor and veterinarian to improve the veterinarian's knowledge and understanding of the new legislation.

Since 2010, the focus on pig farmers has increased, using the Yellow Card Initiative and applying national targets for reduction of antimicrobial use (see section: The Yellow Card Initiative on Antibiotics in the 2010s).

The DVFA provides guidance to farmers and veterinarians through visits, inspections, newsletters and web-based information. In addition, the DVFA verifies that all farmers and veterinarians adhere to legislation through three types of inspections: standard inspections take place on a regular basis and cover all aspects of the legislation; priority inspections are based on risk criteria (e.g. the results of previous inspections); and additional inspections are performed as part of specialist campaigns with different focus areas announced every year. In 2018, focus areas included how farmers should deal with sick and injured pigs, the cleaning and disinfection of lorries transporting pigs, and the use, registration and storage of therapeutic zinc oxide. An inspection campaign is announced on the DVFA home page ahead of time, as well as through

meetings with the DVA and farmer organizations. The aim is to raise awareness about prudent use of antimicrobials and to ensure adherence to regulations. The inspection visits on farms are generally unannounced. When farm records reveal gaps (e.g. missing registrations of usage in the herd), the veterinary officer revisits the herd to ensure that registration is completed correctly. If a farmer does not comply with the regulations within a set time frame, legal steps may be taken, for example, a fine may be issued.

MANDATORY LABORATORY DIAGNOSTICS

In 2014, the DVFA implemented mandatory laboratory diagnostics in relation to oral group medication for respiratory or gastrointestinal pig diseases. The veterinarian in charge is required to sample and submit diagnostic material for antimicrobial susceptibility testing prior to prescribing group antibacterial medication. This results in the submission of thousands of faecal samples each year, in particular with respect to gastrointestinal diseases as they remain the primary reason for oral antimicrobial treatments. The veterinarian is further required to evaluate the laboratory result and, where necessary, change the treatment accordingly. In cases where a causal bacterium is not identified in successive submissions, the veterinarian and farmer are required to consider alternative management and treatment strategies.

TERMINATION OF GROWTH PROMOTERS IN THE MID-1990S

In many countries, including Denmark, antimicrobials had been used in animal production since the early 1950s in order to promote animal growth and improve feed utilization. At that time there was an overlap between the antimicrobial agents used for growth promotion and those used for treatment. Concerns about the increasing levels of AMR led to the formation of the Swann Committee in the United Kingdom in 1969 (Swann, 1969). The Committee concluded that the use of antimicrobial growth promoters (AGPs) selected for resistance was transferable between bacterial species and could therefore cause problems for the treatment of bacterial infections in humans. The report recommended that antimicrobial agents used for therapy should not be used for growth promotion. Following this, a number of antimicrobial agents were banned for use as AGPs in Denmark and subsequently in other EU Member States (European Commission, 2005). The available evidence indicates that unintended consequences from national-level restrictions on antimicrobial use in food animals are temporary and minor (McEwen *et al.*, 2018).

In the early 1990s, eight antimicrobials were approved in the EU for use as growth promoters. While these were not agents that were used therapeutically, six of them belonged to classes of antimicrobials used for treatment of

humans or animals. One agent was avoparcin, closely related to vancomycin, which is an antimicrobial used in human medicine for the treatment of infections by multiresistant gram-positive bacteria such as *Enterococcus faecium*.

By the late 1980s, vancomycin-resistant enterococci (VRE) and staphylococci had been detected in hospitals in the United Kingdom and France (Uttley *et al.*, 1988; Leclercq, 1988), despite limited use of vancomycin in human medicine. In 1993, scientists isolated VRE from food animals in the United Kingdom and in 1994, in Germany and Denmark (Klare *et al.*, 1995; Bates, Jordens and Lancet, 1993; Aarestrup, 1995). In Denmark, a limited survey of organic and conventional broiler flocks suggested that occurrence of VRE was associated with the use of avoparcin. The finding received considerable scientific and public attention and was a driving factor in initiating a stepwise phasing out of the use of AGPs in Denmark through a combination of industry initiatives and national legislation.

Initially, use of avoparcin as an AGP was banned by law in May 1995, followed by prohibition of virginiamycin as an AGP in broilers, cattle and finishing pigs in February 1998. A few months later, the pig industry voluntarily ceased use of all AGPs in finishing pigs. All use of AGPs in food-producing animals was banned by December 1999, and by 2000 there was no further documented use.

This sequence of events demonstrates that the decision and implementation of cessation took some time: farmers recognized the need for this action, but they also had to learn how to adapt to the new situation – changing feed, introducing new management practices and employing prevention, in particular of enteric diseases in weaner pigs. A combination of legislative change and close engagement between government and the production sectors was applied to ensure compliance based on an understanding of why change was necessary.

AMR is dynamic; terminating the use of avoparcin led to a rapid decline in occurrence of VRE (Figure 4). Similarly, once tylosin (an antibiotic in the macrolide group) ceased to be used for growth promotion, a significant decline in resistance was observed (Figure 4). However, tylosin continued to be used for therapy.

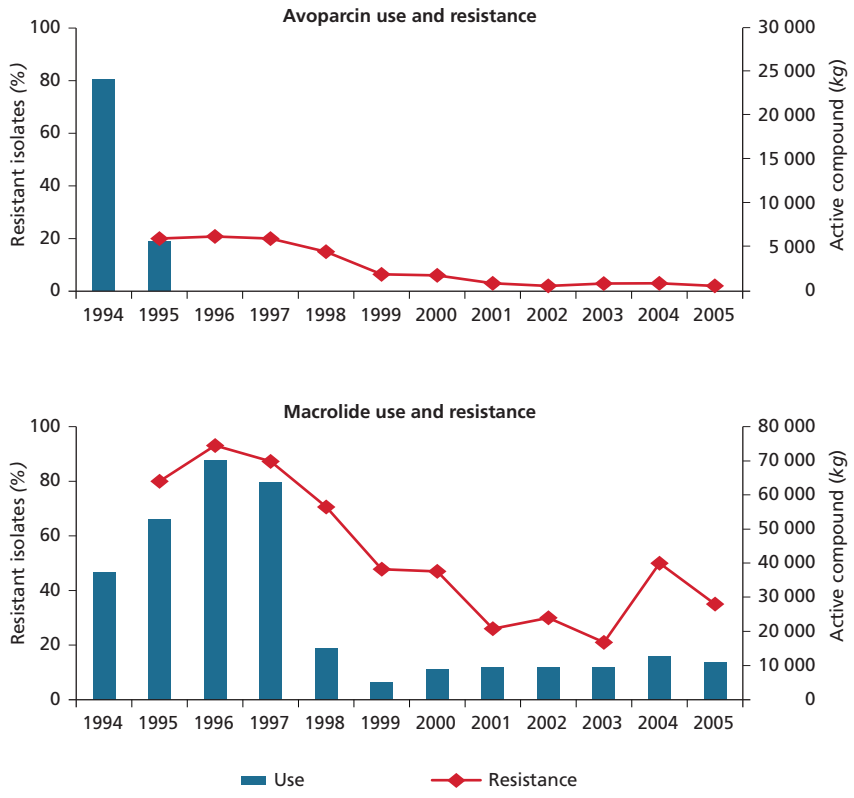
Financial and welfare effects of phasing out growth promoters

Following the voluntary ban on antimicrobial growth promoters for finishers in 1998, a study performed in finisher farms (Larsen, 2002) revealed little effect in terms of pig health and productivity; 11 percent of finisher farms reported negative effects potentially attributable to the ban. Overall, daily weight gain in weaner pigs, on the national level, decreased slightly between 1998 and 2000 (Figure 5). After 2000, the daily weight gain increased, and became stable in 2007 (Laxminarayan, Van Boeckel and Teillant, 2015).

Antimicrobial therapeutic use in Danish animal production increased from 62 tonnes to 81 tonnes between 1999 and 2000 (DTU Food and SSI, 2001) (see Figure 2). The Danish VetStat system was yet to be implemented, and

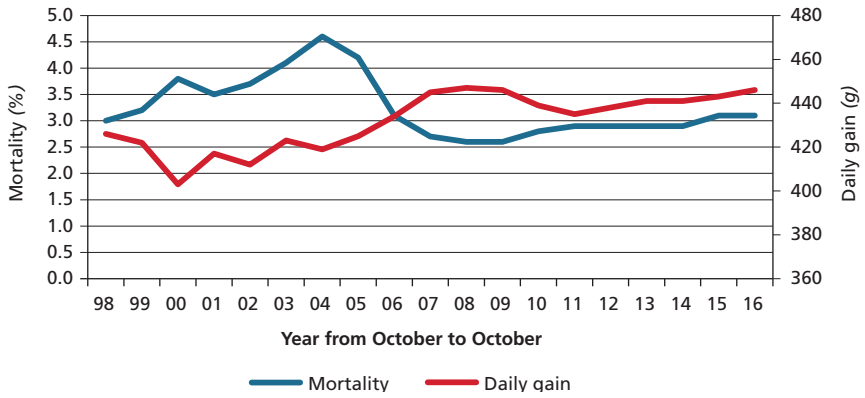
there are therefore insufficient data to attribute the increase to a specific species or age group of animals. However, in the months following the ban on AGPs, submissions to the diagnostic laboratory increased dramatically, and diagnosis of *Lawsonia* quadrupled in the fourth quarter of 1999. Observations by practising veterinarians at the time indicate that much of the

FIGURE 4. Termination of AGPs, 1994–2015



Source: DANMAP.

FIGURE 5. Effects of AGP termination on mortality and daily gain in weaner pigs, 1994–2016



Source: DAFC.

increase in antimicrobial use was for treatment of growing pigs with infections such as *Lawsonia*; it is therefore plausible that the increase was due to the termination of AGPs. However, the overall reduction in antimicrobial use achieved by phasing out AGPs was several times higher than the increase in therapeutic use.

Mortality in weaner pigs increased from 3.2 percent in October 1999 to 3.8 percent in October 2000, and average daily weight gain decreased from 422 g to 403 g in the same period (Figure 5). In subsequent years, mortality continued to increase due to the introduction in the pig population of the PCV2-related disease, post-weaning multisystemic wasting syndrome (PMWS). However, following the introduction of vaccines against PCV2, post-weaning mortality remained at approximately 3 percent (Figure 5).

From 1999 to 2000, the estimated increase in the production cost of one pig as a result of the ban on AGPs was approximately 1 percent – approximately EUR 1 (WHO, 2002). The long-term effect is difficult to estimate, due to the wide range of factors influencing productivity. Nevertheless, the heavily export-oriented Danish pig industry has remained competitive in the global market.

THE HEAVILY EXPORT-ORIENTED DANISH PIG INDUSTRY HAS REMAINED COMPETITIVE IN THE GLOBAL MARKET

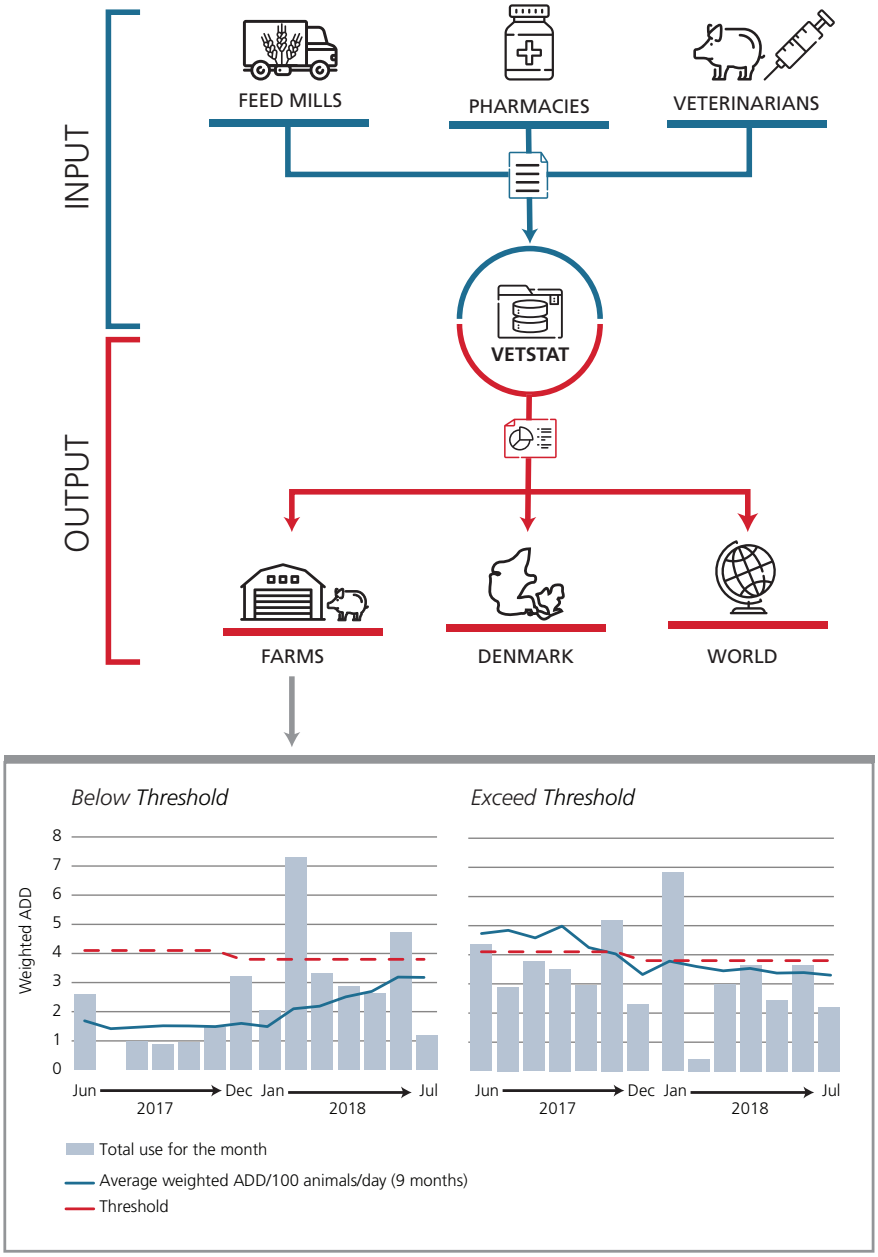
THE YELLOW CARD INITIATIVE ON ANTIBIOTICS IN THE 2010s

Between 2001 and 2009, the rise in total antimicrobial consumption in food-producing animals was in line with the increased production of pigs. This raised public awareness of the situation and the Danish Government decided that a reduction of 10 percent in antimicrobial use, relative to 2009 levels, had to be achieved by 2013. This political objective targeted pig farmers with the highest levels of consumption. At the time, more than 80 percent of antimicrobials sold for use in animals were used for pig production. The Danish Veterinary and Food Administration, therefore, called on the Danish Agriculture and Food Council and the Danish Veterinary Association to discuss possible actions to address the issue.

As a result, the Yellow Card Initiative on Antibiotics was introduced in 2010, with support from the DVA and pig industry organizations. The Yellow Card Initiative was tailor-made for the Danish context; other countries may find other solutions more appropriate. Danish VetStat data revealed wide variation in antimicrobial consumption between the different pig farms. Therefore, the Yellow Card Initiative aimed to target farms with the highest consumption of antimicrobials. The term "yellow card" comes from soccer, where a yellow card signals a warning. If a player violates the rules again while having a yellow card, a red card is issued and the player is suspended from the next match.

THE YELLOW CARD INITIATIVE AIMED TO TARGET FARMS WITH THE HIGHEST CONSUMPTION OF ANTIMICROBIALS

FIGURE 6. VetStat data input and output



Note: The graphs show two views from the database as they appear to the farmer or the veterinarian. The right graph shows a farm that has exceeded the threshold and received a yellow card; the left graph shows variation in consumption below the threshold.
Source: DVFA.

Responsibility for the VetStat database was transferred to the DVFA in 2010; VetStat became an advisory tool for veterinarians and a means for the DVFA to regulate the consumption of antimicrobials on each farm.

When the antimicrobial use thresholds set by the DVFA (Figure 6) are exceeded, the farmer receives a yellow card. If the farmer does not lower antimicrobial consumption below the thresholds within a set time frame, a red card will be issued with further legislative implications, including a mandatory

WHEN A YELLOW CARD IS ISSUED THE FARMER AND CONSULTING VETERINARIAN TAKE IMMEDIATE ACTION TO BRING ANTIMICROBIAL USE BACK BELOW THE YELLOW CARD THRESHOLD

©DVFA

reduction of the stocking density of animals (DVFA, 2018b). The system supports the reduction of antimicrobial use in pig production, and importantly, a red card has never needed to be issued. When a yellow card is received, the farmer and the consulting veterinarian take immediate action to bring antimicrobial use back below the yellow card threshold within nine months.

A study shows that following the first year of the Yellow Card Initiative, profits fell by 1 percent for farms above the yellow card threshold (Belay, 2017) as a result of the greater investments required to reduce antimicrobial use to below threshold values. Farmers above the yellow card threshold faced increased expenses for vaccines, better feed, and veterinary consultations, indicating a focus on disease prevention in farms with high use of antimicrobials (Belay, 2017).

Thanks to the Yellow Card Initiative, both farmers and veterinarians gained increased awareness of AMR and antimicrobial use, resulting in a sharp drop in antimicrobial consumption: the target of 10 percent reduction in the use of antimicrobials for food-producing animals was achieved by 2013. The new national target for 2015–2018 is a further 15 percent reduction in antimicrobial use in pigs (compared with 2014). This target was set in 2015 as part of a political action plan to reduce livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) in pigs. Each time a new national target is announced, the Danish Agriculture and Food Council supports the targets and actively helps its members – the farmers – achieve the goals.

The Yellow Card Initiative, using data from the VetStat database, has been key in allowing the authorities to meet the reduction targets. In 2016, the initiative was further developed with implementation of the "Differentiated Yellow Card Initiative", weighting the use of each antimicrobial agent according to the importance of the specific antimicrobial class in development of AMR. This formed part of the LA-MRSA action plan and was originally proposed by the DVA. The differentiated yellow card adds a multiplication factor to some antimicrobial agents. The multiplication factors are determined by the DVFA with the objective of mitigating the risk for each class of antimicrobials. They are decided based on the available knowledge of resistance development from a One Health perspective, and are intended to help achieve the targets in the LA-MRSA action plan. One target of the LA-MRSA action plan was a reduction in the use of tetracycline for pigs. To achieve this, the DVFA decided to raise the multiplication factor of tetracycline to 1.2 within the Differentiated Yellow Card Initiative. Public debate ensued about whether this was sufficient to reach the target and, consequently, the multiplication factor was further increased to 1.5 shortly after.

A concern raised by farmers and veterinarians is that decreasing antimicrobial consumption may lead to the under-treatment of animals on farms. However, the DVFA conducts annual welfare inspections at farms enabling the detection of any decrease in overall welfare resulting from tight antimicrobial laws.

Furthermore, the close relationship between veterinarians and farmers through the VASC ensures that any problems are detected at an early stage. The DVFA has observed no welfare problems arising from the Yellow Card Initiative.

The Differentiated Yellow Card Initiative has proven an effective tool for promoting prudent antimicrobial use in general and for changing the pattern of antimicrobial types used. It has been observed that when changes in the thresholds are announced, farmers adjust their consumption patterns before the first yellow cards are issued after the notice period.

REGULATION OF ANTIMICROBIALS OF LAST RESORT TO LIMIT ANTIMICROBIAL RESISTANCE

THANKS TO THE NATIONAL GUIDELINES, THE USE OF ANTIMICROBIALS HAS FALLEN DURING THE LAST FIVE YEARS

The first One Health Danish national action plan on AMR was published in 2010 (Indenrigs-og Sundhedsministeriet and Ministeriet for Fødevarer, Landbrug og Fiskeri, 2010); the Danish health authorities subsequently (in 2012) developed guidelines for use of antimicrobials in humans. The guidelines cover general recommendations on the use of antimicrobials for human treatment in primary and secondary care and underline the importance of rational use of specific antimicrobials. Fluoroquinolones, cephalosporins and carbapenems were assigned for the treatment of patients who were severely ill. Thanks to the national guidelines, combined with a general increased awareness of the need for a more rational antimicrobial policy in the human health sector, the use of these antimicrobials has fallen during the last five years, reducing the risk of development of resistance to these important medicines. The goal of the second national action plan published in 2017 is to further reduce the use of these critical antimicrobials (DMH, 2017).

In 2013, differentiated taxes on antimicrobials for veterinary use were introduced, based on a political decision. While the tax on critically important antimicrobials, such as fluoroquinolones and third- and fourth-generation cephalosporins, was increased to 11 percent, vaccines are not subject to taxation. The DVFA does not consider the taxes themselves to change the usage pattern; taxes serve to promote more prudent usage. The tax revenue is part of the budget for the veterinary regulatory authority.

The DVFA is responsible for the risk mitigation of the use of antimicrobials in pigs and other food-producing animals. Guidelines for veterinarians on the prudent use of antimicrobials were published in 2010 and revised in 2018 (see section: Organizational and governmental initiatives); much earlier, in the mid-1990s, the National Veterinary Laboratory issued similar treatment recommendations.

Fluoroquinolones

Fluoroquinolones were first registered on the market in 1991. The DANMAP reports from 2000 and 2001 revealed an increase in the use of fluoroquinolones (DTU Food and SSI, 2001, 2002). This was cause for concern and the author-

©FAO/Giulio Napolitano

ities decided to regulate usage in 2002, allowing the veterinarian to prescribe fluoroquinolone for pigs only when the need was substantiated by an antibiogram. The relevant documentation had to be forwarded to the authorities within two weeks of initiating the treatment. In 2016, the use of fluoroquinolones was further restricted through the Differentiated Yellow Card Initiative. Since the legislation was enacted in 2002, the use of fluoroquinolones has dropped from 200 kg in 2001 to almost zero (DTU Food and SSI, 2002; SSI, DTU Vet and DTU Food, 2018).

Third- and fourth-generation cephalosporins

Use of third- and fourth-generation cephalosporins increased after 2000. The risk of promoting widespread resistance to cephalosporins was discussed among scientists, authorities and the industry. In July 2010, the Danish Agriculture and Food Council (DAFC) asked practising veterinarians and farmers to terminate use of third- and fourth-generation cephalosporins in pig production. This voluntary cessation has been very effective and annual consumption is now less than 1 kg. Together with fluoroquinolones, cephalosporins were also further restricted through the Differentiated Yellow Card Initiative. Decreased use, biosecurity and good hygiene during slaughter have contributed to reducing occurrences of resistance to third- and fourth-generation cephalosporins and they are rarely found in isolates from pig meat (SSI, DTU Vet and DTU Food, 2018).

THE DANISH AGRICULTURE AND FOOD COUNCIL ASKED PRACTISING VETERINARIANS AND FARMERS TO TERMINATE USE OF THIRD- AND FOURTH-GENERATION CEPHALOSPORINS IN PIG PRODUCTION

Colistin

The overriding concern of the Danish authorities is to make sure that antimicrobials of last resort in human medicine, such as colistin, retain their efficacy. Detection of colistin resistance on a mobile element in several bacteria of animal origin was reported in 2015; this colistin resistance was found in many countries worldwide in 2016 (European Centre for Disease Prevention and Control, 2017). In 2016, the European Medicines Agency (EMA) recommended that colistin should only be used as a second-line treatment in animals (EMA, 2016). Although Denmark was well below the annual colistin-use threshold suggested by EMA, the Danish Government increased the multiplication factor for colistin in the Differentiated Yellow Card Initiative as a precautionary measure; the use of colistin for pigs has since been almost zero.

The risk mitigation of antimicrobials of last resort has been handled in various ways: direct regulation, voluntarily ban and integration in the benchmark system for pig producers.

©DVFA

4. PUBLIC CALL FOR CHANGE

Most antimicrobials used in the treatment of pigs are identical, or closely related, to antimicrobials used for therapy in humans. Use of antimicrobials in humans and food-producing animals – such as pigs – can potentially lead to development of antimicrobial-resistant bacteria as well as selection and dissemination of existing resistance traits. Resistant bacteria can spread from animals to humans, where they can lead to infections and treatment failure. Once resistant bacteria are established in the human population, the risk of dissemination through human-to-human contact increases significantly. Human-to-animal dissemination should also not be ignored. Resistant bacteria can spread across borders via international trade and travel, making AMR a global issue. The world has seen several examples of drug-resistant infections in humans, some of which are associated with resistance traits transferred from livestock. Examples include mobile ESBL- or colistin-resistance genes in *Escherichia coli*, and livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA CC398). Often these transferable resistant bacteria or resistance genes cause public concern, resulting in a raised public profile and corresponding public calls for action. In Denmark, the emergence and transmission of LA-MRSA CC398 among pigs is an example of a specific resistance trait leading to an increased focus on AMR.

RESISTANT BACTERIA CAN SPREAD ACROSS BORDERS VIA INTERNATIONAL TRADE AND TRAVEL, MAKING AMR A GLOBAL ISSUE

In Europe, LA-MRSA was detected both in livestock and in people who worked with livestock in France and the Netherlands in 2005 (Broens *et al.*, 2011; Armand-Lefevre, Ruimy and Andremont, 2005). As a result, the EU conducted a baseline study in 2008, which showed that these bacteria also occurred in low prevalence (3 percent) in Danish pig herds (European Authority, 2009). All human cases of LA-MRSA in Denmark (independent of whether detected via screening, e.g. human carrier state, or the cause of an infection) became notifiable in 2006 and the surveillance of MRSA, as reported in the annual DANMAP report, documented an increasing number of LA-MRSA cases detected in humans from 2006 to 2014 (DFVF and SSI, 2007; DTU Food and SSI, 2015). The number then stagnated, with a small decrease reported in 2017 (SSI, DTU Vet and DTU Food, 2018). In 2017, a total of 1 212 humans were either carriers or infected with LA-MRSA CC398, corresponding to 35 percent of all registered MRSA cases (SSI, DTU Vet and DTU Food, 2018).

LA-MRSA spread among pig herds is facilitated by the movement of pigs and by people visiting or working between herds. Due to increasing levels of

LA-MRSA CC398 in Danish pigs – reaching 68 percent of Danish slaughter pig herds – in 2014, the authorities established an expert panel to seek scientific advice (DVFA, 2014). The recommendations from the expert panel formed the basis for the political agreement on LA-MRSA in 2015, resulting, among other initiatives, in a reduction of the use of tetracyclines (see section: The Yellow Card Initiative on Antibiotics in the 2010s), as tetracycline use was suspected to be a driver for the prevalence of LA-MRSA. Furthermore, a target was set to reduce antimicrobial use in pigs by 15 percent by 2018.

In spite of these initiatives, the prevalence of LA-MRSA CC398 increased further to 88 percent of the slaughter pig herds tested in 2016, and there was public concern about the possible consequences. Among humans in Denmark, the number of LA-MRSA cases detected similarly increased; though many of these human cases are carriers not associated with an infection. LA-MRSA CC398 was linked to seven fatal cases between 2003 and 2017 – albeit all in patients who had other severe disease conditions. In pig production, LA-MRSA CC398 is not normally a cause for morbidity among animals and is therefore not a cause for treatment.

In 2017, the authorities established a second expert panel, where it was pointed out that LA-MRSA is one of many threats from resistant bacteria, but not the most serious (DVFA, 2017b). The mitigation of LA-MRSA in Danish pig herds, as recommended by the experts, is focused on controlling the transmission of LA-MRSA from farms rather than trying to eliminate the bacteria. This strategy of control entails containing LA-MRSA in the herds through

a focus on good hygiene practice through, for example, mandatory showering, changing of clothes, handwashing and disinfection. These are all elementary preventive biosecurity measures in contamination mitigation and may also avoid spread of other resistant bacteria.

In general, infections associated with resistant bacteria are potentially lethal for humans. Treatment may be expensive and poses an economic burden on the human health sector; AMR is thus an important focus area for government and research. LA-MRSA CC398 is a notable human health hazard and implementation of the relative risk mitigation measures represents a significant challenge. Given the One Health nature of LA-MRSA, it is vital to involve risk communication and behaviour change experts to ensure tailored messaging and hence encourage uptake of these measures.

©DVFA

5. FUTURE INITIATIVES TO LOWER ANTIMICROBIAL USE

Policies and initiatives to decrease antimicrobial use are constantly evolving. In Denmark, discovery of new resistance patterns, disease outbreaks, stakeholder opinions, and changes in public awareness or political focus drive the development of new initiatives. In 2017, as part of a broad political agreement between all the parties in parliament, it was decided to set up an Advisory Committee on Veterinary Medicines, establish new national targets for antimicrobial use and reduction, and highlight champion farms. This impartial Committee initiated its work in the autumn of 2018.

The Advisory Committee on Veterinary Medicines comprises veterinary and human medicine experts. They come from the major Danish universities, the Danish Medicines Agency, Statens Serum Institut (SSI), the Danish Veterinary Association and the DVFA. Their role involves advising the Minister of Environment and Food on veterinary issues, but – importantly – they work independently of the DVFA. One of the first issues faced by the Committee is the new national targets for antimicrobial consumption. The current national target is a 15-percent reduction in antimicrobial use for pigs by the end of 2018; new targets are needed for the coming years and the Committee will help establish these targets.

The Yellow Card Initiative targets those farms with the highest consumption. In order to encourage farms to further decrease their consumption, champion farms with low levels of use will be highlighted. The political agreement specifically states that the scheme for the champion farms must be designed by the DVFA with input from the DVA, the DAFC, Aarhus University, University of Copenhagen, animal rights organizations and the association for organic farming. The criteria for champion farms are yet to be determined.

The details of the above-mentioned initiatives are still being discussed and finalized. As in the past, stakeholders will be consulted. There are a wide range of interests to be voiced and it is not expected that everyone will be in agreement. Nevertheless, when all are seated around the same table and all voices are heard, it is easier to reach a common understanding.

WHEN ALL ARE SEATED AROUND THE SAME TABLE AND ALL VOICES ARE HEARD, IT IS EASIER TO REACH A COMMON UNDERSTANDING

©DVFA

6. KEY FACTORS FOR THE DANISH SUCCESS AND LESSONS LEARNED

KEY SUCCESS INSTRUMENTS

VetStat

Denmark has taken timely action on emerging AMR concerns. The close surveillance of the use of antimicrobials at the farm level has been – and still is – an important tool to provide a detailed understanding of antimicrobial usage, which has formed the basis for a number of interventions by stakeholders and allowed the impact of these interventions to be tracked.

Veterinary Advisory Service Contracts

Herd veterinarians have become the primary advisory experts to farmers on herd health management, animal welfare and disease prevention; the contracts have reaffirmed the value of the veterinarian–farmer relationship and focused attention on a holistic approach to livestock health and husbandry.

The Yellow Card Initiative on Antibiotics

The Yellow Card Initiative has proven to be an important and effective tool in reducing consumption in the pig sector, promoting prudent use of antimicrobials and specifically discouraging the use of certain critically important antimicrobials.

KEY SUCCESS ACTIONS

Strict biosecurity measures and the SPF system have kept Denmark free from many pig diseases and helped contain infected animals so that the spread between farms is limited. The focus on keeping diseases out of farms is the most important step to lower antimicrobial consumption.

STEPWISE PHASING OUT OF GROWTH PROMOTERS GAVE FARMERS TIME TO ADJUST

The phasing out in 2000 of AGPs in Denmark showed that it was feasible to reduce the use of antimicrobials for pigs and maintain sustained low usage in a pig industry with high productivity, with no detrimental effects on pig health or welfare and at a marginal cost to the farmer. The effects will undoubtedly differ from country to country, but one of the reasons for Denmark's success is the stepwise phasing out of AGPs over several years that gave farmers time to adjust.

Joint applied research activities in the pig industry with collaboration between universities, veterinarians and the authorities have provided new innovative solutions, where herd health management goes hand in hand with increasing productivity and competitiveness.

LESSONS LEARNED

CHANGE TAKES TIME

Change takes time. Most of the initiatives have been implemented gradually, giving farmers and veterinarians time to adjust and devise smart solutions.

Infections in pigs have remained treatable despite a reduction in overall use of antimicrobials and strong limitations on certain antimicrobials of critical importance in human medicine.

The co-creation of incentives by the collaborative efforts of the public and private sectors to meet the political targets and ultimately drive changes in mitigating the AMR threat has been hugely successful in Denmark. The well-organized Danish agricultural industry has been an important factor in achieving this success.

Denmark has strong private and public structures to aid the implementation of the above-mentioned initiatives. The proposed solutions may not be directly transferable to other countries as they may have different incentives to drive change at all levels of society. However, this short report aims to provide inspiration for reducing antimicrobial use in a collaborative way, and thereby contribute to the global battle against AMR.

REFERENCES

Aarestrup, F. 1995. Occurrence of glycopeptide resistance among *Enterococcus faecium* isolates from conventional and ecological poultry farms. *Microbial Drug Resistance*, 1(3): 255–257.

Armand-Lefevre, L., Ruimy, R. & Andremont, A. 2005. Clonal comparison of *Staphylococcus aureus* isolates from healthy pig farmers, human controls and pigs. *Emerging Infectious Diseases*, 11(5): 711–714.

Bates, J., Jordens, Z. & Lancet, S.J. 1993. Evidence for an animal origin of vancomycin-resistant enterococci. *Lancet*, 342(8869): 490–491.

Belay, D. 2017. *Economics of information and incentives in regulation of market failure: Information disclosure, impact evaluation, market design, antibiotics and commodity markets.* Department of Food and Resource Economics, Faculty of Science, University of Copenhagen. (PhD report)

Broens E.M., Graat E.A., Van der Wolf P.J., Van de Giessen, A.W. & De Jong, M.C. 2011. Prevalence and risk factor analysis of livestock associated MRSA-positive pig herds in the Netherlands. *Preventive Veterinary Medicine*, 102(1): 41–49.

DAFC. 2018a. *Statistik 2017: Grisekød* (*Statistics 2017: Pigmeat*). Copenhagen. (in Danish)

DAFC. 2018b. *Fakta Om Erhvervet 2017: Fødevareklyngen Har Kurs Mod Fremtiden* (*Facts and figures 2017, the food cluster is heading for the future*). Copenhagen. (in Danish)

DAFC. 2018c. *SPF system Denmark, CHR lookup.* [Cited 20 October 2018]. http://spfsus.dk/en

DANMAP. 2018. Collection of all published DANMAP reports. [Cited 20 October 2018]. https://www.danmap.org/Downloads.aspx

Danish Institute for Food and Veterinary Research (DFVF) & Statens Serum Institut (SSI). 2007. *DANMAP 2006 – Use of antimicrobial agents and occurrence if antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. (also available at https://www.danmap.org/Downloads.aspx).

Danish Ministry of Health (DMH). 2017. *National handlingsplan for antibiotika til mennesker.* (*National action plan for human antibiotics*). Copenhagen. (also available at https://www.sum.dk/~/media/Filer%20-%20Publikationer_i_pdf/2017/Antibiotika-handlingsplan-fremmod-2020/DK-Handlingsplan-05072017.pdf). (in Danish)

DMH & MEFD. 2017. *One health strategy against antibiotic resistance.* (also available at http://extwprlegs1.fao.org/docs/pdf/den171513.pdf).

DTU Food & SSI. 2001. *DANMAP 2000 – Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans.* (also available at https://www.danmap.org/Downloads.aspx).

DTU Food & SSI. 2002. *DANMAP 2001 – Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark.* (also available at https://www.danmap.org/Downloads.aspx).

DTU Food & SSI. 2015. *DANMAP 2014 – Use of antimicrobial agents and occurrence if antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. (also available at https://www.danmap.org/Downloads.aspx).

DVFA. 2014. *MRSA risk assessment: Prepared by the MRSA expert group.* Glostrup, Denmark.

DVFA. 2017a. *Fødevarestyrelsens Handlingsplan Mod Antibiotikaresistens.* (*The Danish Veterinary and Food Administration's action plan against antibiotics resistance*). (also available at https://www.foedevarestyrelsen.dk/SiteCollectionDocuments/Kommunikation%20og%20Kunderaadgivning/Om%20F%C3%B8devarestyrelsen/Handlingsplan.pdf). (in Danish)

DVFA. 2017b. *MRSA risiko og håndtering. Rapport ved MRSA-ekspertgruppen.* (*MRSA risk and handling. Report by MRSA Expert Group*). Glostrup, Denmark. (in Danish)

DVFA. 2018a. *Guideline for prescribing antimicrobial for pigs.* (also available at https://www.foedevarestyrelsen.dk/SiteCollectionDocuments/Dyrevelfaerd%20og%20veterinaermedicin/Veterinærmedicin/Antibiotika/FVST_Antibiotikavejledning_april_2018_4sidet.pdf). (in Danish)

DVFA. 2018b. *The yellow card initiative on antibiotics* [online]. Glostrup, Denmark. [Cited 22 October 2018]. https://www.foedevarestyrelsen.dk/english/Animal/AnimalHealth/Pages/The-Yellow-Card-Initiative-on-Antibiotics.aspx

EMA. 2016. *Udpated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health.* EMA/CVMP/CHMP/231573/2016. London.

EMA. 2017a. *Sales of veterinary antimicrobial agents in 30 European countries in 2015.* Seventh European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) Report. EMA/184855/2017. London. (also available at https://www.ema.europa.eu/documents/report/seventh-esvac-report-sales-veterinary-antimicrobial-agents-30-european-countries-2015_en.pdf).

EMA. 2017b. *Questions and answers on veterinary medicinal product containing zinc oxide to be administered orally to food-producing species.* EMA/394961/2017. London. (also available at https://www.ema.europa.eu/documents/referral/zinc-oxide-article-35-referral-questions-answers-veterinary-medicinal-products-containing-zinc-oxide_en.pdf).

European Authority. 2009. Analysis of the baseline survey on the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in holdings with breeding pigs. *EFSA Journal*, 7(11): 1376.

European Centre for Disease Prevention and Control. 2017. *Surveillance of antimicrobial resistance in Europe 2016. Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net).* Stockholm, ECDC.

European Commission. 2005. *Ban on antibiotics as growth promoters in animal feed enters into effect.* Press Release Database, IP/05/1687. Brussels. [Cited 20 October 2018]. http://europa.eu/rapid/press-release_IP-05-1687_en.htm

European Commission. 2018. *Residues of veterinary medicinal products.* [Cited 20 October 2018]. https://ec.europa.eu/food/safety/chemical_safety/vet_med_residues_en

European Union Law. 1996. Council Directive 96/23/EC of 29 April 1996.

FAO. 2011. *One Health: Food and Agriculture Organization of the United Nations Strategic Action Plan.* Rome. (also available at http://www.fao.org/docrep/014/al868e/al868e00.pdf).

FAO. 2016a. *Drivers, dynamics and epidemiology of antimicrobial resistance in animal production.* Rome. (also available at http://www.fao.org/3/a-i6209e.pdf).

FAO. 2016b. *The FAO action plan on antimicrobial resistance 2016–2020.* Rome. (also available at http://www.fao.org/3/a-i5996e.pdf).

Filippitzi, M.E., Brinch Kruse, A., Postma, M., Sarrazin, S., Maes, D., Alban, L., Nielsen, L.R. & Dewulf, J. 2017. Review of transmission routes of 24 infectious diseases preventable by biosecurity measures and comparison of the implementation of these measures in pig herds in six European countries. *Transboundary and Emerging Diseases,* 65(2). (also available at https://doi.org/10.1111/tbed.12758).

Indenrigs- og Sundhedsministeriet & Ministeriet for Fødevarer, Landbrug og Fiskeri. 2010. *Fælles antibiotika- og resistenshandlingsplan.* (*Joint antibiotic and resistance action plan*). (also available at https://www.sum.dk/Aktuelt/Nyheder/Sundhedspolitik/2010/Maj/~/media/Filer%20-%20dokumenter/Antibiotikaresistens/Handlingsplan_mod_antibiotikaresistens.ashx). (in Danish)

Klare, I., Heier, H., Claus, H., Reissbrodt, R. & Witte, W. 1995. *VanA*-mediated high-level glycopeptide resistance in *Enterococcus faecium* from animal husbandry. *FEMS Microbiology Letters*, 125(2–3): 165–171. (also available at https://academic.oup.com/femsle/article/125/2-3/165/537045).

Larsen, P.B. 2002. *Consequences of termination of AGP use for pig health and usage of antimicrobials for therapy and prophylaxis.* Working Paper for WHO Report 10, pp. 68–71. Copenhagen, Danish Institute for Food and Veterinary Research.

Laxminarayan, R., Van Boeckel, T. & Teillant, A. 2015. *The economic costs of withdrawing antimicrobial growth promoters from the livestock sector.* OECD Food, Agriculture and Fisheries Papers, No. 78. OECD Publishing. (also available at http://dx.doi.org/10.1787/5js64kst5wvl-en).

Leclercq, R., Derlot, E., Duval, J. & Courvalin, P. 1988. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. *New England Journal of Medicine*, 319(3): 157–161.

MEFD. 2017a. *Animal health in Denmark 2016*. 1st ed. Glostrup, Denmark, Danish Veterinary and Food Administration. (also available at https://www.foedevarestyrelsen.dk/Publikationer/Alle%20publikationer/Animal%20Health%20in%20Denmark%202016.pdf).

MEFD. 2017b. *Bekendtgørelse Om Salmonella Hos Svin.* (*Executive Order on* Salmonella *in pigs*). BEK No. 604, 1 June 2017. (in Danish)

MEFD. 2017c. *Konsumægsbekendtgørelsen.* (*Executive Order on table egg production*). BEK No. 1413, 4 December 2017. (in Danish)

MEFD. 2017d. *Kvægbekendtgørelsen.* (*Executive Order on cattle*). BEK No. 1326, 29 November 2017. (in Danish)

MEFD. 2017e. *Rugeægsbekendtgørelsen.* (*Executive Order on hatching egg*). BEK No. 1355, 29 November 2017. (in Danish)

MEFD. 2017f. *Slagtefjerkræbekendtgørelsen.* (*Executive Order on slaughter poultry*). BEK No. 77, 20 January 2017. (in Danish)

Ministry of Environment and Food of Denmark – Environmental Protection Agency (MEFD–EPA). 2017. *Overview of the Danish regulation of nutrients in agriculture & the Danish nitrates action programme.* Copenhagen (also available at https://eng.mst.dk/media/186211/overview-of-the-danish-regulation-of-nutrients-in-agriculture-the-danish-nitrates-action-programme.pdf).

Ministeriet for Fødevarer, Landbrug og Fiskeri. 1997. *Rapport om forbedring af sundhedstilstanden i danske husdyrsbesætninger og om reduktion af forbruget af antibiotika og antimikrobielle vækstfremmere.* (*Report on improving health status in Danish livestock determinations and reducing consumption of antibiotics and antimicrobial growth promoters*). Copenhagen. (in Danish)

OIE. 2015. *OIE list of antimicrobial agents of veterinary importance.* Paris.

OIE. 2018a. *List of FMD free Member Countries.* [Cited 20 October 2018]. http://www.oie.int/en/animal-health-in-the-world/official-disease-status/fmd/list-of-fmd-free-members/

OIE. 2018b. List of CSF free Member Countries. [Cited 20 October 2018]. http://www.oie.int/animal-health-in-the-world/official-disease-status/classical-swine-fever/list-of-csf-free-member-countries/

Pig Research Centre. 2018. *Zoonotic biosecurity*. Copenhagen, Danish Agriculture and Food Council. [Cited 20 October 2018]. http://www.pigresearchcentre.dk/Pig%20Production/MRSA/Entry%20room.aspx

Postma, M., Backhans, A., Collineau, L., Loesken, S., Sjölund, M., Belloc, C., Emanuelson, U., Grosse Beilage, E., Stärk, K.D. & Dewulf, J. 2016. The biosecurity status and its associations with production and management characteristics in farrow-to-finish pig herds. *Animal*, 10(3): 478–489. (also available at https://www.ncbi.nlm.nih.gov/pubmed/26567800).

SSI, DTU Vet & DTU Food. 2018. *DANMAP 2017 – Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. Copenhagen. (also available at https://www.danmap.org/Downloads.aspx).

Statens Veterinære Serumlaboratorium (SVS), Veterinær- og Fødevaredirektoratet (VF) & SSI. 1998. *DANMAP 97 – Consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark.* Copenhagen. (also available at https://www.danmap.org/Downloads.aspx).

Swann, M. 1969. *Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine.* 19702204579. London, H.M. Stat. Off. 83 pp.

Uttley, A., Collins, C., Naidoo, J. & George, R. 1988. Vancomycin-resistant enterococci. *Lancet*, 1(8575–8576): 57–58.

WHO. 2002. *Impacts of antimicrobial growth promoter termination in Denmark.* Geneva. [Cited 22 October 2018]. http://www.who.int/iris/handle/10665/68357

WHO. 2015. *Global action plan on antimicrobial resistance.* Geneva. (also available at http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf).

WHO. 2017. *Critically important antimicrobials for human medicine: Ranking of antimicrobial agents for risk management of antimicrobial resistance due to non-human use.* Geneva.

This publication describes an arduous campaign to tackle the use of antimicrobials – specifically antibiotics – in the Danish swine-producing sector thanks to the collaboration between the regulatory sector within the Ministry of Environment and Food, private veterinary practitioners and swine producers. The document is a retrospective tribute to all those who had the foresight to make significant changes to ensure consumer protection – improving hygiene at primary sites, developing options for intervention, identifying sites for intervention, setting targets, restructuring the relationship between the veterinary services and farmers, and implementing changes in behaviour for greatest impact.

ISBN 978-92-5-131221-6

9 789251 312216

CA2899EN/1/01.19