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FINAL REPORT OF A FACT-FINDING MISSION
CARRIED OUT IN
DENMARK
FROM 01 FEBRUARY 2016 TO 05 FEBRUARY 2016
IN ORDER TO
GATHER INFORMATION ON THE PRUDENT USE OF ANTIMICROBIALS IN
ANIMALS

In response to information provided by the Competent Authority, any factual error noted in the draft report has been corrected.

Executive Summary

This fact-finding mission took place in Denmark from 1 to 5 February 2016 and was the first in a planned series of missions to nine Member States during 2016. The objectives of this fact-finding mission were to gather further information on the practical implementation of measures aimed at tackling the issues concerning antimicrobial resistance relating to the use of veterinary medicines and identify examples of good practice which could be helpful to other Member States in addressing this issue.

Overall, the report concludes that there are longstanding and highly developed official and voluntary (professional and industry) policies in place regarding the availability and use of antimicrobials (including the critically important antimicrobials) in animals. A noticeable factor is the limitation of dispensing of veterinary medicinal products by veterinarians to non-profit sales. The implementation of these policies is supported by detailed recording and monitoring systems and targeted control actions and sanctions for non-compliance with the official rules. There are indications that these policies have led to more prudent and reduced use of antimicrobials both in production and companion animals. Despite the multifactorial and complex epidemiology of antimicrobial resistance, detailed analysis of the data collected in Denmark (including on sales and antimicrobial resistance monitoring) has shown some impacts of these measures on the levels of antimicrobial resistance in animals, food and humans.

Various aspects of the comprehensive measures put in place in Denmark aimed at encouraging the prudent use of antimicrobials in animals and tackling the broader issue of antimicrobial resistance could serve as an illustration of potential good practices to other Member States.

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ABBREVIATIONS AND DEFINITIONS USED IN THIS REPORT

Abbreviation	Explanation
CHR	Central Husbandry Register
CIAAs	Critically important antimicrobials
DANMAP	Danish Integrated Antimicrobial Resistance Monitoring and Research Programme
DSAVA	Danish Small Animal Veterinary Association
DTU	Danish Technical University
DVFA	Danish Veterinary and Food Administration
EQS	Environmental quality standard
ESBL	Extended-spectrum β -lactamase producing organisms
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
L-MRSA	Livestock-associated methicillin-resistant <i>Staphylococcus aureus</i>
MCR-1	Plasmid-mediated colistin resistance mechanism MCR-1 gene
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MRSP	Methicillin-resistant <i>Staphylococcus pseudintermedius</i>
VetStat	The Danish system for surveillance of the use of medicines in animals

1 INTRODUCTION

This fact-finding mission, carried out in agreement with the Danish competent authorities, took place in Denmark from 1 to 5 February 2016 and was the first in a planned series of missions to nine Member States during 2016. The mission team comprising of two auditors from DG Health and Food Safety, was accompanied throughout the mission by representatives of the central competent authority, the Danish Veterinary and Food Administration (DVFA). An opening meeting was held on 1 February 2016 with the central competent authorities. At this meeting the objectives and scope of, and itinerary for, the fact-finding mission were confirmed.

2 OBJECTIVES AND SCOPE

The objectives of this fact-finding mission were to:

- a) Gather further information on the practical implementation of measures aimed at tackling the issues concerning antimicrobial resistance relating to the use of veterinary medicines.
- b) Identify examples of good practice which could be helpful to other Member States in addressing this issue.

In terms of scope, the mission team examined the regulatory framework on veterinary medicines and on medicated feed currently in place in Denmark (including for companion animals) and the implementation of existing recommendations and guidelines on the prudent use of antimicrobials in veterinary medicine – including those published by the Commission referred to in section 3. The following topics were not included in the scope of this mission: (i) the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria in certain food-producing animal populations and in food and (ii) the control of residues and contaminants and the use of veterinary medicinal products in food-producing animals. These two topics were the subject of audits in September 2015 (DG(SANTE)/2015-7383) and in June 2010 (DG(SANCO)/2010-8440), respectively.

In pursuit of these objectives, the following meetings and visits took place:

Visits / Meetings		Comments
Competent authority	Central	Opening and closing meetings with the national competent authorities
	Regional/ Local	1 Meeting with the Veterinary Task Force in one region and during on-the-spot visits to a veterinary practice and farm
Monitoring and surveillance	1	Danish Technical University Food
Veterinary Associations	2	Danish Veterinary Association, Danish Small Animal Veterinary Association
Veterinary Practice	1	Treating both farm and companion animals
Farms	1	Pig farm
Feed mill	1	Producing medicated feed for food producing animals (aquaculture)

3 MISSION RATIONALE

This fact-finding mission forms part of one of a number of initiatives included in the European Commission's action plan against the rising threats from antimicrobial resistance, and is specifically linked to actions 2 and 3 of the associated road map¹: namely to strengthen the regulatory framework on veterinary medicines and on medicated feed and to introduce recommendations for prudent use in veterinary medicine, including follow-up reports. Separate actions are foreseen under the road map concerning the prudent use of antimicrobials in human medicine.

In preparing its guidelines for the prudent use of antimicrobials in veterinary medicines (Commission Notice: 2015/C299/04 of 11 September 2015²), the Commission received information highlighting a number of measures already taken by Member States on this topic. In order to gain a more comprehensive overview of the efforts being made within the European Union (EU) to encourage the prudent use of antimicrobials in veterinary medicine, a questionnaire was sent by DG Health and Food Safety to all Member States in September 2015 and nine Member States were selected to be involved in this series of fact-finding missions. The main points from these fact-finding missions and the questionnaire responses will be presented in an overview report intended to highlight good practices and particular challenges identified in applying the prudent use of antimicrobials in veterinary medicine.

4 FINDINGS AND CONCLUSIONS

4.1 BACKGROUND

4.1.1 *Sales of antimicrobial veterinary medicinal products*

1. According to the most recent European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) report for 2013³, sales of antimicrobials, including the critically important antimicrobials (CIAs), for use in animals in Denmark are relatively low compared to other Member States. The ESVAC report attributes the relatively low sales of antimicrobials in Denmark to the strict measures taken on their distribution and use. DVFA advised the mission team that, to date, possible adverse impacts on animal health and welfare of low or reduced use of antimicrobials in animals in Denmark have not been identified.
2. In 2014, 75% of all antibiotics sold were destined for pigs, with weaning pigs accounting for 42% of the antibiotics given to pigs (approximately 19 million pigs slaughtered in Denmark during 2014 and 11 million weaners exported).

¹ http://ec.europa.eu/health/antimicrobial_resistance/docs/roadmap_amr_en.pdf

² http://ec.europa.eu/health/antimicrobial_resistance/docs/2015_prudent_use_guidelines_en.pdf OJ 11.9.2015 C 299/7 – C 299/26

³ http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/10/WC500195687.pdf

3. According to DVFA, medicated feed is largely produced only for use in aquaculture and it is not permitted to manufacture such feed on farms. For other species of farmed animals, oral powders (via feed or water) are preferred over medicated feed. In 2014, DVFA introduced new mandatory requirements concerning antibiotic treatments administered via feed and water for herds of pigs (see section 4.3.1.1).

4.1.2 *Organisations for policy development and implementation*

4. The political support for the development of policies to encourage the responsible use of antibiotics to maintain low levels of antimicrobial resistance in Denmark is reflected in the current four-year Veterinary Accord II (covering the period 2013 to 2016) between the Danish government and DVFA, which sets out priority areas of work under four different pillars. One of the pillars concerns the responsible use of antimicrobials in maintaining the low levels of antimicrobial resistance and under this, eight policy initiatives have been identified. These include further developments of existing policies in areas such as differentiated taxes for antimicrobials and adjustments to the thresholds for antimicrobial use in the pig sector as part of the 'yellow card scheme' (see section 4.3.1.1). Other areas include an action plan regarding livestock-associated methicillin-resistant *Staphylococcus aureus* (L-MRSA), follow-up of an initiative on the group treatment of pigs and a targeted reduction in the use of tetracyclines. DVFA highlighted that the latest Veterinary Accord needed to be balanced, be economically neutral and not put further administrative or economic burdens on the industry.
5. DVFA is responsible for developing and implementing the policy initiatives set out in the Veterinary Accord II, in many cases with the cooperation and involvement of the professional associations. These include the Danish Veterinary Association (90% of Danish veterinarians are members), the Danish Small Animal Veterinary Association (DSAVA), the Danish Association of the Veterinary Pharmaceutical Industry, universities and the relevant industry sectors. These professional associations and the industry sectors have also taken their own policy initiatives regarding the prudent use of antimicrobials in animals, taking into account the work being done by colleagues in other countries. In this respect, the Danish Veterinary Association has held discussions during annual meetings with its counterparts in France, Netherlands, Germany etc. and also with other relevant bodies such as the Federation of Veterinarians of Europe (see section 4.3).
6. The veterinary medicines department of the Danish Medicines Agency has a mission to secure access to safe, efficacious veterinary medicinal products of the highest quality that will not have adverse effects on public health (animal and human) or the environment. It is responsible *inter alia* for the authorisation of veterinary medicinal products, ensuring the product information is up-to-date and for the approval and inspections of feed mills producing medicated feed. The Danish Antimicrobials Council which includes human and veterinary stakeholders has been established and is addressing *inter alia* the threat posed by antimicrobial resistance.

4.2 POLICIES REGARDING THE AVAILABILITY OF ANTIMICROBIAL VETERINARY MEDICINAL PRODUCTS

4.2.1 *Authorisation, distribution and storage*

7. All 211 antimicrobial veterinary medicinal products intended for use in both food-producing animals and companion animals in Denmark are prescription-only medicines (information available at www.produktresume.dk). The Danish Medicines Agency has currently issued one special licence (for example for medicinal products intended for off-label use authorised for entry from another Member State or imported from a third country) concerning gentamicin for use in weaning pigs. The preventive treatment of animals with antimicrobials is prohibited in Denmark.
8. Since 1995, the dispensing of medicines by veterinarians for the treatment of animals under their care has been limited to non-profit sales. As part of the reasoning for introducing this rule, the competent authorities questioned whether professionals such as veterinarians whose incomes may have depended partly on the sale of antimicrobials could have been expected to consistently apply prudent use guidelines which might have limited such income. Current data show that 4% of reported sales of antimicrobial veterinary medicinal products for production animals (defined as food-producing animals and fur animals) were made by veterinarians while 94% were sold directly from pharmacies to farmers and 2% of sales relate to the production of medicated feed and use of coccidiostats in feedmills.
9. As a general rule, following a diagnosis, a private veterinary practitioner may supply or prescribe antimicrobials for further treatment of production animals to be administered by the farmer for up to 5 days. If additional treatment is needed, a follow-up visit by the veterinarian is required. For cows, the private veterinary practitioner must administer all treatments unless a 'Veterinary Advisory Service Contract' exists between the private veterinary practitioner and the farmer (see also section 4.3.1). For aquaculture, the private veterinary practitioner may either supply antimicrobials to be administered by the farmer for up to 5 days or prescribe antimicrobials to be administered by the farmer for up to 10 days.
10. Farmers are only allowed to store antimicrobials (in secure, clean and appropriate conditions) within the prescription period, unless that prescription has been renewed. Otherwise, after expiry of the prescription period the farmer is required to dispose of the antimicrobials.
11. The disposal of antimicrobials for food-producing animals, including the disposal of any unused medicated feed, is classified as healthcare risk waste in the national Guideline on Disposal of Healthcare Waste, No 4, 1998. Pharmacies are obliged to accept residues of medicines (such as antimicrobials) for destruction from consumers (not including farmers).

12. A range of differentiated taxes on antimicrobials have been applied since 2013 in order *inter alia* to promote the use of vaccines instead of antimicrobials and to discourage the use of critically important antimicrobials (CIAs). The tax rates applied are: 0% on vaccines, 0.8% on narrow-spectrum penicillins and other veterinary medicines, 5.5% on other veterinary antimicrobials and 10.8% on CIAs. The mission team was informed by DVFA that, although these taxes generate useful funds to finance activities on antimicrobial resistance, they do not appear to greatly impact on consumption or usage patterns of veterinary antimicrobials. An evaluation of the impact of these taxes and any need for their adjustment is foreseen under the current Veterinary Accord II (see point 4).
13. Veterinarians also reported to the mission team that the cascade rules concerning veterinary medicinal products set down in Articles 10 and 11 of Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products might oblige them to use an antimicrobial from a higher level in the prescribing pyramid. For example, if a microbiological test indicates bacteria susceptible to enrofloxacin (registered for veterinary use) and sulphonamides/trimethoprim (perhaps not registered for veterinary use), the rules on applying the cascade would oblige non-prudent use of these antibiotics (using enrofloxacin which is from a higher level of the prescribing pyramid).

4.2.2 *Special conditions applicable to critically important antimicrobials*

14. The Danish Medicines Agency confirmed that the product information for all veterinary medicinal products containing quinolones and/or fluoroquinolones and cefquinome and ceftiofur as active substances has been updated in line with the referral outcomes specified in Commission Decision C(2010)4684 of 1 July 2010 and Commission Implementing Decision C(2012)182 of 13 January 2012.
15. Fluoroquinolones are considered as a last resort veterinary medicine in Denmark with supporting documentation being needed to justify their use. In production animals, veterinary practitioners are only allowed to use, dispense or prescribe veterinary medicinal products containing fluoroquinolones for a maximum treatment period of five days if an antimicrobial susceptibility test carried out in a laboratory using an accredited method verifies that the agent causing the disease is not sensitive to other registered antimicrobials.
16. In case of acute illness, treatment with medicinal products containing fluoroquinolones can be initiated before the result of the antimicrobial susceptibility test is available, on the following conditions:
 - The result of an antimicrobial susceptibility test carried out in the last eight days (in a laboratory using an accredited method) from a similar case in the herd is available.
 - The antimicrobial susceptibility test verifies that the agent causing disease is not sensitive to other registered antimicrobials.

- The private veterinary practitioner can substantiate an acute illness history with high mortality in the herd.
17. The private veterinary practitioner is required to report the following information to DVFA within 14 days after finishing the fluoroquinolone treatment: date of initiation and completion of the treatment, the number of animals treated, the diagnosis and result of the test, the farm holding number and the authorisation number and signature of the veterinary practitioner.
 18. The poultry industry voluntarily ceased using certain CIAs (cephalosporins) in 2000. In 2002, official restrictions were introduced on the use of fluoroquinolones (e.g. enrofloxacin, difloxacin and marbofloxacin) in food-producing animals, with such antimicrobials only being allowed to be used if a laboratory test shows that no other antimicrobial will be effective.
 19. The Danish pig industry introduced a voluntary ban on the use of 3rd and 4th generation cephalosporins in 2010, which resulted in a dramatic fall in their use. The Danish cattle industry introduced a similar voluntary ban in 2014 resulting in a downward trend in their systemic and intramammary use in cattle. Downward trends concerning resistance to cephalosporins in *Escherichia coli* isolated from broiler meat, beef and pork have also been reported in recent years in Denmark (see section 4.2.3.1).

4.2.3 *Monitoring and surveillance on the use of antimicrobials in animals*

4.2.3.1 *Danish Integrated Antimicrobial Resistance Monitoring and Research Programme*

20. Denmark has for many years had risk management strategies in order to combat the development of antimicrobial resistance and control the use of antimicrobials, the development of which was driven by the previously high level of antimicrobials as growth promoters in the early 1990s. The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) which has been operational since 1995 is a collaborative project involving the Danish Veterinary Institute, DVFA, Danish Medicines Agency and Statens Serum Institut. Since 1997, an annual report has been produced, available on the website www.danmap.org. Its objectives are to:
 - Monitor the consumption of antimicrobials in food and animal production and in humans.
 - Monitor antimicrobial resistance in bacteria isolated from food and animals.
 - Study associations between antimicrobial consumption and antimicrobial resistance and trend analysis.
 - Identify routes of transmission of antimicrobial resistance and areas for further research.
21. Surveillance methods under DANMAP include the following:
 - Active veterinary surveillance: random sampling of herds at slaughter for broilers, pigs and cattle (including the requirements under Commission Implementing

Decision 2013/652/EU of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria), sampling of Danish and imported meat at retail, wholesale and point of entry levels and monitoring of antimicrobial use via VetStat (see section 4.2.3.2). Imports, including from other Member States, are tested in a non-discriminatory, case-by-case fashion in a similar way to domestic products.

- Passive veterinary surveillance: encompassing diagnostic submissions from veterinarians, isolates from the existing salmonella surveillance programmes in pigs, poultry and bovines and meat thereof.
 - Passive human surveillance: encompassing diagnostic submissions from doctors, recording of human antimicrobial consumption and through national projects.
22. DANMAP is considered to provide baseline data on antimicrobial resistance, record trends in antimicrobial resistance and consumption, monitor the association between the use of antimicrobial agents and the resistance level and as a tool to assess the impact of interventions at national level. The DVFA uses the DANMAP data in the planning of future activities on antimicrobial resistance, based on the trends and conclusions emerging from the annual DANMAP reports.
23. DANMAP has concluded that at the population (national) level resistance does reflect the usage of antimicrobials and differences are seen between isolates from domestic and imported products. However, many exceptions to this are also seen, for example clonal spread of resistant strains such as monophasic *salmonellae*, showing that the epidemiology of antimicrobial resistance is clearly multifactorial. In the future new approaches such as mapping the antimicrobial resistance genes of entire microbiota could be considered.
24. DANMAP has also concluded that the prudent use of antimicrobials in veterinary medicine does have an implication for human medicine, for example concerning campylobacter, extended spectrum β -lactamase (ESBL) producing genes in *E. coli* from humans and *E. coli* isolates from foods (with an overlap for a low proportion of these isolates), fluoroquinolone resistance and the continued effectiveness of penicillins in primary healthcare. Nevertheless the epidemiology of antimicrobial resistance in humans is also complex, with travel-associated cases and associations with imported foodstuffs such as ready-to-eat greens.

4.2.3.2 VetStat

25. The use of antimicrobials in production animals is recorded by DVFA in a central database called VetStat which has been in place since 2000. This data is categorised *inter alia* on the basis of individual herds, animal species and different animal age groups. According to DVFA, the sales of coccidiostats have also been recorded in VetStat since 2000.
26. The objectives of VetStat, herd level monitoring of antimicrobial agents are as follows:

- To obtain data, facilitating control of prudent use strategies and possible interventions.
 - To contribute to the clarification of the complex epidemiology of antimicrobial resistance through investigations on the relationship between the use of antibiotics and resistance.
 - To help veterinarians in their daily routine.
27. When antimicrobial veterinary medicinal products are dispensed in pharmacies, data are automatically captured on the identification numbers of the prescribing veterinarian, the destination farm, the quantity of products prescribed and, the target animal species, age group, relevant disease code category and date of supply of the medicine, and these data are transferred to VetStat. Data on antibiotics used by veterinary practitioners are also captured automatically during the billing process and are transferred electronically to VetStat. The mission team was informed by DVFA that the use in animals of antimicrobial medicines authorised for humans would also be captured in VetStat. Even if small animal veterinary practices do not use VetStat, such medicines would still be supplied by pharmacies and so recorded in VetStat, although it could not be distinguished whether the medicine was used in a horse, dog, cat etc.
 28. The automated data capture features of the VetStat system have been designed to avoid any additional work or costs for the prescribing veterinarian or supplying pharmacy. The Danish government funded the original system design and implementation costs and the system is closely interlinked with the national cattle identification database. VetStat also provides the basis for national data for Denmark supplied to the ESVAC project.
 29. An official database of all veterinary practitioners is in place (VetReg) which is linked to a database of all herds in Denmark (Central Husbandry Register (CHR)) and also to VetStat. Age-group dependent benchmark values on the use of antimicrobials are established from VetStat data for pigs and cattle. Although small animal veterinarians and horses are not specifically included as categories in the VetStat database, it is possible to estimate the levels of antimicrobial use in companion animals (see point 27).
 30. VetStat also benefits from detailed information on all farms being present in the CHR: including unique farm identification numbers, details on the numbers of animals/ pens, the type of farm (layers, broilers or breeders in the case of poultry, dairy or beef for cattle), identification details for the owner and attending veterinary practitioner and records of individual animal movements for cattle farms and herd movements for pig farms.
 31. VetStat is used by the authorities for crude monitoring (use or no use of antimicrobials on farms), risk modelling, risk-based controls, preparation of inspections and follow-up to examine the impact of various initiatives taken. It is also used to monitor developments over successive years, to identify trends. Associated national action plans have been developed for pigs in 2005, for all food animals in 2007 and the yellow card system for pigs was developed in 2010. VetStat also enables the prescribing patterns of

veterinarians and their actual use of antibiotics in relation to guidelines currently in place to be compared, as well as facilitating audits and supervision of selected veterinarians and selected farms taking into account the yellow card system. Thresholds for the use of antimicrobials on cattle farms (two separate thresholds currently for cows, calves and young cattle) have been introduced in 2014 (see section 4.3).

32. VetStat also allows farmers and veterinarians to compare their use of antimicrobials in a standardised and objective way to general use patterns across the industry, and whether adaptations in feed, housing, stocking density or other animal husbandry factors might allow their use of antimicrobials to be reduced. Data regarding use of antimicrobials on a farm are presented as monthly figures and a rolling nine monthly average figure, and comparisons with regional and national average use patterns are also possible.
33. The Danish authorities noted that VetStat is heavily dependent on certain IT infrastructure and so this model might not be readily replicated in other Member States. The ability to monitor sales in this way is facilitated by the fact that most antimicrobials are distributed via pharmacies and in addition, veterinarians have little economic incentive for over-prescribing antimicrobial veterinary medicines.

Conclusions on policies regarding the availability of antimicrobial veterinary medicinal products

34. The comprehensive official rules and industry policies on the availability of antimicrobials (including CIAs) for animals and the detailed recording and monitoring systems in place provide a sound foundation for the implementation of policies and targeted control actions to further encourage their prudent use. Despite the multifactorial and complex epidemiology of antimicrobial resistance, detailed analysis of the data collected in Denmark (including on sales and antimicrobial resistance monitoring) has shown some impacts of these measures on the levels of antimicrobial resistance in animals, food and humans.

4.3 POLICIES AND CONTROL ACTIONS ON THE USE OF ANTIMICROBIALS IN ANIMALS

4.3.1 Policies for production animals

35. Official guidelines on the use of antimicrobial agents in pigs and cattle have been available since 1996 in Denmark. Initially, guidelines were developed by the National Veterinary Laboratory (currently the National Veterinary Institute DTU). Since 2005, the guidelines have been updated by DVFA in collaboration with the National Veterinary Institute DTU, National Food Institute DTU, the Danish Veterinary Association, university experts, the Danish Association of the Veterinary Pharmaceutical Industry and the Danish Agriculture and Food Council. The latest update was in 2013. These guidelines provide specific recommendations on the prudent use of antimicrobial agents for the treatment of all common indications in major production animal species. It was highlighted by DVFA that industry stakeholders are

involved in the preparation of all action plans and veterinary agreements on topics such as antimicrobial resistance and the prudent use of antimicrobials.

36. In 2010, a Veterinary Advisory Service Contract was made mandatory for large herds of pigs and cattle through which farmers are encouraged to have a much closer working relationship with their veterinarians and to work more on preventive medicine. The imposition of these arrangements was estimated to offset any loss of income of veterinarians resulting from the prohibition of profiting from the sale of medicines (see section 4.2.1) as well as promoting a higher standard of professional conduct in the veterinary profession.
37. The contracts require regular visits by the veterinarian to the farm, with the focus on advising and preventing illness rather than only treatment, improving the standard of animal health, minimising the risk of infectious diseases occurring, optimising the use of antibiotics to prevent resistance and improving animal welfare.
38. The mission team was informed by DVFA that such contracts have also been introduced for fur farming (principally for animal welfare reasons). They have not been introduced for poultry farms since the use of veterinary medicines is generally low and the industry did not request such a scheme to be applied.
39. Farmers must attend a course on the use of medicines for production animals before they are allowed to administer medicines, including antimicrobials. The aim of the course is for the participants to obtain theoretical and practical knowledge on the safe management of medicines and to obtain basic knowledge of the relevant legislation. The course, which lasts approximately eight hours, must be approved by DVFA. Guidelines for the course are publicly available. An industry guideline for all farmers has also been developed and approved by the authorities in 2010 which provides guidance for documentation, usage, storage and disposal of medicines.
40. The Danish Association of the Veterinary Pharmaceutical Industry has provided a booklet made with the objective to give animal holders simple and clear advice on the correct use of veterinary medicinal products. This association also provides product user information on veterinary medicinal products marketed in Denmark and information on disinfectants and poisons. This guidance is provided in the form of a booklet, a website and a mobile phone app. A catalogue is based on the product summaries of product characteristics and has the objective to ensure the most appropriate choice and use of veterinary medicinal products.
41. The pig industry published in 2011 a guideline for the responsible use of antimicrobials.
42. Research on relevant topics such as alternatives to antimicrobials, reduction in herd usage and links to animal welfare are currently being funded nationally in Denmark.
43. Current and future initiatives for production animals include revising the existing best practice guideline for the treatment of pigs (including input from the medical profession, veterinarians, farmers, the pharmaceutical industry and scientific experts), examining the

use of zinc oxide in pigs (regarding the potential environmental impact, links to MRSA and co-resistance), developing a differentiated yellow card scheme (creating incentives to move further towards prudent use) and evaluating the existing rules on the group treatment of pigs. For cattle potential areas include the development of different thresholds for antibiotic use in the cattle sector (a new threshold for slaughter/ veal calves because of differences between types of production). More generally, studying the use of colistin and associated plasmid-mediated colistin resistance mechanism MCR-1 gene (MCR-1) human resistance and, due to cross-resistance with MRSA, potentially phasing out the use of tetracyclines and switching their associated use to other antimicrobials is also being considered.

44. DVFA are currently examining the issue surrounding possible illegal import of antibiotics for use in production animals, amidst a concern that initiatives to limit use especially in the pig sector could result in excessive pressure on farmers to reduce use and drive individuals towards the illegal import of medicines instead. The mission team was informed by DVFA that approximately ten cases of illegal medicines on farms have been identified by the Veterinary Task Force over the last 10 years, generally involving small quantities of medicines.
45. As well as being regulated under Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to veterinary medicinal products and Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency), the use of medicines including antibiotics in aquaculture is also regulated under environmental legislation, specifically the Water Framework Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy and Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council.
46. In this context, medicines such as antibiotics are considered as substances which can pollute water body areas and Member States can implement quality standards to ensure that emissions do not exceed permitted limits in the receiving water body areas. The establishment of environmental quality standards (EQS) is implemented in Danish legislation through Order number 1070 of 9 September 2015, also taking into account the risk of antimicrobial resistance developing in environmental bacteria.
47. An official Guidance Document No. 27 Technical Guidance for Deriving Environmental Quality Standards is available under the Common Implementation Strategy for the Water Framework Directive (2000/60/EC), Technical Report 2011-055. Up to four standards are established per substance to protect against acute and chronic effects in

both fresh and salt water. Taking florfenicol as an example the following EQS are applied in Denmark: 9 µg/l for chronic fresh water, 0.42 µg/l for chronic marine waters, 21 µg/l in acute fresh water and 1.3 µg/l in acute marine waters.

48. Effluent time is defined as the time from when the effluent starts until 90% of the substance has been removed. For florfenicol the effluent time has been set as 21 days for a treatment of 10 days and an effluent value of 61% of the active substance (compared to the amount of active substance administered to the fish) has been calculated and set out in Order No 130 of 8 February 2012.
49. As a result, and in order not to exceed the permitted limits, each Danish aquaculture farm has in practice an upper threshold of the quantity of fish which can be treated at any given time.

4.3.1.1 *Specific policies for the pig sector*

50. The yellow card scheme was introduced in 2010 to identify those farms using higher levels of antimicrobials and to target actions to those, consequently having the highest potential impact on reducing antimicrobial resistance. Age-group dependent benchmark values were established from VetStat data for pigs and the threshold levels for antibiotic use, before incurring a yellow card, have been gradually reduced over succeeding years.
51. Pig farms exceeding threshold levels of antimicrobial use are liable to a yellow card which results in a request to reduce the use of antibiotics within nine months, limitations in re-prescription of antibiotics for use in feed or water, an unannounced official inspection with associated fee, a higher risk of being selected for routine official inspections and relegation of the farm to 'non-compliant status' which results in shorter prescription periods applying and more visits by the private veterinarian being required.
52. The farmer is entitled to appeal and request a hearing before any of the sanctions under the yellow card scheme are imposed. In the vast majority of cases sufficient justification for exceeding the thresholds was given and no yellow card was issued (in the period 2012 to 2015 a total of 188 yellow cards were issued following the examination of 2 078 cases). The most common reasons for such appeals being successful include: errors in the data reported to VetStat (keying in incorrect codes, farm number or animal age group), errors in the delivery of medicines to the farm (incorrect medicine or quantity), the farmers not updating the numbers of animals and animal age groups in the CHR, specific disease problems occurring on the farm (e.g. acute *Actinobacillus pleuropneumoniae* infection in pigs) or personal circumstances (family issues etc.).
53. In June 2014, DVFA introduced legislation on the treatment of pig herds, with the objective of obliging veterinarians to choose the most effective treatment and thereby reducing the use of antibiotics in pigs in order to maintain the low level of antimicrobial resistance in Denmark. These new legislative requirements only apply to veterinarians and pig farmers with Veterinary Advisory Service Contracts (i.e. for large herds). When veterinarians prescribe antibiotic treatments for respiratory or gastrointestinal infections

for administration through feed or water the veterinarians must, in order to verify their clinical diagnosis, take samples for laboratory testing.

54. The samples must be submitted to a laboratory approved by the DVFA and if the test results show that the treatment initiated is not optimal the veterinarian must re-evaluate and correct the treatment as necessary. If the laboratory tests are inconclusive the veterinarian must take samples for additional testing according to relevant laboratory guidelines.
55. Following the initial laboratory test, and regardless of the results, the veterinarian must submit further samples to the laboratory for verification, with the intervals for re-sampling depending on the compliance category of the particular Veterinary Advisory Service Contract in place on that farm. The prescription period for antimicrobials for the treatment of groups of pigs is also shortened in such cases. For most farms one sample per year is sufficient, although this depends on the status of the Veterinary Advisory Service Contract in place.
56. Since veterinarians may only prescribe veterinary medicinal products in connection with a visit to a farm, the veterinarian must consequently visit the farm repeatedly if there is a need for continued use of medication for group treatment of pigs on that farm.
57. During 2014, the pig industry set a target of reducing the use of tetracyclines by 50% by the end of 2015. In 2015, DVFA set a new target for a further 15% reduction in the use of antimicrobials in pigs from 2014 to 2018. From 2010 to date, there has been a 17% reduction in the use of these medicines in pigs and the target of a 10% reduction of antibiotics used in farmed animals from 2009 to 2013 was met.
58. The use of 2 500 ppm zinc oxide in feed for pigs in the first 14 days after weaning is permitted in Denmark, thus reducing the need for the use of antimicrobials during this period.
59. In the veterinary practice visited, the mission team was informed that on occasions the yellow card system may also have unintended effects, such as having to wait to treat pigs if the farmer is close to exceeding the permitted threshold value in order to avoid the consequent penalties. This may be especially a problem with heavier pigs when a greater quantity of medicine would be needed for their treatment. While the veterinarian interviewed accepted that the rules need to be strict and farms treated equally, it was stated that individual farm-to-farm variations and assessments should also ideally be taken into account. They also considered that there may be a risk that a drive towards a continued progressive reduction in antimicrobial use from the existing low levels in Denmark may be more politically desirable rather than always professionally or scientifically justified.

4.3.1.2 *Specific policies for the cattle sector*

60. A similar approach to the yellow card scheme for pigs has also been implemented in the cattle sector, based on age-group dependent benchmark values established from VetStat

data and threshold levels for antimicrobial use. The consequences of exceeding the thresholds for antimicrobial use in cattle farms are less onerous than in pigs. The cattle farms are classified as being of 'non-compliant status' which results in more visits by the private veterinarian being required with the aim of addressing any animal health issues on the farm and reducing associated antimicrobial use.

61. In 2014 and 2015, the examination of cases where cattle farms had exceeded the thresholds for antimicrobial use resulted in approximately 56% (490 farms out of a total of 870 cases) of them being relegated to non-compliant status.
62. In 2010, the Danish cattle industry introduced restrictions on the use of broad-spectrum antibiotics for the treatment of mastitis in cows. Only simple penicillins are allowed for the treatment of mastitis unless a laboratory test shows that these will not be effective. The use of antibiotics for dry cow treatment is only permitted if within the last 35 days an indication has been found that the pathogen is present in at least one mammary gland quarter of the cow.
63. In September 2013, the Danish Veterinary Association published guidelines it has developed on good antibiotic practice for cattle veterinarians. During 2014, the dairy and cattle industry set a further target of a 20% reduction in the overall usage of antimicrobials in their sectors from 2012 to 2018.

4.3.2 *Policies for companion animals*

64. DSAVA has developed guidelines on good antibiotic practice for small animal veterinarians which were published in November 2012. The guideline also exists as a mobile phone app. The guidelines were welcomed by DVFA and considered proactive due to increasing levels of antimicrobial resistance (both in humans and animals), multidrug resistant bacteria such as methicillin-resistant *Staphylococcus pseudintermedius* (MRSP), ESBL producing organisms and MRSA being detected in dogs and cats throughout Europe and no development of new antibiotics for use in animals. Leaflets for pet owners have also been developed on topics such as antibiotics, ESBL and MRSP.
65. Existing guidelines from Sweden, produced in 2002 and revised in 2009, were used as an inspiration for the development of these guidelines for small animal veterinarians, as well as existing guidelines for human medicine. The objectives were *inter alia* to update practising veterinarians, promote bacterial diagnostics and enhance knowledge concerning resistance patterns in small animals in Denmark. The guidelines were developed involving experts involved in academia, teaching and research, with editing input from a microbiologist. A prescribing pyramid was developed, with veterinarians encouraged to use antimicrobials from the bottom of the pyramid such as penicillins and avoiding the use of those at the top of the pyramid (carbapenems, linezolid and vancomycin).
66. The guidelines cover general principles on the prudent use of antibiotics, VetStat data reported in DANMAP on yearly consumption of antibiotics, multi-resistance,

diagnostics and interpretation of results, the peri-operative use of antibiotics, disease-specific recommendations and the handling and disposal of antibiotics, including instructions for pet owners.

67. A follow-up survey of veterinarians found that only 6% stated that they did not use the guidelines, 56% performed more microbial diagnostics as a result of the guidelines and 44% used less perioperative antibiotics. Decreases have also been reported in the quantities of cephalosporins and fluoroquinolones used (almost half of all fluoroquinolones used in Denmark are used in small animal practices).
68. The Danish Veterinary Association has produced guidelines on good antimicrobial practice for horse veterinarians. The guidelines also exist as a mobile phone app which was presented at a recent meeting of the Federation of European Equine Veterinary Associations.

4.3.3 *Control actions*

69. DVFA performs a variety of control actions on farms, veterinary practices etc. concerning the use of medicines. It was emphasised that the guidelines developed by the industry and professional bodies are voluntary and there are no penalties for not respecting these guidelines, although DVFA does take them into consideration when performing control visits. These types of controls performed by DVFA include the following:
 - Zero point controls: random controls to get a reference level of non-compliances on farms and in veterinary practices, the sector and animal species to be targeted. The focus of these varies each year.
 - Prioritised controls: farms and veterinary practices etc. chosen on the basis of risk criteria identified each year, such as use of medicines, herd mortality data, results of previous controls, emerging trends and new rules in place, etc.
 - Veterinary inspection campaigns: concerning areas needing specific focus chosen primarily on a risk basis. During 2015, 10 veterinary inspection campaigns took place, covering amongst other things the herd medication of pigs and biosecurity for outdoor pigs. During 2016, a campaign is scheduled on the correct recording and use of veterinary medicines.
 - Frequency controls: frequencies decided by applicable legislation or on the basis of a risk evaluation of activities.
 - Basic controls: control of farms in relation to cross-compliance performed by the Danish Agri Fish Agency.
70. All prescriptions and the administration of antimicrobials on farms are controlled on a risk basis encompassing approximately 5% of all herds annually in Denmark. Depending on the level of use of antimicrobials at herd level, the number of mandatory herd health visits by a veterinarian and the amount of laboratory tests to perform when treating pigs with flock medication is fixed.

71. Laboratory projects are arranged on a risk basis, in conjunction with DTU, for example concerning the analysis of food of animal origin for residues of antimicrobials. Follow-up controls are scheduled when non-compliances are detected, with proportionate sanctions to be applied including the provision of guidance, issuing of warning orders, injunctions or prohibition orders, issuing of administrative fines or withdrawal of relevant approval/registration.
72. A Veterinary Task Force was established in 2003 which, *inter alia*, carries out inspections on the prescribing and use of veterinary medicinal products. This task force includes 15 veterinarians and 2 legal advisers, with the main tasks being to inspect suspected fraudulent activities in the veterinary field, where citizens deliberately break the law, typically for personal financial gain.
73. Inspections carried out by the Veterinary Task Force include *inter alia* risk-based medicine controls on veterinarians and farmers across Denmark and also based on notifications and complaints from citizens or other stakeholders. The Task Force carries out checks on the illegal import and illegal use of antimicrobials in cooperation with other authorities, monitors the consumption of antimicrobials on pig and cattle farms through the yellow card system and performs inspections in cooperation with police, tax and Board of Health authorities.
74. In 2013-2014, the Veterinary Task Force carried out checks on a total of 75 pet veterinarians including their strategy for the prescription and use of fluoroquinolones and 3rd generation cephalosporins. Of the 50 inspected during 2013, 26 received a warning, mainly for issuing incorrect invoices and 4 for selling parts of packages. Of the 25 inspected during 2014, 2 received a sanction, also related to invoicing problems. Concerning inspections during 2014, for the routine treatment of dermatitis, 32% of veterinarians indicated that they used disinfectant shampoos as their first choice of treatment, 28% amoxicillin / clavulanate and 24% lincosamides, with the applicable prudent use guidance recommending antimicrobials with a narrow spectrum of activity. Under 10% of veterinarians used CIAs on a weekly basis (compared to 20% in 2013) and almost 70% did not use perioperative antimicrobial therapy for routine surgery such as castration and ovariohysterectomy. Improvements were attributed to the publication and dissemination of guidelines for the prudent use of antibiotics in small animals and also newsletters issued to veterinarians on this subject (see section 4.3.2).
75. Another campaign during 2013 addressed the water medication of weaner pigs, with 75 farms using the highest amounts of antimicrobials in weaners being selected and 51 of these randomly chosen for inspection. The inspections included checks that the farmers were recording treatments appropriately, medicating the animals according to instructions received from the veterinarian and if the weaners were being medicated in a systematic and predictable (preventive) pattern in relation to their age, weight and arrival in the weaning area. Of the 51 inspections carried out, 27 showed deficiencies regarding medicine records (8 warnings and 19 fines issued) and 16 did not follow veterinary instructions (3 warnings and 13 fines issued, in each case the medication

period applied was too short and also sometimes for an incorrect indication or at incorrect dose). Thirty two of those inspected stated that they administered antimicrobials in a systematic predictable manner, for example, for a specific period post-weaning. DVFA stated that it was not always clear if the veterinarians had recommended such systematic treatment.

76. A further campaign in 2015 involved unannounced inspections to 73 pig farmers (focussing on medication practices, storage, dosage and administration of medicines) and announced inspections to 64 associated pig veterinarians (focussing on sampling prior to prescribing, use of laboratory diagnostics, lengths of prescription periods and action plans to reduce the use of group treatments on individual farms). Meetings with the industry, the Danish Veterinary Association and individual veterinarians and an information campaign (articles, newsletters etc.) were organised before the inspection campaign took place.
77. Sanctions were issued to 14 of the 64 veterinarians inspected (22%), on issues such as diagnostic samples not being taken, prescription periods being too long, action plans to reduce group treatments not being developed or in one case a farm not being visited before a prescription was issued. Notwithstanding this level of sanctions, it was evident that, in general, veterinarians had implemented the stricter rules concerning treatments of groups of pigs with antimicrobials, farm visits were taking place before antimicrobials were prescribed and 87% of veterinarians had taken the mandatory samples for diagnostic analysis before the treatment of gastrointestinal and/or respiratory diseases. The maximum interval for taking such samples is generally 12 months (8 or 4 months in the case of non-compliant farms).
78. Sanctions (warnings) were issued to 11 of the 73 farms visited (15%), mainly due to deficiencies in the records of veterinary treatments kept on the farms. This was a significant improvement compared to the 53% of farmers sanctioned on this point during the 2013 campaign on in-water medication. It was concluded that in the vast majority of farms inspected, treatments were applied consistently in line with the veterinarians' instructions regarding dosage and with suitable equipment and procedures in place.
79. The Danish Medicines Agency regularly inspects feedmills producing medicated feed to check they fulfil the relevant EU requirements. During a visit to such a feedmill the mission team noted that the inspections cover many aspects of good manufacturing and distribution practices and include checks that medicated feed is only produced on prescription using authorised premixtures and that it is traceable and labelled correctly. Although attention was also paid to measures put in place by the feed business operator to minimise carry-over of medicines from one batch to another and to ensure batches of medicated feed are homogenous, a number of shortcomings were noted by the inspector and mission team. In particular, the feed business operator had only carried out visual checks to verify the homogeneity of feed containing one coloured premix. However, it was not evident how these checks could be relied on to show that the range of different

(undocumented) mixing regimes followed for different size batches and types of premixes used actually result in homogenous mixtures. In addition, the reliability of the last biennial check to verify the effectiveness of measures to reduce carry-over was potentially undermined as the samples had been stored for six months in ambient temperatures prior to being analysed which could lead to the amount of carry-over being under-estimated.

Conclusions on policies and control actions on the use of antimicrobials in animals

80. There are longstanding official rules and industry guidelines to facilitate the prudent use of antimicrobials in animals including thresholds limiting their use in certain key production species. Their implementation is supported by targeted control actions and sanctions for non-compliance with the official rules. Overall, there are indications that these policies have led to reduced or more prudent use of antimicrobials in animals.

5 OVERALL CONCLUSIONS

Overall, the report concludes that there are longstanding and highly developed official and voluntary (professional and industry) policies in place regarding the availability and use of antimicrobials (including CIAs) in animals. A noticeable factor is the limitation of dispensing of veterinary medicinal products by veterinarians to non-profit sales. The implementation of these policies is supported by detailed recording and monitoring systems and targeted control actions and sanctions for non-compliance with the official rules. There are indications that these policies have led to more prudent and reduced use of antimicrobials both in production and companion animals. Despite the multifactorial and complex epidemiology of antimicrobial resistance, detailed analysis of the data collected in Denmark (including on sales and antimicrobial resistance monitoring) has shown some impacts of these measures on the levels of antimicrobial resistance in animals, food and humans.

Various aspects of the comprehensive measures put in place in Denmark aimed at encouraging the prudent use of antimicrobials in animals and tackling the broader issue of antimicrobial resistance could serve as an illustration of potential good practices to other Member States.

6 CLOSING MEETING

A closing meeting was held on 5 February 2016 with the representatives of the central competent authorities. At this meeting, main findings and preliminary conclusions of the mission were presented by the mission team. The central competent authorities did not indicate any disagreement with these.

ANNEX 1 – LEGAL REFERENCES

Legal Reference	Official Journal	Title
Dir. 2001/82/EC	OJ L 311, 28.11.2001, p. 1-66	Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products
Dec. 2013/652/EU	OJ L 303, 14.11.2013, p. 26-39	2013/652/EU: Commission Implementing Decision of 12 November 2013 on the monitoring and reporting of antimicrobial resistance in zoonotic and commensal bacteria
Reg. 726/2004	OJ L 136, 30.4.2004, p. 1-33	Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency
Dir. 2000/60/EC	OJ L 327, 22.12.2000, p. 1-73	Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy
Dir. 2008/105/EC	OJ L 348, 24.12.2008, p. 84-97	Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council
OJC 2010/295	OJ C 295, 29.10.2010, p. 1	Commission Decision of 01-07-2010 concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for veterinary medicinal products for food producing species containing quinolones and/or fluoroquinolones as active substances