4

ANTIMICROBIAL CONSUMPTION IN ANIMALS

4. Antimicrobial consumption in animals

Highlights: There has been an overall decreasing trend in the use of antimicrobials in animals since 2013 and in 2018 the use had been reduced by 14%, equivalent to almost 17 tonnes, compared with 2013. The total use of antimicrobials in animals amounted to approximately 100 tonnes in 2018.

Approximately 75% of all veterinary prescribed antimicrobials are used in the pig sector, which makes pigs the main driver of trends in antimicrobial use in animals. The export of weaner pigs continued to increase in 2018, while the number of pigs slaughtered in Denmark remained approximately at the same level. Measured in treatment intensity (DAPD), the overall use, when adjusted for export, was reduced by 4% from 24 to 23 DAPD in 2018. This means that on a given day in 2018 an estimated 2,3% of all pigs received antimicrobial treatment. In the different agegroups the use was reduced from 97 to 91 DAPD in weaner pigs, from 18 to 17 DAPD in finishers, while it remained at the same level for sows and piglets around 19 DAPD.

The types of antimicrobials used in pigs has also shifted notably. The use of tetracyclines in pigs has been reduced significantly since 2009, and in particular from 2016 to 2018, following the implementation of the differentiated "Yellow card". This initiative also resulted in a close to zero use of colistin, since the first quarter of 2017. However, the reduction in the use of tetracycline and colistin, was mirrored by clear but less marked increases in the use of macrolides and aminoglycosides, especially in weaners.

The overall use for cattle has fluctuated between 12 and 13 tonnes over the past five years. In 2018, more than two thirds were used to treat older cattle (>1 year) and approximately 500 kg were used as intramammary treatment. Measured in DAPD, the antimicrobial use for older cattle (>1 year) has decreased from 4 to 3 DAPD (-13%) over the past decade, while the use for younger cattle (<1 year) has increased from around 5 to 7 DAPD (+43%).

Antimicrobial use in poultry is relatively low (1,326 kg). Notable fluctuations may occur as a result of disease outbreaks in a few large flocks, which was the case in 2014 and 2015. However, since 2015, the use has decreased each year. In contrast, the use of antimicrobials in the aquaculture industry more than doubled (1,860 kg more) in 2018 due to the very warm summer in 2018.

From 2014 to 2017 the use of antimicrobials in fur animals (mainly mink) has increased. In 2018 the industry increased focus on prudent use and developed an action plan to reduce the use within the sector. It is likely the increased focus combined with low occurrence of disease ind 2018 resulted in the observed 40% reduction in antimicrobial use for fur animals (-2,467 kg) in 2018.

Companion animals still use more critically important antimicrobials compared with other species. Almost all fluoroquinolones and more than half of the cephalosporins used in animals are used in dogs and cats. Despite a small increase in use from 2015 to 2016, there has been an overall decreasing trend in the use of antimicrobials in dogs and cats since 2011, with a marked reduction in the use of cephalosporins.

4.1 Introduction

The DANMAP programme began monitoring the national use of antimicrobial agents in humans and animals in 1995. Since the early 1990s, there has been both political and public focus on the consumption of antimicrobial agents in the Danish animal production, which resulted in the discontinued use of antimicrobial agents for growth promotion in the years 1995-1999. The focus on antimicrobial use has continued to increase; more recent initiatives include a voluntary ban on the use of cephalosporins in the pig and cattle production, as well as regulatory legislation regarding therapeutic use.

Figure 4.1 shows the total use of antimicrobials in animals and humans since 1994 and 1997, respectively. Changes in the patterns of antimicrobial use in animals can be explained in part by an increase in pig production over the years, but risk management measures to reduce consumption have also contributed. In addition, the increasing export of pigs at 30-40 kg live weight has also affected the overall use of antimicrobials in animals.

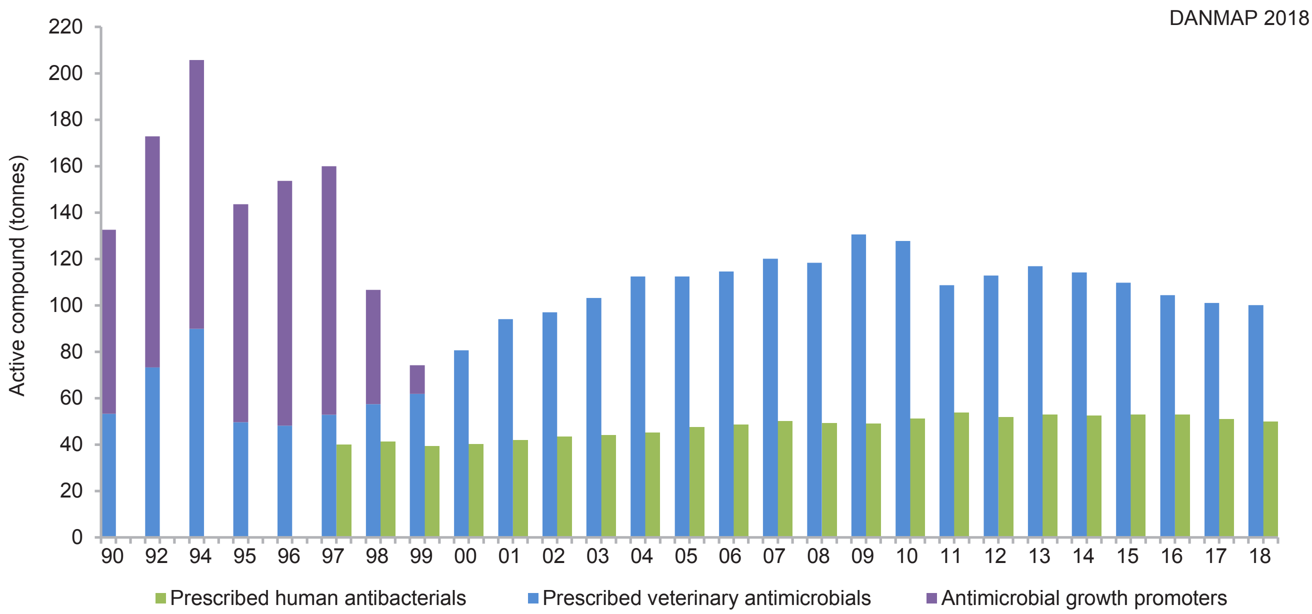
The prescription patterns for animals have clearly been influenced by risk management decisions during the period. For example, the decrease in antimicrobial consumption after 1994 was likely the result of 1) limitation of veterinary practitioners' profit from sales of medicine; 2) implementation of Veterinary Advisory Service contracts (VASCs) with regular visits from the veterinarian in order to promote preventive veterinary strategies and optimise antimicrobial use, and 3) enforcement of the so called "cascade rule" [Order (DK) 142/1993], which limits the use of (cheaper) extemporaneously produced medicines.

Other important interventions were the restriction on the use of fluoroquinolones in production animals through legislation implemented in 2002 and 2003, and the voluntary ban on the use of cephalosporins in the pig industry in 2010 followed by a similar initiative in the dairy cattle industry in 2014.

As a part of the national action plan against antimicrobial resistance, a 10% reduction of antimicrobial use in farm animals by 2014 compared to the 2009 level was set as a national target. To achieve this, the introduction of threshold values for antimicrobial use was adopted with the "Yellow Card" Initiative in 2010. This enforces legal action on pig farmers with high antimicrobial use per pig [DANMAP 2010], and as a result, a decrease in consumption was seen from 2010 to 2011. Effects from other parts of the legislation may be less obvious, but are also likely to have affected prescription patterns. As an example, the rules for group medication in pig herds were tightened in 2014, calling for thorough laboratory diagnoses and frequent veterinary visits when antimicrobials are prescribed for groups of pigs. Furthermore, in 2015 the national action plan to reduce livestock associated MRSA called for a 15% reduction in antimicrobial use in pigs from 2015 to 2018.

In 2016, the "Yellow Card" Initiative was revised, adding on multiplication factors to adjust the consumption of certain antimicrobials. Fluoroquinolones, cephalosporins and colistin (added in 2017) were given the highest multiplication factor of 10. Tetracyclines were given a multiplication factor of 1.2, which was further adjusted in 2017, to a factor of 1.5 [DANMAP 2017]. The effects of this are described in Textbox 4.1.

Figure 4.1 Prescribed antimicrobial agents for humans and all animal species, tonnes active compound, Denmark



Sources: Human therapeutics: The Danish Medicines Agency. Antimicrobials for animals: Data are based on reports from the pharmaceutical industry of total annual sales (until 2001), from the Federation of Danish pig producers and slaughterhouses (1994-1995), from the Danish Medicines Agency and Danish Plant Directorate (1996–2000) and since 2001 from VetStat. For DANMAP 2018, consumption data for 2004-2018 were extracted from VetStat on 3rd March 2019 and includes all antimicrobial agents registered for use in animals

In 2017, The Danish Ministry of Environment and Food and The Danish Ministry of Health presented a new One Health strategy against antimicrobial resistance, setting the framework for reducing the development and occurrence of AMR. At the same time, two national action plans to reduce AMR were introduced, setting specific targets to further reduce the antimicrobial use for both humans and animals in the coming years. As part of the political agreement on the veterinary strategy 2018-2021 (Veterinærforlig III), an Advisory Committee on Veterinary Medicines was established in 2018, Textbox 4.2.

Official treatment guidelines for pigs and cattle have been available since 1996. The guidelines provide specific recommendations for selection of the appropriate antimicrobial treatment of all common indications in the major production animal species. Since 2005, DVFA have updated the guidelines in collaboration with stakeholders and university experts. The guidelines were updated in 2010, when new dynamic evidence based treatment guidelines for pigs were launched [DANMAP 2010, www.fvst.dk], and were further revised in 2017 and the new version published in April 2018. In 2012, the Danish Veterinary Association published treatment guidelines to promote prudent use of antimicrobials in dogs and cats. The guidelines were prepared by clinical specialists and expert scientists from the Faculty of Health and Medical Sciences at the University of Copenhagen and DTU National Food Institute. The treatment guidelines for dogs and cats were revised in 2017 and new guidelines were published in 2018. Similarly, the Danish Veterinary Association published treatment guidelines for use of antimicrobials in horses in 2017.

Finally, in 2017 the EU Commission decided that use of medical zinc has to be phased out completely by 2022 at the latest. Medical zinc is used extensively in the pig production to prevent diarrhoea in weaner pigs.

4.1.1 Data sources

In Denmark, antimicrobials are available by prescription only, and data on antimicrobial use at product level have been collected in Denmark since 1996, including historical data back to 1990.

Since 2001, data on all medicines prescribed for use in animals, including vaccines, antimicrobial growth promoters (no longer permitted) and coccidiostatic agents (non-prescription) have been recorded in the national database VetStat. Since 2010, the VetStat database is hosted and maintained by the Danish Veterinary and Food Administration (DVFA). The data presented in this report were extracted from VetStat on 3rd of March 2019 and have been summarised for DANMAP by the National Food Institute at DTU.

4.1.2 Methods

Metrics of antimicrobial use are numerous, each with its own advantages and limitations. Therefore, the selection of metrics used for monitoring must depend on the monitoring objective and the information available.

The overall amount of antimicrobial agents is measured in kg active compound and is used in section 4.2 for the purpose of an overall crude comparison of antimicrobial use in the veterinary and human sectors (Figure 4.1).

Since 2012, we have further presented 'defined animal daily dose' (DADD) and 'proportion of population in treatment per day' (DAPD) to monitor trends in antimicrobial consumption. These metrics are defined below, and for additional information on methodology, please refer to chapter 9 and the web annex [www.Danmap.org].

DADD - Defined Animal Daily Dose.
DADD is the average maintenance dose per day for the main indication of a drug in the appropriate animal species. The DADD is not defined at product level but for each antimicrobial agent, administration route and animal species; and when appropriate age group. The DADDs have been defined specifically for use in DANMAP based on current knowledge (section 9.2) and may vary from the prescribed daily dose or the recommended dosage in the Summaries of Product Characteristics (SPC) or in the VetStat database.

DAPD - Proportion of population in treatment per day
Trends in antimicrobial usage in pigs, cattle and fur animals are presented in DAPD.

DAPD=DADD per 1,000 animals per day, where 'animals' are represented by their live biomass and adjusted for life-span. The estimated live biomass is expressed as the number of standard animals with an estimated average weight on a given day. This may also be referred to as the 'standard-animals-at-risk'. This metric allows for comparison of antimicrobial use between species with large differences in body-mass and life-span.

The estimated treatment proportion, DAPD, is a statistical measure that provides a rough estimate of the proportion of animals treated daily with a particular antimicrobial agent. For example, 10 DAPDs means that an estimated 1% of the pig population, on average, receives a certain treatment on a given day (see section 9.2). In principle, DAPD as a metric is analogous to DID (defined daily dose per 1,000 inhabitants per day), the metric used to measure antimicrobial consumption in the human sector. Please refer to section 9.8 for a description of DID. In DANMAP 2018 we calculated treatment proportions in pigs, cattle, and fur animals.

Textbox 4.1

Regulation on antimicrobial classes resulted in a shift between antimicrobial classes in pigs 2014-2018.

The 'Yellow card' initiative, with threshold values for antimicrobial use for pigs, has been in place in Denmark since 2010. In 2015, a political decision to promote a more prudent use of antimicrobials was imposed by further regulation. This included assigning weights to the different antimicrobial classes. Three levels of weights were applied in 2016 and modified in 2017: Fluoroquinolones, cephalosporins and colistin (added in 2017) were given the highest multiplication factor of 10. Tetracyclines were given a multiplication factor of 1.2, which was adjusted to a factor of 1.5 in 2017.

The use of fluoroquinolones and 3rd/4th generation cephalosporins in food animals has been negligible in Denmark for several years; therefore, in reality only the use of colistin was affected when critically important antimicrobials were weighted with a factor 10.

Tetracyclines and colistin are mostly used for gastrointestinal disorders in weaner pigs. The assignment of the differentiated weights resulted in an immediate change in usage (Figure 1a). The use of tetracycline was reduced from approximately 12 to 7 tonnes active compound from 2016 to 2018 and colistin dropped from approximately 1 ton to less than 1 kg active compound over the same period. In both cases, the use reduced in antimicrobial classes assigned with a higher factor and increased other classes assigned a lower factor. The reduction in the use of tetracyclines resulted in a marked increase in use of macrolides and the reduction in the use of colistin shifted to an increase in the use of aminoglycosides (Figure 1b).

Figure 1 shows the effect of the differentiation between antimicrobial classes. A marked reduction in the use of tetracyclines (40%) was replaced by an increased use of macrolides (35%, Figure 1a). Figure 1b illustrates the reduction and shift between colistin and aminoglycosides, mostly neomycin. Neomycin was reintroduced to the Danish market in 2017 and seems to be the preferred alternative to colistin. The almost complete phasing out of colistin caused the use of aminoglycosides to double between 2016 and 2018 (measured in kg-doses).

The regulatory intervention clearly triggered a shift between antimicrobial classes. If an important antimicrobial is restricted, it appears more likely to be replaced by another class or active substance than to result in an overall reduction in use. This is an important lesson that needs to be considered for future restrictions. The effect of the current shifts in consumption on antimicrobial resistance is not possible to predict, but will be monitored carefully for possible adverse effects in the future.

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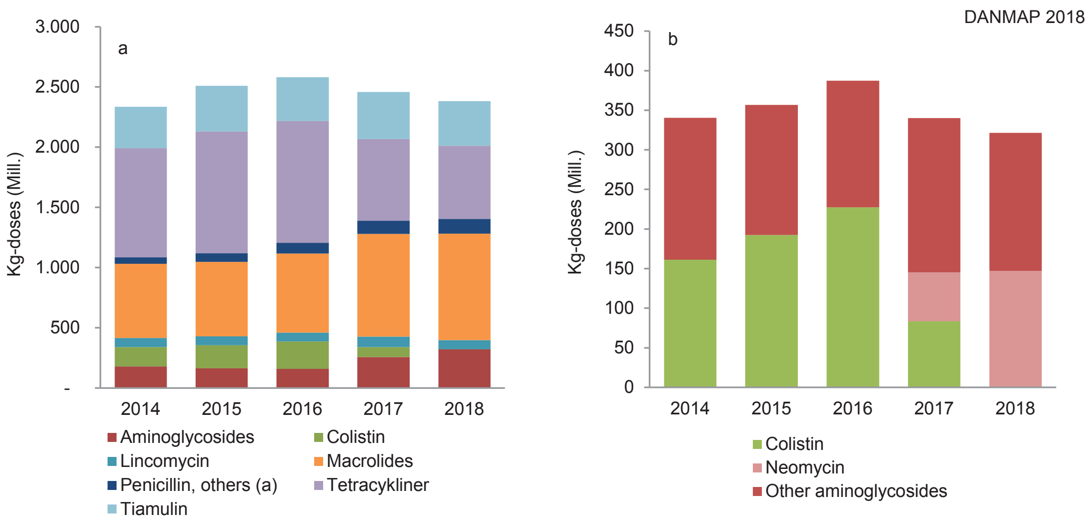
Figure 1. The most frequently used antimicrobials to treat gastrointestinal disorders in weaner pigs (a) and shift in use of colistin, neomycin and other aminoglycosides (b), million kg-doses per year



Note: A kg-dose is a standard maintenance dose per kg live animal per day for a drug used for its main indication, here based on ADDs as defined in VetStat. a) Penicillins with extended spectrum and combination penicillins, incl. b-lactamase inhibitors

4.2 Total antimicrobial consumption in animals

The total use of antimicrobial agents in all animals, amounted to 100.1 tonnes active compound, representing a 1% (808 kg) decrease compared with 2017, Figure 4.1.

In 2018, the antimicrobial use in pigs, cattle, fur animals and poultry comprised approximately 75%, 13%, 4% and 1% of the total antimicrobial consumption for animals, respectively (Figure 4.2). The pig industry is the main driver of antimicrobial usage in animals in Denmark, due to the size of the production. Cattle and pigs comprise almost equal proportions of live biomass. However, the vast proportion of cattle biomass consists of dairy cows, which have very low consumption of antimicrobial agents compared with growing animals.

Historically, the overall use of kg active compound was 51% lower in 2018 compared with 1994. A major part of this reduction can be explained by the discontinued use of growth promoters from 1994 to 1999.

Between 2000 (start of VetStat) and 2009 the amount of kg active compound increased by 62% (Figure 4.1). During this period the number of pigs produced also increased as did the proportion of pigs exported live at approx. 30 kg. Since then, the proportion of exported live pigs has continued to increase, while there has been an overall gradual decreasing trend in the use of antimicrobials in animals and in 2018 the antimicrobial use was approximately 23% lower than in 2009.

4.3. Antimicrobial consumption by animal species

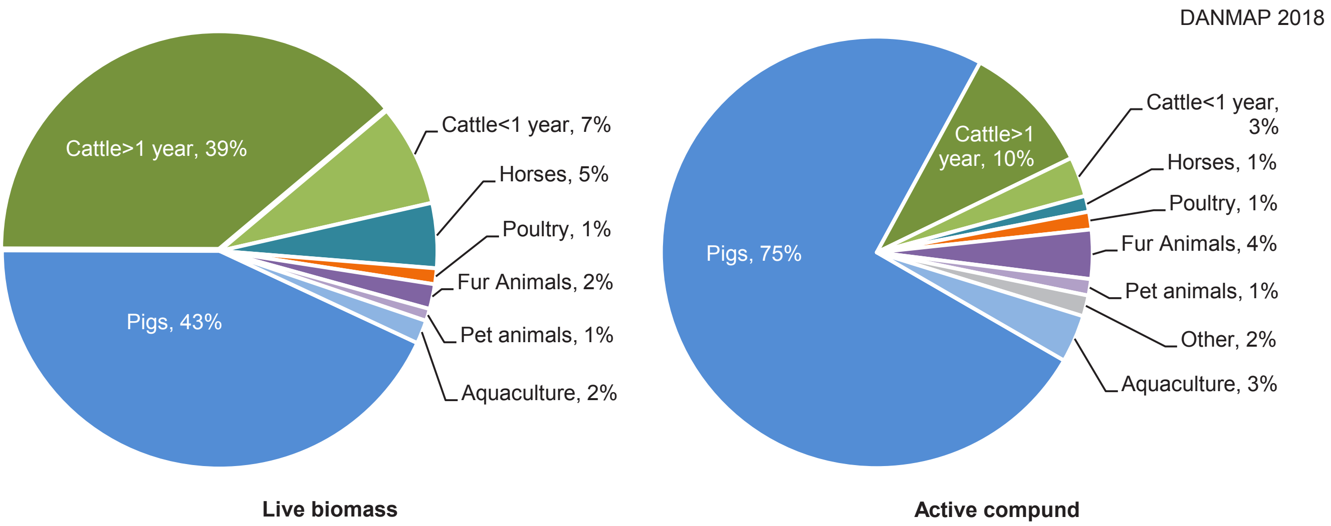
4.3.1 Antimicrobial consumption in pigs

The majority of antimicrobial use in animals is used in the production of pigs. The total antimicrobial consumption in pigs (sows and piglets, weaners, finishers) was 74.7 tonnes active compound (Table 4.1), which was 277 kg less than in 2017.

The treatment proportion (DAPD) of the total population reflects the trends in selection pressure within the population. The treatment intensity is much higher in weaners than in finishers and sows. The treatment proportions (DAPD) in the pig population overall and by age group are presented in Figures 4.3 and 4.4 and the DADD's are shown in the web annex (Table A4.1 and in the DADD description).

The large differences in DAPDs between age groups affects the DAPD of the total population and trends are influenced by changes in population structure. As an example, increased export of live pigs just after weaning could lead to an increase in DAPD in the total pig population, since the exported pigs were only in the country, when the treatment proportion was highest. Approximately 42% of the pigs produced in 2018 were exported as live pigs at approximately 30 kg (Table 3.1), in 2009 this percentage was approximately 24%. When estimating DAPD for all age groups in the pig production, we account for changes in export of weaners by calculating an adjusted treatment proportion, referred to as $DAPD_{adj}$, see section 9.2.2.

Figure 4.2 Distribution of live biomass and antimicrobial consumption in main animal species, tonnes, Denmark



Note: The live biomass is estimated from census data (pigs, cattle and pet animals) and production data (poultry, fur animals, aquaculture). For poultry, the figures comprise only the biomass for the main production types (turkeys and broilers). The live biomass estimates for poultry, aquaculture, horses and pet animals are based on 2012 data and may well be underestimated. The estimation procedures are described in section 9.2

Historically, the treatment proportion (DAPD) increased from 2004 to 2009, followed by a decrease in 2010 and 2011, which is considered a result of the “Yellow Card” initiative (DANMAP 2010). Since 2013, there has been a gradual decrease in treatment intensity for all age groups (Figure 4.3).

In 2018, the antimicrobial consumption in pigs, measured in $DAPD_{adj}$, decreased from approximately 24 to 23 (Figure 4.3) when adjusted for export. Also, measured in $DAPD_{adj}$, the antimicrobial use in pigs was 32% lower in 2018 than in 2009 (Figure 4.3).

Within the different age groups, the most remarkable change was seen for weaners, where the treatment proportion decreased from 97 to 91 DAPD, a decrease not apparent when inspecting crude consumption data in Table 4.1. The treatment proportion was also reduced in the finishers, from 18 to 17 DAPD, but remained at the same level in the sows and piglets around 19 DAPD (Figure 4.3). Thus, on a given day in 2018, approximately 2% of sows and piglets, 1-2% of finisher pigs and just around 9% of weaner pigs were treated with antimicrobials.

Changes to the “Yellow Card” initiative were implemented in 2016 and 2017, i.e. multiplication factors of 1.5 and 10 were applied to the use of tetracyclines and colistin, respectively, to promote further reduction (see Textbox 4.1).

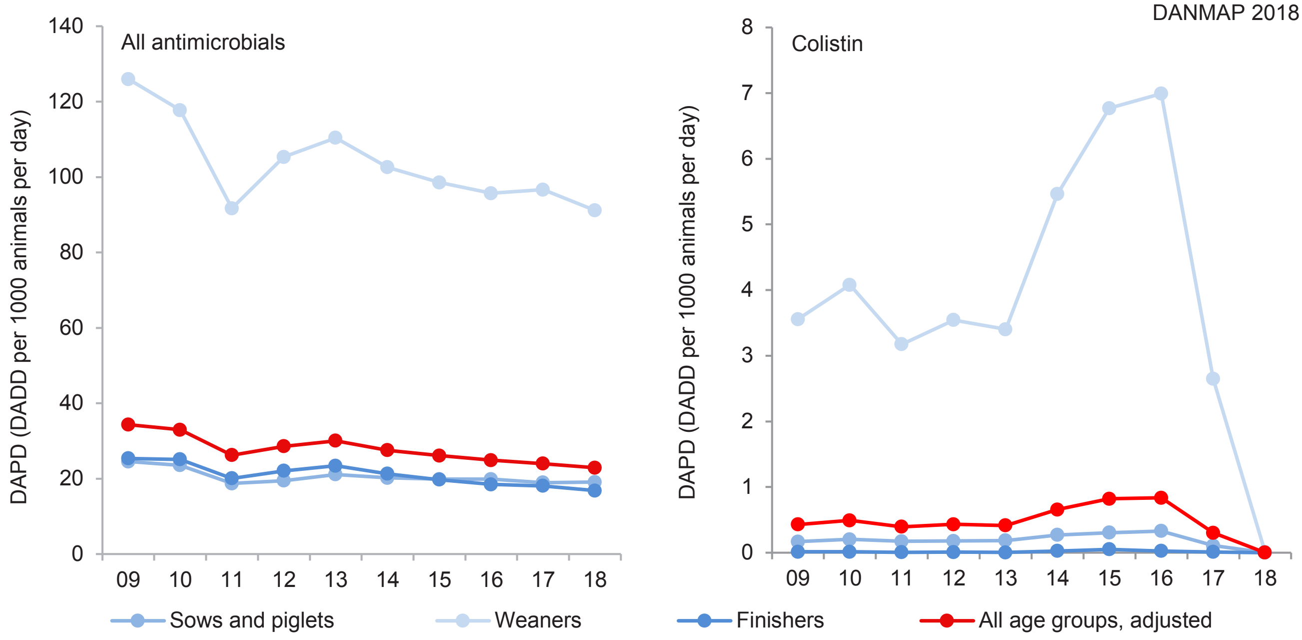
The National MRSA Action plan aimed to reduce the antimicrobial use in pigs by 15% in 2018, compared to 2014. In 2018,

Table 4.1. Antimicrobial use (kg active compound) by animal species and age group, Denmark DANMAP 2018

Therapeutic group	Aminoglycosides	Amphenicols	Cephalosporins	Fluoroquinolones	Lincosamides	Macrolides	Other AB	Other quinolones	Penicillins, b-lactamase sensitive	Penicillins, others(a)	Pleuromutilins	Sulfonamides and trimethoprim	Tetracyclines	Total 2017	Total 2018
Pigs	*8296*	*388*	*<1*	*0*	*1978*	*12056*	*<1*	*0*	*16551*	*8715*	*7627*	*6080*	*12965*	*74935*	*74658*
Sows and piglets	1854	279	<1	0	441	624	<1	0	8764	3605	937	4654	1174	21752	22331
Finishers	173	9	<1	0	701	3457	0	0	5867	734	3827	236	3475	19354	18479
Weaners	6270	100	<1	0	837	7976	<1	0	1920	4376	2863	1190	8316	33828	33848
Cattle	*901*	*837*	*79*	*<1*	*11*	*245*	*3*	*0*	*7627*	*730*	*0*	*879*	*1553*	*12370*	*12865*
Intramammaries	38	0	68	0	9	0	<1	0	287	131	0	<1	0	502	533
Cows and bulls	215	12	10	<1	<1	97	<1	0	6627	470	0	767	894	9056	9093
Calves <12 months	614	803	<1	<1	<1	145	3	0	574	118	0	105	615	2557	2978
Heifers and steers	34	22	<1	0	<1	3	0	0	139	11	0	7	44	255	261
Poultry	*51*	*0*	*0*	*<1*	*26*	*162*	*0*	*0*	*323*	*212*	*<1*	*37*	*516*	*1491*	*1326*
All poultry excl. turkeys	45	0	0	<1	23	95	0	0	216	121	<1	37	163	851	699
Turkeys	6	0	0	0	3	67	0	0	107	91	0	0	353	640	627
Other production animals	*164*	*330*	*<1*	*<1*	*62*	*468*	*<1*	*896*	*11*	*2144*	*<1*	*2701*	*497*	*7879*	*7274*
Aquaculture	0	323	0	<1	<1	0	0	896	0	45	0	2293	<1	1697	3557
Fur animals	161	6	0	<1	62	466	<1	0	5	2095	0	402	491	6156	3689
Other	2	1	<1	<1	<1	2	<1	0	6	4	<1	6	5	25	28
Companion animals(b)	*7*	*<1*	*97*	*15*	*62*	*2*	*41*	*1*	*29*	*681*	*<1*	*1441*	*41*	*2472*	*2418*
Pets(c)	6	<1	97	15	62	2	41	1	20	681	<1	261	37	1287	1224
Horses	<1	<1	<1	0	0	<1	<1	0	10	<1	0	1179	4	1184	1194
Unspecified(d)	*278*	*7*	*4*	*1*	*9*	*17*	*2*	*7*	*801*	*140*	*4*	*175*	*98*	*1744*	*1541*
Total	9697	1563	180	16	2147	12951	46	904	25341	12622	7632	11313	15669	100890	100082

Note: Data for 2018 were extracted from VetStat 3rd March 2019. Only the ATCvet group contributing mostly to the antimicrobial group is mentioned. Combination drugs are divided into active compounds
a) Penicillins with extended spectrum and combination penicilins, incl. b-lactamase inhibitors
b) In DANMAP 2016, new principles were applied to estimate the antimicrobial use for companion animals, see section 4.2.2
c) Approximately 242 kg of the sulfonamides and trimethoprim registered for pets are products (oral paste) typically used for horses
d) This includes data on sheep and goats (13 kg), data where the animal species has not been defined or where the age group does apply to the designated animal species

Figure 4.3 Total antimicrobial use and use of colistin in the pig production, DAPD, Denmark



Note: Sows and piglets includes treatment in boars. DAPDs are calculated as the number of standard doses for one kg animal divided by the estimated live biomass in the age group of the total population (in tonnes). DAPDs for "all age groups" are adjusted for export of pigs at 30 kg (see text)

the overall use in the pig production was reduced by approximately 13% when measured in kg active compound.

Tetracyclines has been one of the most commonly used antimicrobials in the Danish pig production for more than a decade. It is almost exclusively administered orally, and is especially used for treatment of gastrointestinal disease in weaners and finishers. The overall use of tetracyclines has decreased since 2013 and in 2018 the treatment proportion was at the lowest levels registered in the last 14 years, with the most marked changes following the recent adjustments changes to the "Yellow Card" initiative (Figure 4.4). Measured in $DAPD_{adj}$, the use of tetracyclines, in all age groups was reduced by 49% from 2015 to 2018 and by 63% since 2009. The proportion of weaners treated with tetracyclines on any given day has decreased from approximately 5% in 2009, to less than 2% in 2018. Also, the use of colistin, formerly one of the "first choice" antimicrobials for treating gastroenteritis, was almost completely stopped, as a consequence of the most recent adjustments to the "Yellow Card" initiative. In contrast, the use of other antimicrobial agents has increased, particularly the use of aminoglycosides (mainly neomycin) and macrolides, see Figure 4.3 and 4.4 and Textbox 4.2.

Use of the critically important antimicrobial agents, fluoroquinolones and 3rd and 4th generation cephalosporins was close to zero in 2018 (Figure 4.5).

Use of medical zinc in pigs

In the latest issues of DANMAP, we have presented the use of medical zinc in pigs (Figure 4.6). This is relevant, because its use may select for antimicrobial resistance in some bacteria, including MRSA. Medical zinc, in the form of zinc oxide, is prescribed to piglets after weaning to prevent or treat diarrhoea. Following a steady increase, the use of zinc for pigs peaked at 548 tonnes in 2015. In 2017, the European Commission announced an EU wide withdrawal of medical zinc for pigs effective from June 2022. Already in 2016, the Danish pig industry launched an action plan to help the pig producers reduce the use of zinc. This was followed up by an updated action plan in 2018. The use of medical zinc was reduced by 4% from 533 to 509 tonnes in 2018.

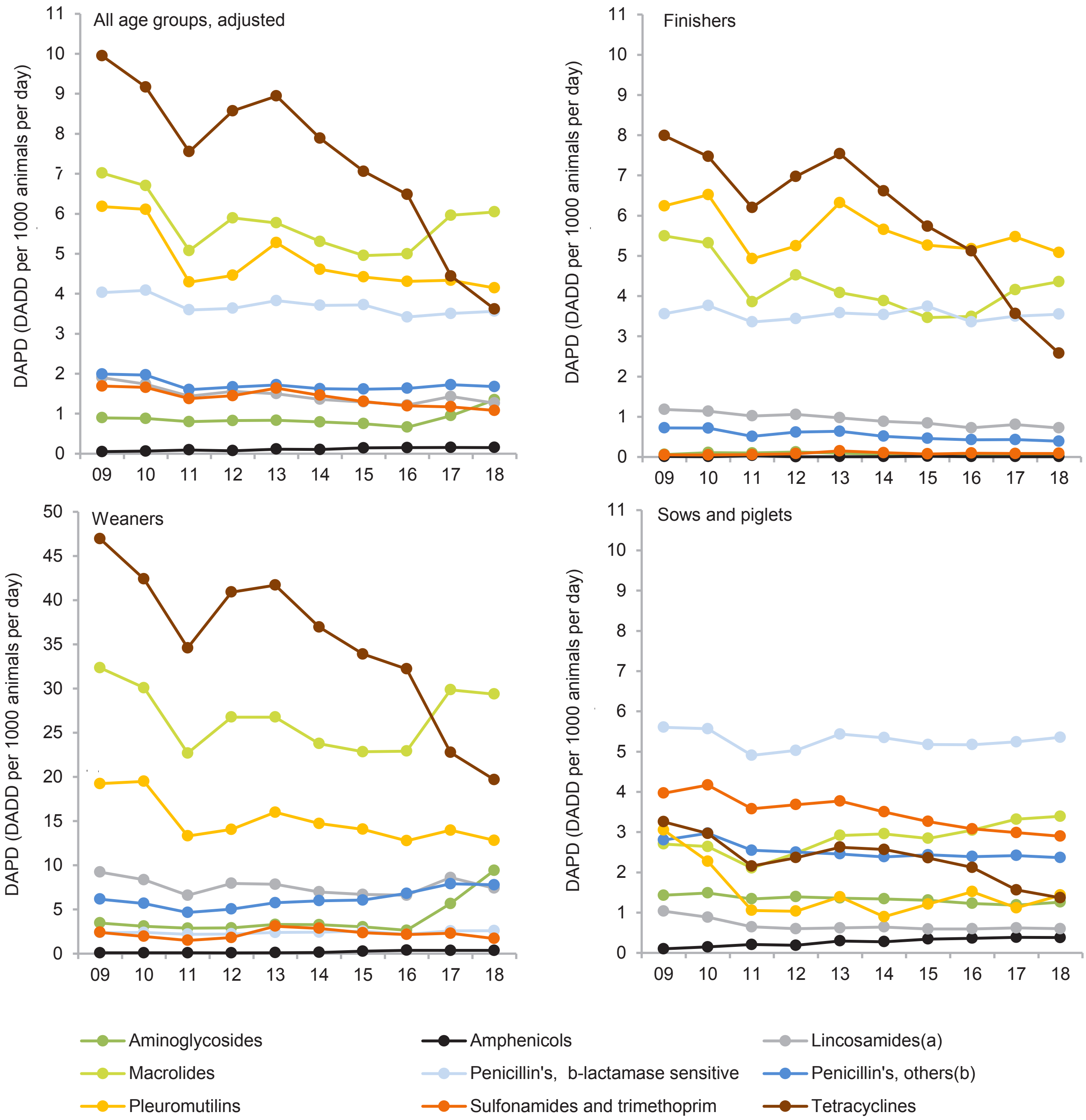
4.3.2 Antimicrobial consumption in cattle

Legislation supported thresholds for antimicrobial use in cattle have been in place since 2011. The overall consumption of antimicrobials in cattle has fluctuated between 12 and 13 tonnes for the past 5 years. In 2018, approximately 13 tonnes were registered for use in cattle, of which approximately 500 kg were used for intramammary treatment, either for therapeutic use or for dry cow treatment. More than two-thirds of the kg active compound were used to treat cows and bulls older than 24 months old (Table 4.1).

The production of veal and beef has remained relatively stable over the past 5-10 years, while the production of milk has increased steadily, Table 3.1.

Figure 4.4. Antimicrobial use in the total pig production and in each age group, DAPD, Denmark

DANMAP 2018



Note: Intramammaries, gynecologicals and topical drugs not included. The age group "sows and piglets" includes treatment in boars. DAPDs are calculated as the number of standard doses for one kg animal divided by the estimated live biomass in the age group or the total population (in tonnes). DAPDs for "all age groups" are adjusted for export of pigs at 30 kg (see text).
a) Lincosamide/spectinomycin combinations comprise 76% of this group
b) Penicillins with extended spectrum and combination penicilins, incl. b-lactamase inhibitors

Since 2010, there has been an overall decrease in systemic treatment for adult cattle (>12 months) of 16% measured in DAPD. The main indication for systemic treatment in adult cattle was mastitis and beta-lactam sensitive penicillin accounted for approximately two thirds of the antimicrobials used in this age group followed by tetracyclines (17%). The use of macrolides constituted 2% in 2018, Figure 4.7 and Figure 4.8.

For young cattle (<12 months) antimicrobial use has increased by 43% from 2009 to 2018 when measured in DAPD. The main indication for systemic treatment in calves is respiratory disease followed by joint/limb infections and gastrointestinal diseases. The DAPD of amphenicols (florfenicol) has increased steadily over the past decade and have become the most frequently prescribed antimicrobial class

Figure 4.5 Use of 3rd and 4th generation cephalosporins in pigs and cattle, kg active compound, Denmark

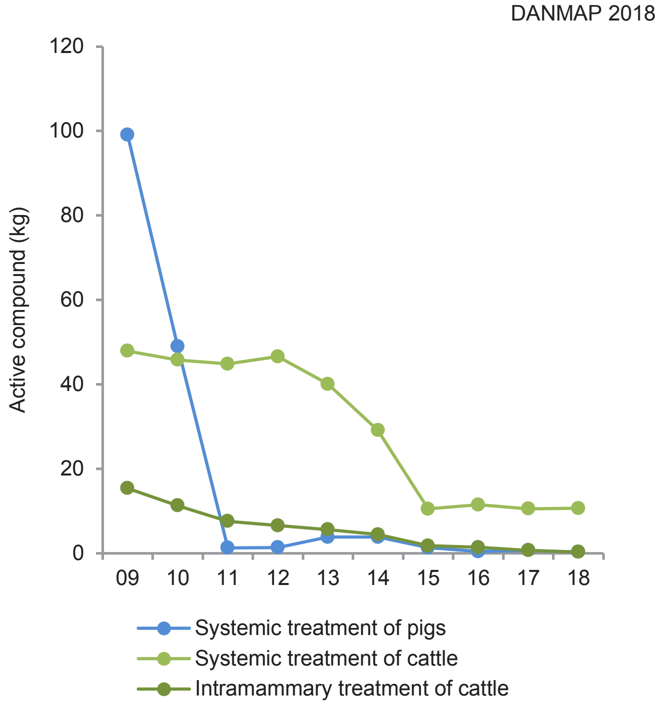
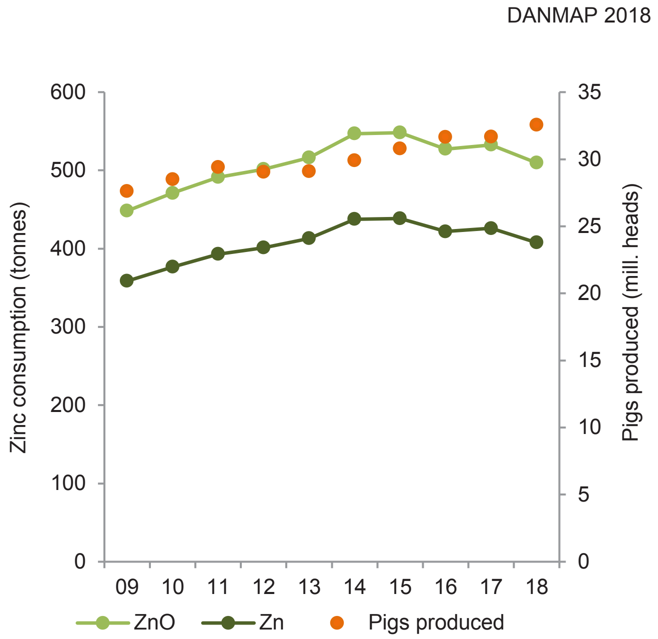


Figure 4.6 Usage (in tonnes) of medical zinc - zinc oxide (ZnO) and zinc (Zn) - in the pig production, Denmark



Note: The most commonly used product is zinc oxide (ZnO) which contains 80% zinc and which is largely insoluble in water

(28%), followed by tetracyclines and macrolides (25% and 20%, respectively).

The use of fluoroquinolones in cattle has been close to zero for the last decade. Fluoroquinolones may only be prescribed in food producing animals, as a last-line drug, based on microbiological analysis and susceptibility testing in an accredited laboratory. Use of fluoroquinolones in food producing animals is also notifiable to the DVFA.

In 2014, the cattle industry decided to phase out the use of 3rd and 4th generation cephalosporins used for systemic treatment (orally and parenterally), which caused the use to drop significantly in 2015, but has since then stabilised at approximately 10 kg per year. In 2018, the use of cephalosporins for systemic treatment in cattle and calves had been reduced by 64% and 51%, respectively, compared with 2015. The use of 3rd and 4th generation cephalosporins is shown in Figure 4.5.

The board of Danish dairy and beef producers has recently renewed its strategy for good udder health. The goals are a 20% reduction in use of antimicrobials for treatment of mastitis and other cattle diseases, as well as a lowering of geometric mean bulk tank cell counts to 150.000 by the year 2020. In addition, the dairy industry will promote use of dry-cow therapy and mastitis treatment with simple penicillins.

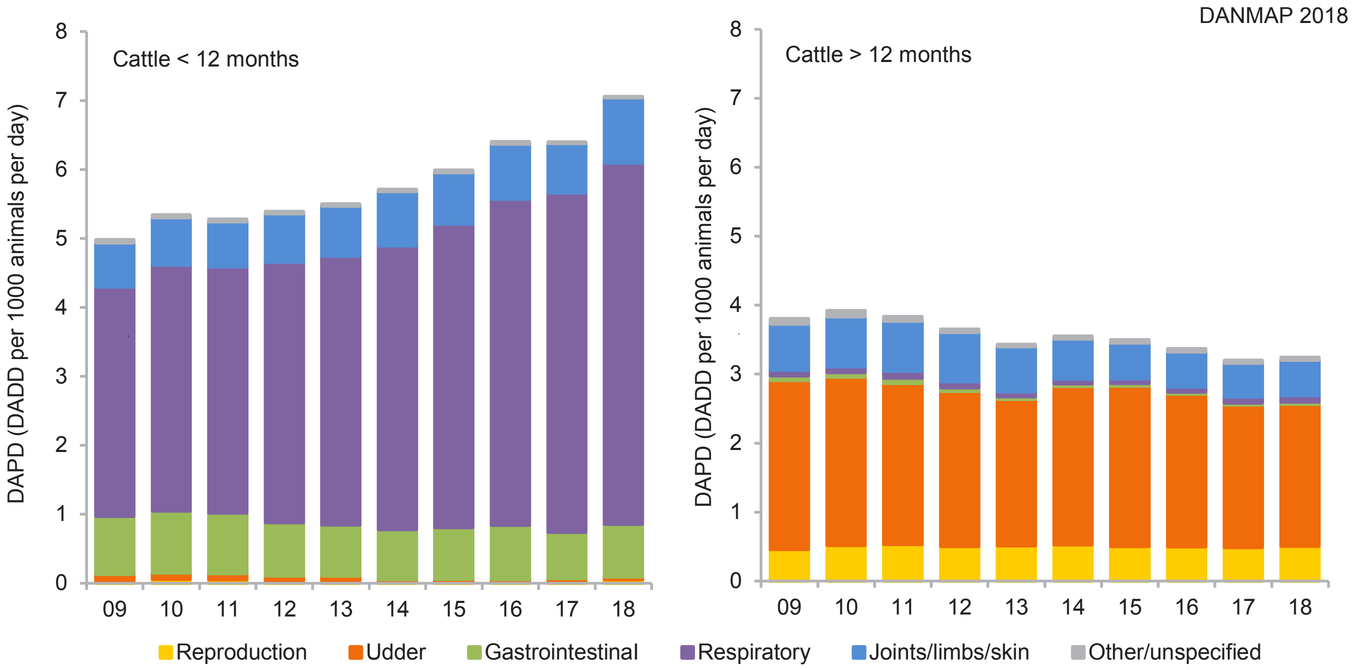
The majority of antimicrobials administered parenterally in cattle are used in dairy cows (Table 4.1) primarily to treat mastitis. The use of intramammary treatment is shown in Tables 4.2 and 4.3.The overall use in total DADD per cow per year has remained at the same level for the past decade, but the usage pattern has shifted away from the 3rd and 4th generation cephalosporins.

The number of dry-cow antibiotic treatments has increased since 2009. The relative proportion of dry-cow treatment versus therapeutic treatment has shifted markedly from 22% versus 78% in 2010 to 48% versus 52% in 2018 (Table 4.3). Dry-cow treatment is only allowed following diagnostic testing, where the presence of bacteria causing mastitis has been confirmed (Order nr 1647, 18/12/2018).

4.3.3 Antimicrobial consumption in poultry

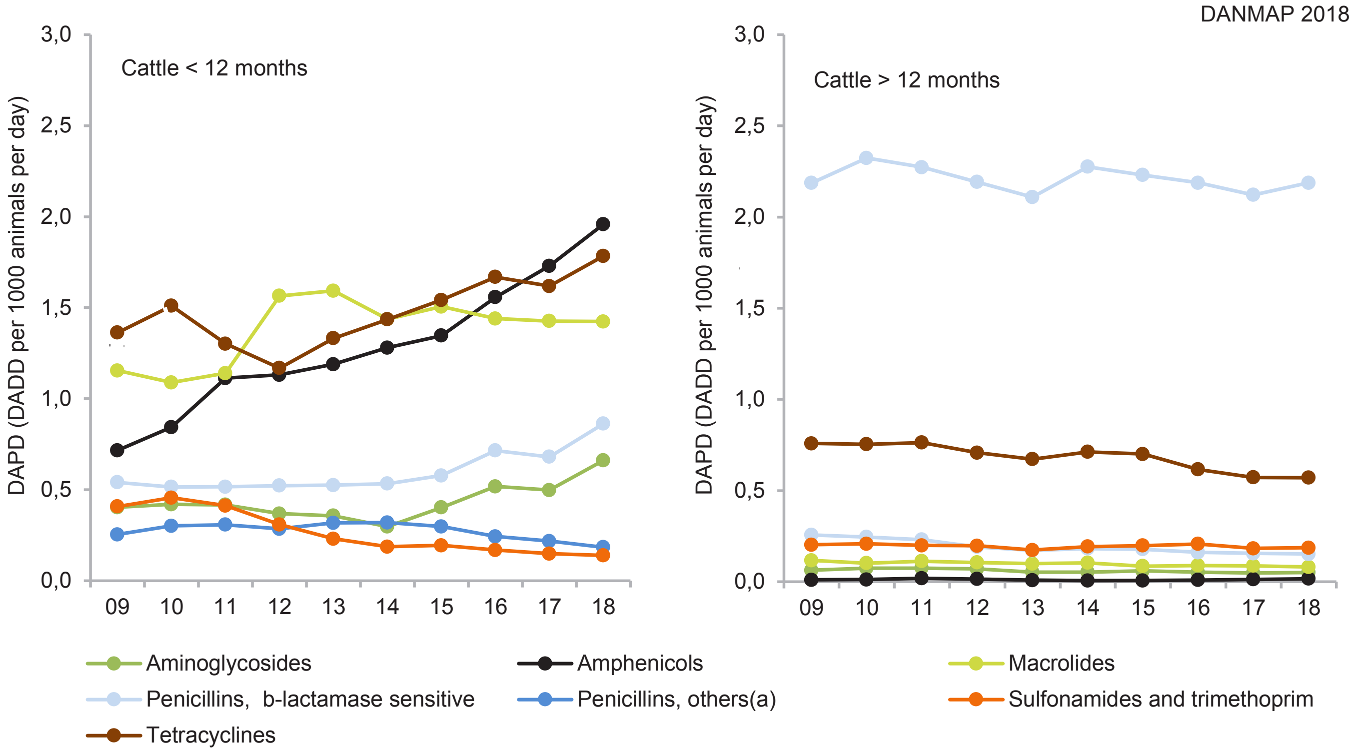
The poultry production comprises broiler production, egg layers and turkey production in sequence of magnitude. In addition, there is a small production of ducks, geese, and game birds. Danish broiler farms have a very high level of biosecurity and the antimicrobial consumption in broiler production is generally low compared with other species. Accordingly, disease outbreaks in just a few farms can markedly affect and cause considerable fluctuations in the national statistics on antimicrobial usage in the broiler sector (Table 4.4).

Figure 4.7 Indications for use of antimicrobials in cattle, DAPD, Denmark



Note: Intramammaries, gynecologicals and topical drugs not included. DAPDs are calculated as the number of standard doses for one kg animal divided by the estimated live biomass in the age group (in tonnes)

Figure 4.8 Use of antimicrobial agents in cattle, DAPD, Denmark



Note: Intramammaries, gynecologicals and topical drugs not included. DAPDs are calculated as the number of standard doses for one kg animal divided by the estimated live biomass in the age group (in tonnes)
a) Penicillins with extended spectrum and combination penicilins, incl. b-lactamase inhibitors

Table 4.2. Use of antimicrobial agents for intramammary application in cattle, 1000s DADD, Denmark DANMAP 2018

Doses per antimicrobial class	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Aminoglycoside-benzylpenicillin(a)	169	135	94	70	69	103	143	154	206	180
Cephalosporins, 1st gen.	97	97	103	111	117	113	96	89	86	113
Cephalosporins, 3rd and 4th gen.	73	53	36	31	26	21	8	6	3	1
Penicillins(b)	191	238	271	288	287	292	275	262	216	251
Others(c)	17	15	12	9	9	11	11	10	11	19
Total DADD	570	559	516	510	508	540	0	521	522	563
Total DADD per cow per year	1.0	1.0	0.9	0.9	0.9	1.0	0.0	0.9	0.9	1.0

Note: For intramammary treatment, 1 DADD is defined as the dose to treat two teats for 24 hours
a) Mainly dihydrostreptomycin-benzyl penicillin combinations; includes also combinations of penicillin/aminoglycoside with bacitracin or nafcillin (QJ51RC)
b) Includes benzylpenicillin, cloxacillin, and cloxacillin-ampicillin combinations (QJ51CE, QJ51CF, QJ51RC)
c) Lincosamides, neomycin-lincomycin combinations and trimethoprim-sulfonamide combinations

Table 4.3. Number of treatments with antimicrobial agents for intramammary application in cattle,1000s DADD, Denmark DANMAP 2018

Total doses per indication	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Dry-cow treatment (4 teats)	75	84	94	110	125	140	152	160	168	193
Therapeutic treatment (2 teats)	397	370	329	290	258	259	229	202	186	176
Dry-cow treatment, porportion of total	16%	19%	22%	27%	33%	35%	40%	44%	48%	52%

In late 2014 and throughout 2015 several outbreaks increased the total use. In 2016, use of antimicrobials in poultry (excl. turkeys) decreased sharply again and in 2018 the usage was further reduced to 699 kg (Table 4.1). For the past decade, cephalosporins have not been used in the poultry industry, the the use of fluoroquinolones has been close to zero and the use of colistin less than 10 kg per year.

VetStat does not allow differentiation of the use of antimicrobials between different sectors of the poultry production. The consumption in turkeys was identified by combining information from the Central Husbandry Register and collating this with information from VetStat.

The annual usage in turkeys can also be notably affected by disease outbreaks in few flocks. In 2018, the antimicrobial use was approximately at the same level as in 2017, of which more than half (56%) was tetracyclines (Table. 4.1).

4.3.4 Antimicrobial consumption in aquaculture, fur animals and companion animals

Antimicrobial consumption in aquaculture is mostly influenced by the summer temperatures, because bacterial diseases are more likely to occur when temperatures are high. In recent years, the aquaculture industry has developed new and better vaccines and improved vaccination strategies to reduce the risk of diseases that may require antibiotic treatment. The

Table 4.4 Use of antimicrobial agents in poultry, kg active compound, Denmark DANMAP 2018

	Aminoglycosides	Amphenicols	Fluoroquinolones	Lincosamides	Macrolides	Other AB	Other quinolones	Penicillins, b-lactamase sensitive	Penicillins, others	Pleuromutilins	Sulfonamides and trimethoprim	Tetracyclines	Total
2014	21	9	<1	10	359	2	0	120	326	<1	83	617	1548
2015	258	4	1	129	114	7	0	184	500	<1	446	796	2441
2016	60	5	<1	24	153	6	0	239	225	<1	111	749	1571
2017	65	5	<1	32	206	0	1	321	293	<1	85	483	1491
2018	51	0	<1	26	162	0	0	323	212	<1	37	516	1326

Note: Data were extracted from VetStat 3rd March 2019. VetStat does not differentiate between use in the different sectors of poultry production.

summer of 2018 was exceptionally warm and this was clearly reflected in a antimicrobial use that more than doubled from 1,697 kg in 2017 to 3,557 kg in 2018. However, the use was still lower than in 2014, when the use in aquaculture peaked at 5,116 kg (Table 4.5).

Mainly three compounds are used in aquaculture; sulphonamide/trimethoprim (64%), 1st generation quinolones (25%) and amphenicols (9%). Compared with 2017, it seems that the usage pattern has shifted towards use of sulphonamide/trimethoprim (40% in 2017) and away from quinolones and amphenicols (38% and 21% in 2017, respectively) (Table 4.4).

The use of antimicrobials in mink has a distinct seasonal variation, with high use from the spring, when the mink kits are born and again when they are weaned. Furthermore, there is usually an increase in antimicrobial use again in the autumn. The production of mink has increased over the last decade, peaking at 18.8 million in 2015. In 2018, 17.6 million mink were produced in Denmark, Table 3.1 (Source: Kopenhagen Fur).

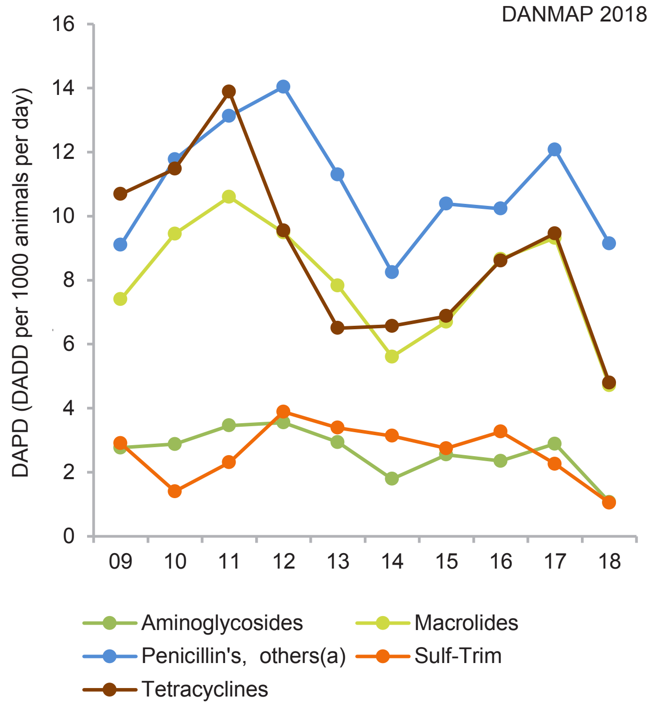
With the exception of 2013 and 2014, the use of antimicrobial agents in mink production increased every year for more than a decade until 2017, from less than two tonnes in 2004 to more than 6 tonnes in 2017. As a response, the industry increased focus on reducing the antimicrobial use and developed an antimicrobial action plan in cooperation with the Danish Food and Veterinary Administration, The Danish Veterinary Association and the veterinary practitioners. Remarkably, already in 2018 the use was reduced by 40%, from 6,156 kg in 2017 to 3,689 kg in 2018, or 42% when measured in DAPD, (Figure 4.10). The action plan and ongoing research projects are described in Textbox 4.4.

Table 4.5 Use of antimicrobial agents for aquaculture measured in kg active compound, Denmark DANMAP 2018

	Amphenicols	Other quinolones	Sulfonamides and trimethoprim	Other AB	Total
2014	297	1678	3132	9	5116
2015	311	1005	1650	5	2970
2016	315	893	1086	12	2307
2017	350	637	679	31	1697
2018	323	896	2293	46	3557

Note: Data were extracted from VetStat 3rd March 2019. Other AB include mainly penicillins with extended spectrum and combination penicilins, incl. b-lactamase inhibitors (98%) and tetracyclines (2%)

Figure 4.10 Use of antimicrobial agents in fur animals, DADP, Denmark



Note: Intramammaries, gynecologicals and topical drugs not included. DAPDs are calculated as the number of standard doses for one kg animal divided by the estimated live biomass in the total population (in tonnes)
a) Penicillins with extended spectrum and combination penicillins, incl. b-lactamase inhibitors

It is particularly the use of tetracyclines, penicillins with extended spectrum, combinations penicillins and macrolides that have fluctuated over the past three years (Figure 4.10). Use of fluoroquinolones and cephalosporins in the fur animal production has been close to zero for more than a decade.

The information available on antimicrobial consumption in companion animals was not as complete as for production animals, because antimicrobials used for companion animals may be registred in VetStat without defining target animal species. It is assumed that a substantial part of the prescriptions, where no animal species is given have been used for companion animals. This proportion has been estimated using similar principles as described in DANMAP 2016. The estimated antimicrobial use for horses and pets are shown in Tables 4.6 and 4.7.

The overall antimicrobial use for horses appears to have a slightly increasing trend over the past five years from 1,047 kg active compound in 2014 to 1,194 kg in 2018. Sulphonamide/trimethoprim, administered mainly as oral paste, constitutes the majority of antimicrobial use in horses (98%). In addition 242 kg active compound sulphonamide/trimethoprim (oral paste for horses) was registered for use in cats and dogs (Table 4.7).

Table 4.6. Estimated use of antimicrobial agents for horses, kg active compound, Denmark DANMAP 2018

	Penicillins, b-lactamase sensitive	Sulfonamides and trimethoprim	Tetracyclines	Other AB	Total
2014	15	1024	6	2	1047
2015	10	1049	4	4	1067
2016	8	1117	5	1	1131
2017	9	1172	3	1	1184
2018(a)	10	1179	4	1	1194

Note: Data were extracted from VetStat 3rd March 2019.
The estimates include all antimicrobial agents registered, by either the pharmacy or veterinarians for use in horses. Antimicrobial agents, where no animal species was given, were allocated to horses based on relevant type of preparation (e.g. oral paste) or registration. Antimicrobials administered parenterally - with no information on animal species - are not included.
Other AB include mainly aminoglycosides (67%), cephalosporins (13%) and macrolides (11%)
a) In 2018, additionally 242 kg of the sulfonamides and trimethoprim registered for pets were products (oral paste) typically used for horses (included in Table 4.6)

A large proportion of antimicrobials used for dogs and cats are prescribed for the treatment of chronic or recurrent disease, mainly dermatitis. Due to the close contact between owners and their pets, the repeated use of critically important antimicrobials may pose a risk to the owners.

The use of fluoroquinolones for use in pets, mainly dogs and cats, was 15 kg, which represented the majority of fluoroquinolones used in all animals. Similarly, the pets accounted for more than half (97 kg or 54%) of the use of cephalosporins used in animals (Table 4.7). However, antimicrobial use in pets appears to be shifting away from the use of cephalosporins towards broad spectrum penicillins, in particular amoxicillin with beta-lactamase inhibitor.

Since the treatment guidelines by Danish Veterinary Association were first published (November 2012, revised version 2018), the use of cephalosporins has been reduced by 64%. The guidelines recommend that use of critically important antimicrobials should be reduced as much as possible, demonstrating the effect of science-based treatment guidelines to control antimicrobial use.

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Table 4.7 Estimated use of antimicrobial agents for dogs and cats measured in kg active compound, Denmark DANMAP 2018

	Aminoglycosides	Amphenicols	Cephalosporins	Fluoroquinolones	Lincosamides	Macrolides	Other AB	Other quinolones	Penicillin's, b-lactamase sensitive	Penicillin's, others(a)	Pleuromutilins	Sulfonamides and trimethoprim	Tetracyclines	Total
2014	8	<1	213	14	69	6	35	1	31	653	<1	300	35	1366
2015	7	<1	157	14	68	5	33	0	25	655	1	235	39	1240
2016	6	<1	137	15	69	3	31	<1	20	718	<1	276	40	1318
2017	6	1	111	14	67	2	31	0	19	718	<1	280	38	1287
2018(b)	6	<1	97	15	62	2	41	1	20	681	<1	261	37	1224

Note: Data were extracted from VetStat on 3rd March 2019. Data include all antimicrobial agents registered, by either the pharmacy or veterinarians for use in pets. Furthermore, antimicrobial agents, where no animal species is given, were allocated to pets based on relevant type of preparation (eg. tablets, eye- or eardrops) or registration. Antimicrobials administered parenterally - with no information on animal species - are not included
a) Penicillins with extended spectrum and combination penicilins, incl. b-lactamase inhibitors
b) In 2018, approximately 242 kg of the sulfonamides and trimethoprim registered for pets are products (oral paste) typically used for horses

Textbox 4.2

Establishment of an Advisory Committee on Veterinary Medicines

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. This impartial Committee initiated its work autumn 2018. The Advisory Committee on Veterinary Medicines comprises veterinary and human medicine experts from University of Copenhagen, Danish Technical University, the Danish Medicines Agency, the Danish Health Authority, Statens Serum Institut, the Danish Veterinary Association and the Danish Veterinary and Food Administration.

The Council will discuss and contribute to the solution of specific tasks in the field of antimicrobials and offer guidance to initiatives on antimicrobial use and resistance. Its objective is to provide evidence-based professional advice for the Minister of Environment and Food in relation to the use of veterinary medicine and to tackle related issues proactively.

One of the first issues faced by the Committee is new national targets for antimicrobial consumption. The current national target was 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 advise the Minister on these targets.

In the coming years the Advisory Committee on Veterinary Medicines will also be addressing the following issues:

- The Committee will assess the situation and advise on possible actions, if the presence of livestock MRSA at herd level for a given animal species exceeds 10%.
- The Committee will prepare "good clinical practice" for the veterinary practitioners' activities.
- The Committee will regularly contribute with recommendations as a basis for decisions in relation to prudent use of veterinary medicine, including treatment guidelines.
- The Committee will assist the Danish Veterinary and Food Administration in assessing and clarifying risk assessments in order to ensure evidence-based decisions in relation to appropriate use of antibiotics in livestock production.
- The Committee will propose criteria and weighting in the Yellow card initiative for pig producers.
- The Committee may contribute to evaluations in connection with the resistance monitoring of all animal species.

The Advisory Committee on Veterinary Medicines is working in line with a One Health approach, and supplements the Danish National Antimicrobial Council established in 2010, and can be contacted at vetmed@fvst.dk

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Textbox 4.3

OUA – an up and coming special production

OUA is the Danish acronym for "Opdrættet uden antibiotika", which means raised without the use of antibiotics (in English: RWA = Raised Without Antibiotics). This type of production, now well established as a special production in Danish pig production, was initiated to meet a growing customer demand particularly from countries outside Denmark.

Danish Crown, which identified a market for this type of production, first embarked on the OUA project in collaboration with SEGES Danish Pig Research Centre in 2014. Initial trials were conducted at two farms on the island of Bornholm where it was shown that a large number of pigs could be produced without the use of antibiotics, with the proviso that the production of such pigs from birth to slaughter involves additional costs, which ultimately means higher meat prices in order for OUA production to be viable.

Since the experiment was completed, several pig farms have been converted to OUA herds and now counts 51 herds with more to come. In 2018, approximately 6,000 OUA pigs were slaughtered per week. This figure has increased to 7,000-7,500 pigs per week since the start of 2019.

Photo: Danish Crown

Facts: What is OUA?

OUA is the Danish acronym for "Opdrættet uden antibiotika", which means bred without the use of antibiotics. Such production requires the following:

- No antibiotics from birth to slaughter;
- Only vegetable-based feed although milk and dairy products are allowed;
- The pigs are tagged with special OUA tags, which are removed if they are treated;
- An annual, independent production audit is carried out.

Higher price for OUA pigs

As with other special productions, OUA pigs require a market and consumers who are willing to pay a higher price for the meat. OUA production demands extra close monitoring and thus additional working hours for the teams working in the housing units, which, in turn, means higher production costs. As well as the increased need for monitoring the pigs, OUA production needs better disease prevention, including more frequent use of vaccines and more expensive feed. That said, sick pigs that require treatment are treated accordingly – just like any other pig. If a pig is treated with antibiotics just once, it is no longer classified as an OUA pig and will not be sold as such.

The future of Danish OUA

There is support for OUA production from the pig industry as long as it remains a special production for which there is a market. In recent years, Danish Crown has seen a growing demand for OUA pigs, particularly from abroad. Here, there is strong awareness of Danish special productions because of the great confidence in what Denmark is already known for, i.e. high and uniform quality, low antibiotic consumption and traceability back to the producer.

OUA pigs have also attracted interest in Denmark. From the start of 2019, a large, nationwide supermarket started to sell pork from Danish OUA herds only. Other countries also raise pigs without the use of antibiotics, but the requirements differ from country to country. In some, the set of rules defining this type of production is somewhat loose, while in other countries they are much stricter.

OUA production – can we improve?

The art of raising OUA pigs is, of course, to produce as many pigs as possible without the use of antibiotics. Reports from many of these herds indicate that some of the challenges are the same – there are certain infectious diseases that are quite difficult to manage and prevent. Danish Crown, SEGES Danish Pig Research Centre in collaboration with university researchers have therefore embarked on a research partnership supported by GUDP (Green Development and Demonstration Programme). The aim is to solve some of these disease challenges – both for the benefit of OUA producers and for all conventional pig herds, with the ultimate aim of paving the way for even better OUA production in Denmark in the future.

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Textbox 4.4

Antimicrobial use in mink – action plan/research projects

Antimicrobial use in the Danish mink industry has increased significantly over the last decade. From 2008 to 2017 the total amount of prescribed antimicrobials increased substantially (Figure 1). As almost no antimicrobial agents are registered for use in mink, the prescription is mostly off-label. This, combined with the lack of a dosage regime makes it critically important with a guideline for prudent use of antimicrobial agents for mink.

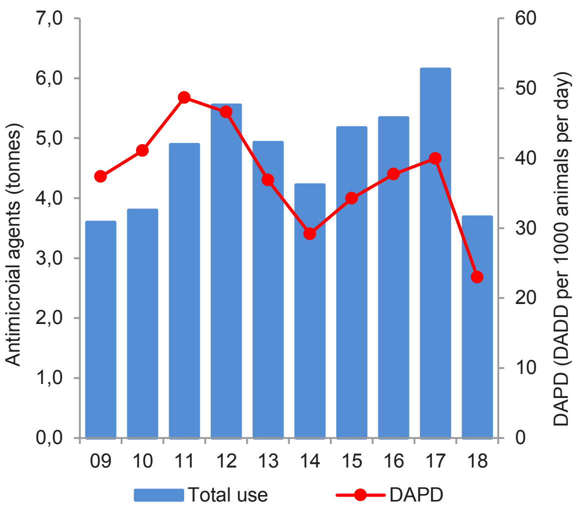
As a response to the increase in antimicrobial use, the Danish mink breeders organization (Kopenhagen Fur) initiated an antimicrobial action plan in cooperation with the Danish Veterinary and Food Administration, the Danish Veterinary Association and the veterinary practitioners. The action plan was launched in autumn 2018, with an overall aim to phase out the use of medical zinc oxide and to reduce the antimicrobial use for mink to 4,000 kg by 2022. The action plan includes 18 targets related to Benchmarking and Best Practice.

Benchmarking. To promote the highest degree of transparency, the antimicrobial use for Danish mink farms will be quantified in a comparable manner (DADD/biomass) and benchmarked across farms, veterinarians and feed producers. Recent studies have found that veterinarians and feed producers have a significant impact on the antimicrobial use. Therefore, the antimicrobial use relating to veterinarians and feed producers, will be quantified based on the antimicrobial use prescribed for mink on affiliated farms. The antimicrobial use in the individual mink farms, should be assessed annually by the farmer in cooperation with the farm veterinarian. Preferably, this annual assessment will be incorporated into the Veterinary Advisory Service contracts (VASCs).

Furthermore, the antimicrobial use by Danish mink farms will be included on an internal performance list used to rank farms in terms of productivity (reproduction and fur quality).

Oral administration of antimicrobial treatment to female mink.
Photo: Julie Melsted Birch, Kopenhagen Fur

Figure 1 Use of antimicrobial agents in fur animals, Denmark
DANMAP 2018



continued ... Textbox 4.4

Best Practice. A substantial part of the scientific foundation of the action plan is based on recent and ongoing research projects carried out in collaboration with the Danish universities. In 2017 Kopenhagen Fur, DTU and Copenhagen University initiated two industrial Ph.d. projects supported by Innovationsfonden and Pelsdyravlernes Forskningsfond. The aim of the projects is to provide data on pharmacokinetics and antimicrobial resistance as well as data for determination of MIC breakpoints. Together, these two projects initiated in early 2017 are expected to provide the evidence based knowledge needed to support a best practice guideline with dosage and product recommendations for antimicrobial use in mink. However, the antimicrobial action plan already makes provision for the voluntary stop for use of zinc oxide, while the use of tetracyclines should be supported by an antimicrobial susceptibility test.

Antimicrobial group treatment must be supported by diagnostic tests carried out by a competent laboratory, while the Danish Veterinary and Food Administration has been requested to reduce the prescription period related to group treatments to a maximum of five days. In addition, practical possibilities to treat smaller groups of animals on-farm are being investigated.

Finally, the antimicrobial action plan includes points on preventive measures, which may result in a reduced antimicrobial use. This includes studies on breeding more robust mink, alternative treatment methods such as probiotics, as well as the impact of feed and feeding strategies on the occurrence of diarrhea. Furthermore, the plan includes points giving an increased focus on disease prevention, especially during the spring and summer, where a large part of the antimicrobial consumption occurs.

The effect of the antimicrobial action plan is dependent on a high level of commitment, from the breeders, the Danish Food and Veterinary Authorities, The Danish Veterinary Association and the veterinary practitioners. Therefore, a continuous focus on communication and sharing of knowledge is essential. To keep momentum, the Danish Veterinary Association has chosen to make a Mink theme at the upcoming annual meeting for Danish Veterinarians in 2019, where the antimicrobial use and latest research on the topic will be presented.

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