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SUMMARY DANMAP 2020

Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark

Statens Serum Institut
National Food Institute, Technical University of Denmark

SUMMARY • DANMAP 2020

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Contents

DANMAP is based on strong collaboration between several institutions and contributions from staff across many specialities and professions. The DANMAP report is collated each year by the Technical University of Denmark (DTU) and Statens Serum Institute (SSI). Both DANMAP partners, their collaborators, data sources and data flow of the surveillance programme are shown in Figure 1.1.

1. Introduction

The Danish integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) was founded in 1995. Its launch followed increasing concern in Denmark about the effect of antimicrobial use in food animal production on the emergence of antimicrobial resistance and its consequences for human and animal health.

DANMAP's integrated surveillance of antimicrobial consumption and resistance in bacteria from food animals, food and humans is based on the concept of 'One Health' – a collaborative, multidisciplinary initiative across human and animal sectors. It was a trail-blazing concept in the 1990s but quickly gained international recognition and has been adopted by many other countries since then. A key objective of DANMAP is further understanding of the association between antimicrobial use (AMU) and the occurrence of antimicrobial resistance (AMR) across animal and human populations. It provides an evidence base for decision-making in the fight against AMR and helps to put science and public health into action. DANMAP's surveillance data informed the development of the current One Health Strategy and National Action Plans in the veterinary and human sector in Denmark.

In celebration of the programme's 25 year jubilee, this summary DANMAP report 2020 has been developed to complement the traditional, more comprehensive DANMAP report 2020. The summary report features the most important findings of DANMAP in 2020, including the impact of the COVID-19 pandemic on AMR and AMU. It aims to inform healthcare professionals, scientists, decision-makers and everybody else with an interest in AMR and AMU.

Figure 1.1 Organisation of the DANMAP collaboration regarding data and data flow

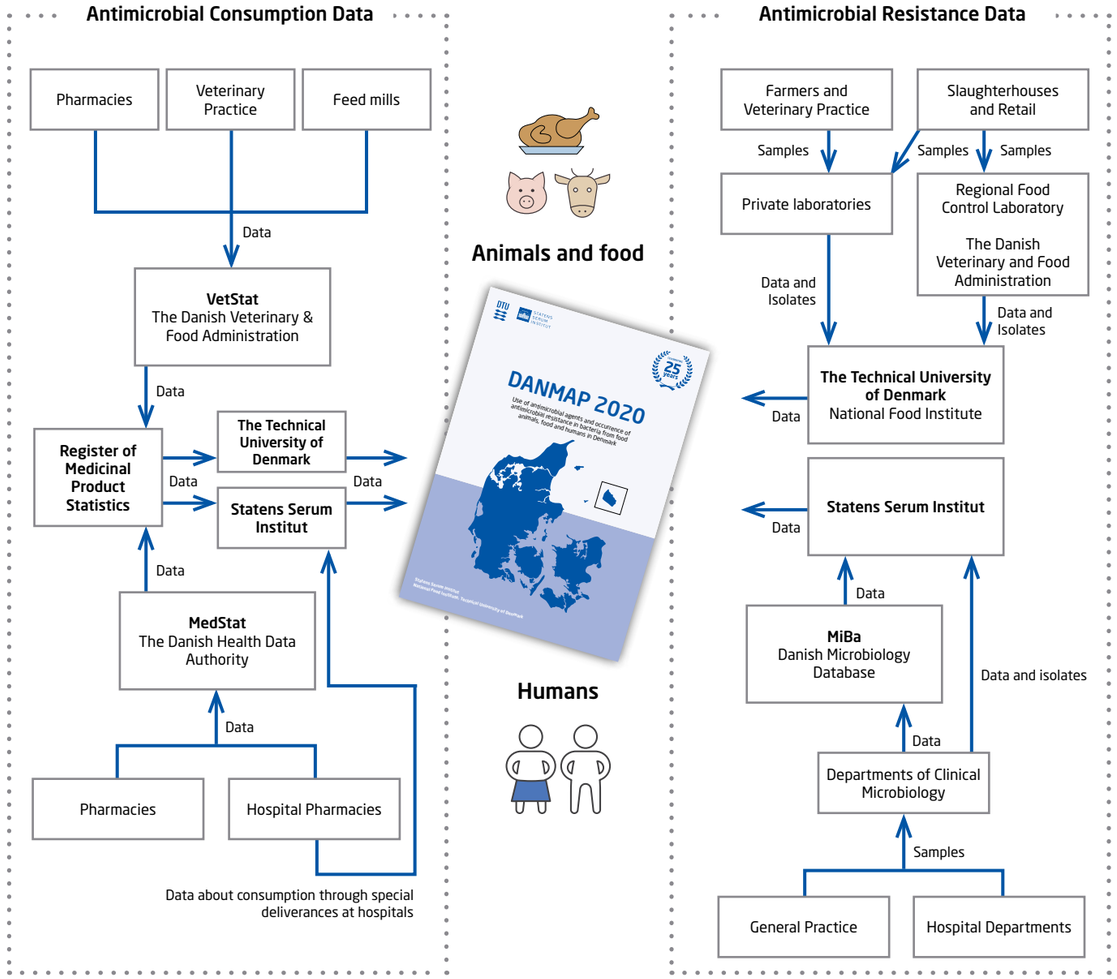
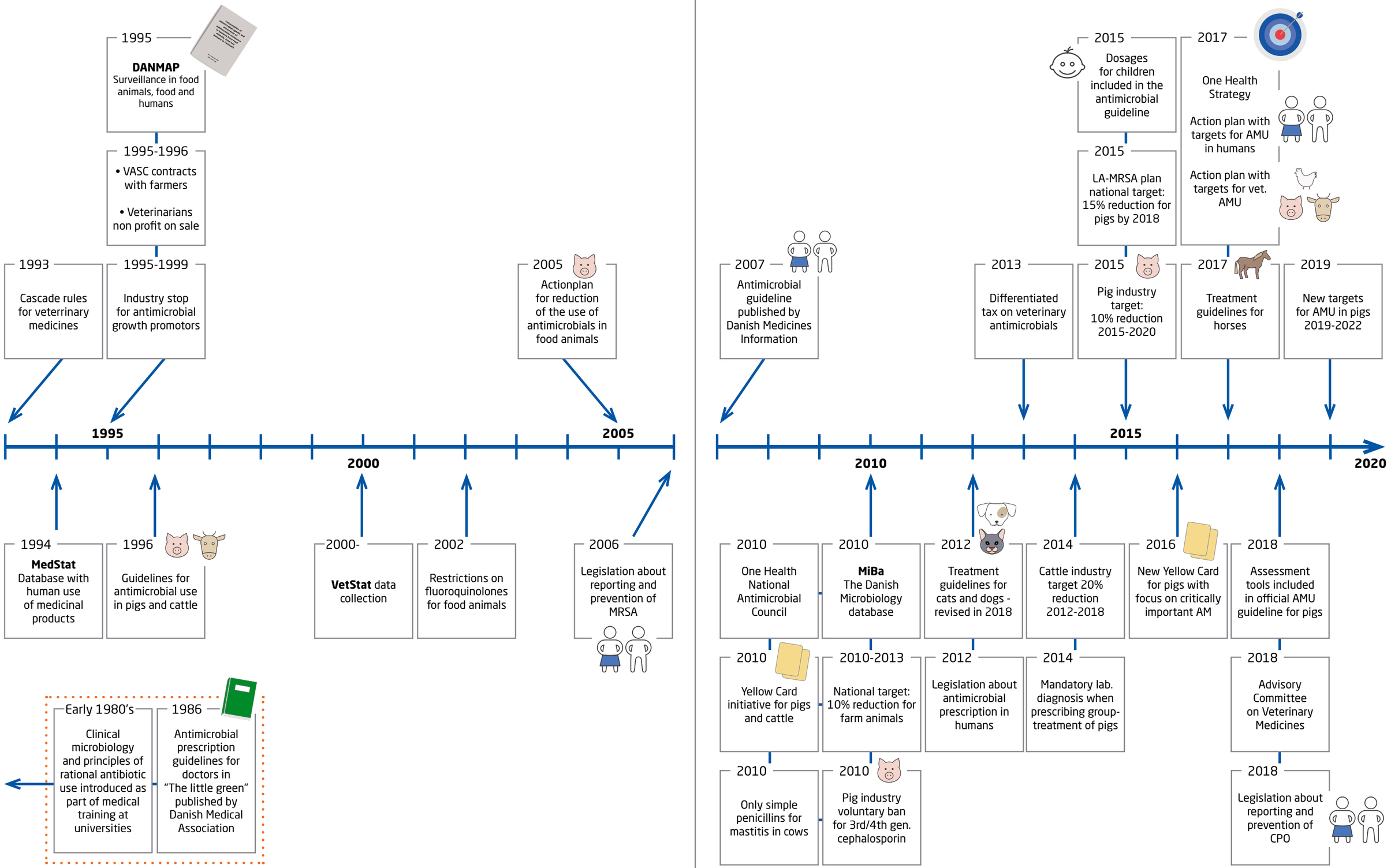


Figure 1.2 Timeline with initiatives for the prevention and control of AMR and prudent antimicrobial use in animal and public health in Denmark



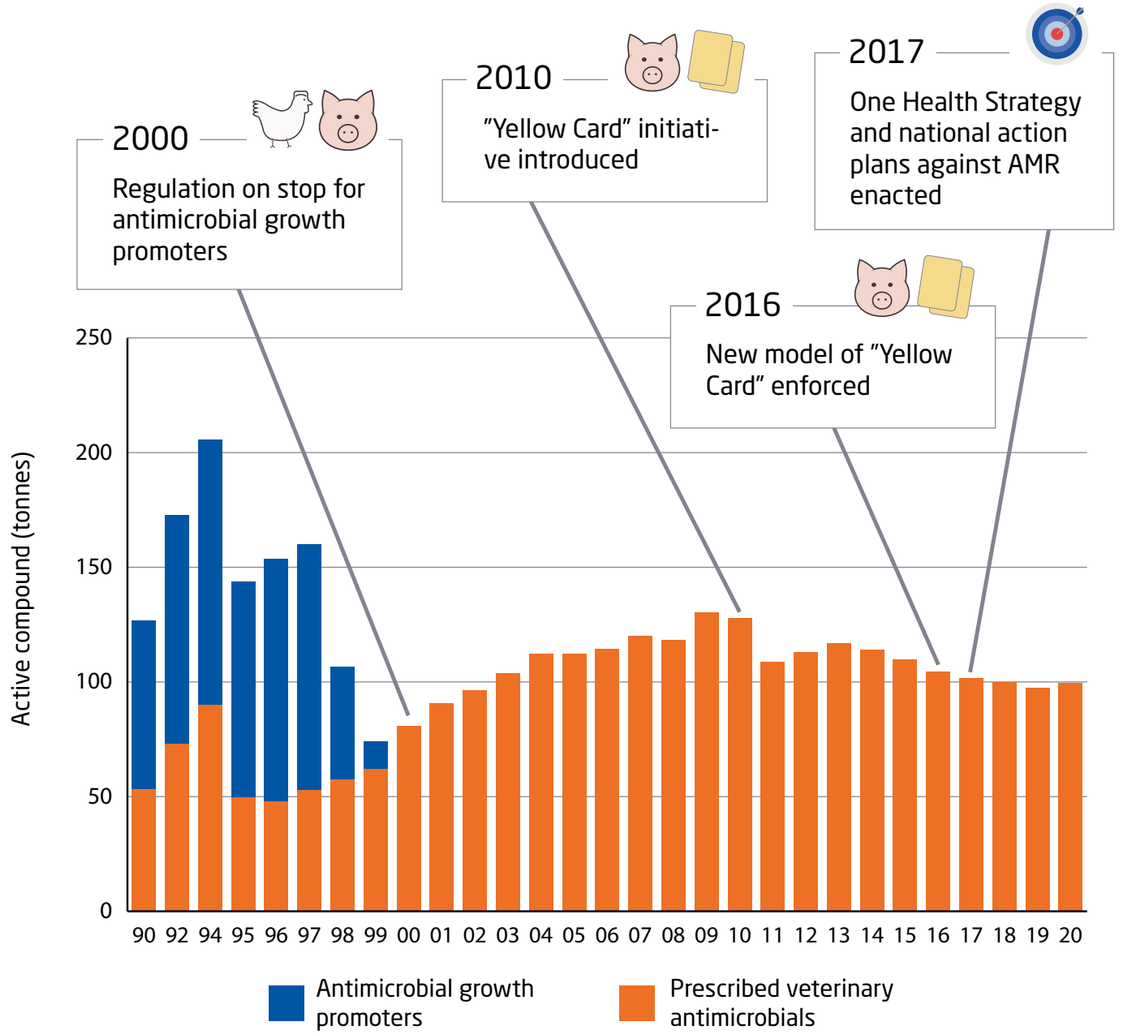
2. Antimicrobial consumption in animals

The DANMAP programme has monitored antimicrobial consumption in animals since 1995. DANMAP's surveillance of antimicrobial consumption in animals is based on sales data from pharmacies, veterinary practices and feed-mills. Since 2001, all medicines prescribed for use in animals have been recorded in the national database, VetStat, which is maintained by the Veterinary and Food Administration (Figure 1.1). The data on antimicrobial consumption presented in DANMAP, are extracted from VetStat each year.

Since DANMAP was established, many initiatives have been taken on to reduce the use of antimicrobials in both animals and humans (Figure 1.2 and 2.1). These include discontinued use of antimicrobial agents for growth promotion, voluntary bans on the use of cephalosporins in the pig and cattle production, as well as regulatory legislation regarding therapeutic use (Figure 1.2).

Figure 2.1 shows the antimicrobial use in animals, along with important initiatives that have had a marked effect on the antimicrobial use in animals. The most remarkable changes in antimicrobial consumption in animals was the ban on antimicrobial growth promoters in the late nineties. Over time, antimicrobial use in animals has been affected, not only by the risk management measures established to reduce consumption, but also by changes in the animal production, especially increases in pig production.

Figure 2.1 Antimicrobial consumption and important initiatives to reduce antimicrobial use in animals, Denmark, 1990-2020



The Yellow Card Initiative

The Yellow Card initiative was introduced in 2010 to reduce the use of antimicrobials in pig production in Denmark. The initiative targets farms with highest consumption of antimicrobials and works as an incentive for pig producers to contribute towards the goal of reducing the overall use of antimicrobials (see DANMAP 2010).

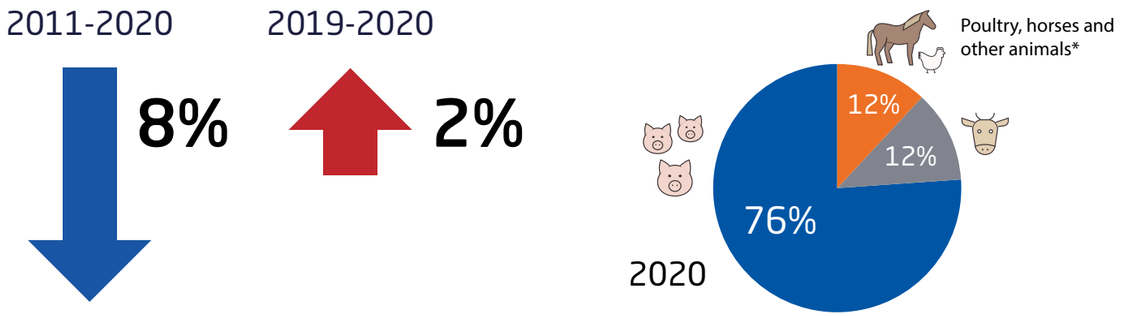
In 2016, the Danish Veterinary and Food Administration (DVFA) developed the Yellow Card further and added multiplication factors to adjust the use of specific antimicrobial agents. The multiplication factors were determined by the DVFA and are used as risk mitigation tools for each class of antimicrobials.

Fluoroquinolones and cephalosporins are classified as critically important for treatment of humans and have been allocated the highest multiplication factor of ten. Fluoroquinolones are also under further restrictions by Danish law and the Danish pig industry voluntarily phased out the use of 3rd and 4th generation cephalosporins in 2010. Tetracyclines have been given the multiplication factor of 1.5, to promote further reduction in tetracycline use for pigs.

Following the European Medicines Agency (EMA) recommendation that colistin should only be used as a second line treatment in animals, colistin was also given a multiplication factor of ten as a precautionary measure.

The differentiated Yellow Card has proven to be an efficient tool to promote prudent overall antimicrobial use in pig herds and to discourage use of certain critically important antimicrobials.

Figure 2.2 Changes in overall antmicrobial use in animals and distribution (%) of antimicrobial consumption by main animal species, Denmark



* Other animals include fur animals, aquaculture and pets

Animal definitions

Sow: Any breeding female pig on the farm.

Piglet: The new-born pig is called a piglet from birth until they are permanently separated (weaned) from the sow at 3-4 weeks of age. The weight of the piglet at weaning is approximately 7 kg.

Weaner: Any pig of 7-30 kg live weight after it has been weaned (dry diet and water only).

Finishers: Pigs from 30-100 kg live weight, after the weaner stage until the time of slaughter.

Metrics for measuring antimicrobial use in animals

Metrics of antimicrobial use are numerous, each with its own advantages and limitations. In DANMAP, antimicrobial consumption is measured in kg active compound or as treatment proportions.

Kg active compound: Provides of an overall crude comparison of antimicrobial use in the veterinary and human sectors. Importantly, it does not account for changes in population sizes or changes in usage patterns.

DADD (Defined animal daily dose): The average maintenance dose per day for a drug used for its main indication in the appropriate animal species.

DAPD (DADD per 1,000 animals per day): This metric takes into account differences in body-mass and lifespan. It provides an estimate of the proportion of animals treated daily with a particular antimicrobial agent. For example, 10 DAPDs indicate that an estimated 1% of the population, on average, receives a certain treatment on a given day (see DANMAP 2020, Materials and Methods).

In 2020, approximately two thirds of all antimicrobials prescribed in Denmark, were prescribed for veterinary use. The total use of antimicrobials in animals amounted to 99.5 tonnes of active compound.

From 2013 to 2019, the overall antimicrobial use in animals decreased, each year. However, this trend was broken in 2020, when the total use of antimicrobials increased by 2% (+2,250 kg) compared to 2019 (Figure 2.2). This increase may partly be due changes in the animal production, e.g. an increase in the pig production, which is the main driver of antimicrobial usage in animals in Denmark (Figure 2.2). In 2020, the pig sector used approximately 76% of all veterinary-prescribed antimicrobials, equal to 75.9 tonnes active compound.

Measured in treatment proportion, which includes adjustments for changes in production and export of pigs, an estimated 2.3% (23 DAPD) of all pigs received antimicrobial treatment per day in 2020. In 2010, when the Yellow Card initiative was introduced, approximately 3.5% of all pigs received treatment per day. Furthermore, the treatment proportion (measured in DAPD) is much higher in weaners than in the other age groups. Thus, on a given day in 2020, between 1-2% of the sows and piglets and finisher pigs and 9% of the weaner pigs received antimicrobial treatment. Levels that were quite similar to 2019.

Over time, the types of antimicrobials used in pigs has changed notably

For many years, tetracyclines was one of the most commonly used antimicrobials in the pig production. Several initiatives have aimed at reducing the use of tetracyclines, since use of tetracycline can select for livestock associated methicillin resistant *Staphylococcus Aureus* (LA-MRSA). The use of tetracyclines in pigs has decreased significantly, as a response to the differentiated Yellow Card initiative. Similarly, critically important antimicrobials such as fluoroquinolones, cephalosporins and colistin, have been phased out. During the same period, increases in the use of macrolides and aminoglycosides occurred (Figure 2.3).

Increase in the use of medical zinc in pigs

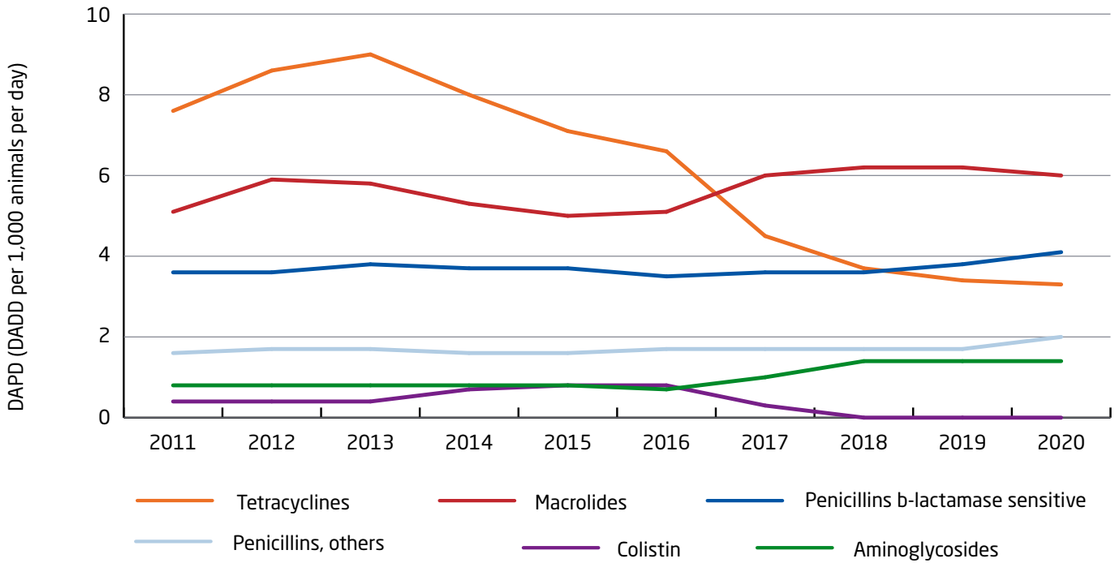
Medical zinc is prescribed to newly weaned pigs to prevent or treat diarrhoea. Monitoring of medical zinc is relevant, since it may select for antimicrobial-resistant bacteria including LA-MRSA. In 2017, The European Commission has announced an EU-wide withdrawal of medical zinc, effective per June 2022. Following a 13% decrease in the use of zinc oxide from 2015 to 2019, the use of medical zinc oxide amounted to 494 tonnes in 2020, equivalent to a 4% increase compared to 2019. This increase may partly be due to an increase in the pig production in 2020. However, with an annual use of almost 500 tonnes medical zinc, the industry is quite far from the target of zero use, which must be reached by June 2022.

Complete stop of 3rd and 4th generation cephalosporin use in food-producing animals

In 2020, antimicrobials prescribed for cattle amounted to 12.7 tonnes. Approximately 70% were used to treat older cattle (>1 year), 5% of which was for intramammary treatment. Over the past decade, the antimicrobial use for older cattle (>1 year) has decreased from 3.9 to 3.4 DAPD and increased from 5.5 to 8.7 DAPD in young cattle (<1 year). In 2019, the industry banned the use of 3rd and 4th generation cephalosporins for cattle and no use was recorded for cattle in 2020.

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

Figure 2.3 Antimicrobial use in the pig production, DAPD, Denmark, 2011-2020



Only selected antimicrobial classes are included in this figure. Fluoroquinolones and cephalosporins have been phased out. For more details, see DANMAP 2020

Antimicrobial use in other animals

Antimicrobial use in Danish **poultry** is generally low. The statistics may be markedly affected by diseases outbreaks in a few farms. In 2020, the usage increased by 47% to 2,362 kg. Approximately 43% were used for broilers and 44% for turkeys. Increases were seen mainly for tetracyclines prescribed for respiratory disease and macrolides prescribed for enteritis. For the past decade, cephalosporins have not been used in the poultry industry, and the use of fluoroquinolones has been close to zero. Colistin has not been used since 2016.

The use of antimicrobials for **fur animals** (mink) decreased markedly in 2020. This may in part be due to the increased focus on prudent use and low occurrence of disease in the first part of 2020. The overall use amounted to 2,454 kg in 2020, which was 38% less than in 2019 and equivalent to a treatment proportion of approximately 2% (19 DAPD). In the last months of 2020, the majority of Danish mink were culled due to the COVID-19 situation, and little or no antimicrobial use was registered for mink from October to December.

Antimicrobial consumption **in aquaculture** varies considerably with water temperatures, because bacterial diseases are more likely to occur when temperatures are high. The summer of 2020 was not as warm as the previous summers and this was reflected in a 22% decrease in antimicrobial use from 2,522 kg in 2019 to 1,961kg in 2020. Mainly three compounds are used to treat bacterial infections in aquaculture: sulfonamide/trimethoprim (53%), 1st generation quinolones (29%), and amphenicols (17%).

Since 2011, the use of antimicrobials in **dogs and cats** has decreased from (1,491 kg in 2011 vs. 1,232 kg in 2020), with a marked reduction (-72%) in the use of cephalosporins. In 2020, more than half of all veterinary-prescribed cephalosporins were prescribed for dogs and cats. In addition, almost all fluoroquinolones were prescribed for pets, and 3rd and 4th generation cephalosporins were only used in pets (1.2 kg in 2020).

The Danish Veterinary and Food Administration's Action Plans against antimicrobial resistance, 2017 and 2019

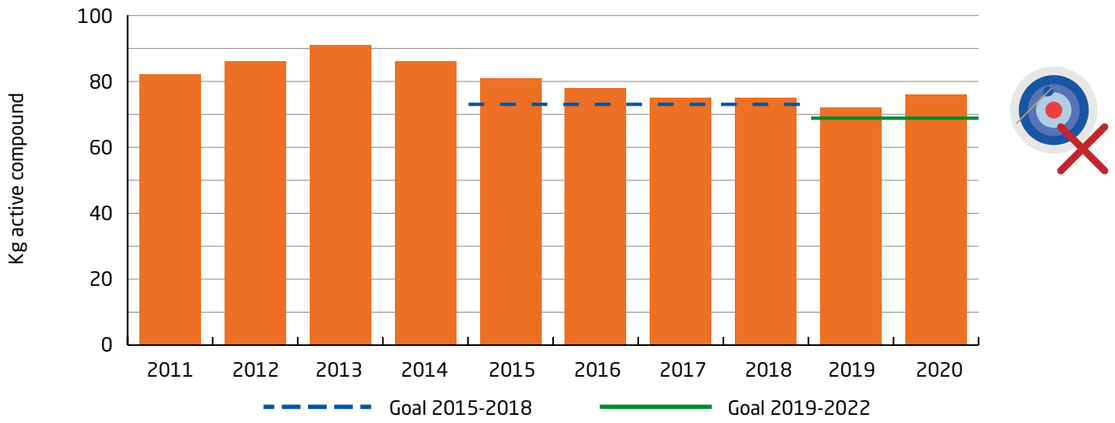
In 2017, the Ministry of Food, Agriculture and Fisheries and the Danish Ministry of Health launched a joint **One Health strategy on tackling AMR**. The aim of the One Health strategy was to provide a framework for strong and coordinated efforts across sectors to combat antibiotic resistance.

At the same time the Danish Veterinary and Food Administration launched an Action Plan against antimicrobial resistance in animals and food. The aim of the action plan was to implement the One Health strategy within the veterinary and food production sectors and the plan included two measurable goals for the reduction of veterinary antimicrobial consumption.

Goal 1: The total amount of antimicrobials used must not increase in 2017, compared to 2016. **This goal was achieved.**

Goal 2: The total amount of antimicrobials used in pigs should be reduced by 15% from 2015-2018, compared to 2014. **This goal was not achieved in 2018 (-13%).** The action plan was extended to 2019, and by then the use had been reduced by 16%. **In 2019, a new national target was determined: 8% reduction (2% per year) in the use of antimicrobials in the pig sector by 2022. The annual 2% reduction was not achieved in 2020** (Figure 2.4).

Figure 2.4 Anitimicrobial use in pigs and goals of the national action plan against antimicrobial resistance, Denmark, 2011-2020



Narrow and broad spectrum antimicrobials

Antimicrobials are not all alike. As for other types of medication, they have different mechanisms of action. Some have a narrow spectrum of action and inhibit a single group of bacteria. These are used in targeted treatment when the disease causing bacteria is known.

Other antimicrobials are broad spectrum and inhibit numerous groups of bacteria at the same time. They are used to treat diseases, before the disease causing bacteria is known. However, antimicrobials also inhibit useful and harmless bacteria such as the commensal bacteria of the gut, which enhances the emergence of resistant bacteria.

Critically important antimicrobials

All antimicrobials are important in the treatment of humans. Either because they need to be available for frequent treatment of common infections, or because they are among the few antimicrobials, that can be used to treat serious infections caused by resistant bacteria. The WHO has given those special global status of "highest priority critically important" to certain types of antimicrobials.

Denmark has declared four types of antimicrobials as 'critically important', namely carbapenems, 3rd and 4th generation cephalosporins, fluoroquinolones and colistin. The use of critically important antimicrobials is either strongly restricted or they have to be used carefully to ensure their effectivity in the future.

3. Antimicrobial consumption in humans

Antimicrobials are crucial for the treatment of infections. However, antimicrobial consumption is at the same time one of the main drivers of antimicrobial resistance. Thus, antimicrobials have to be used prudently in order to ensure their effectivity in the future. DANMAP monitors human and animal antimicrobial consumption to inform prescribers, policy makers and the public as well as to support the development of treatment guidelines and antimicrobial stewardship initiatives.

DANMAP's surveillance of antimicrobial consumption in humans is based on sales data from all public and private healthcare providers in Denmark (Figure 1.1).

Metrics for measuring antimicrobial use in humans

DDD (Defined Daily Dose*): The assumed average maintenance dose per day for a drug used for its main indication in adults.

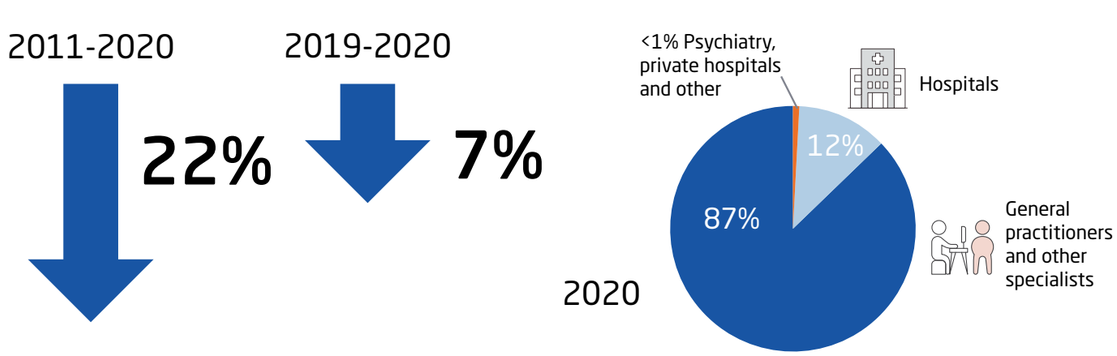
DID: DDD per 1,000 inhabitants per day. The unit takes changes in population size over time into account.

DAD: DDD per 100 admissions. The unit takes changes in hospital activity over time into account.

DBD: DDD per 100 bed-days. The unit takes changes in hospital activity over time into account.

* as defined by the WHO Collaborating Centre for Drug Statistics Methodology

Figure 3.1 Changes in total antimicrobial consumption over time and distribution by health care providers, Denmark



Primary health care is still the main driver of reductions in antimicrobial consumption

In 2020, total antimicrobial consumption in primary health care was 12.8 DID, a 25% reduction since 2011 (17.1 DID) and a 7% reduction since 2019 (13.8 DID), (Figure 3.1). Consumption decreased across all age groups between 2019 and 2020 except for adolescents (20-24 years).

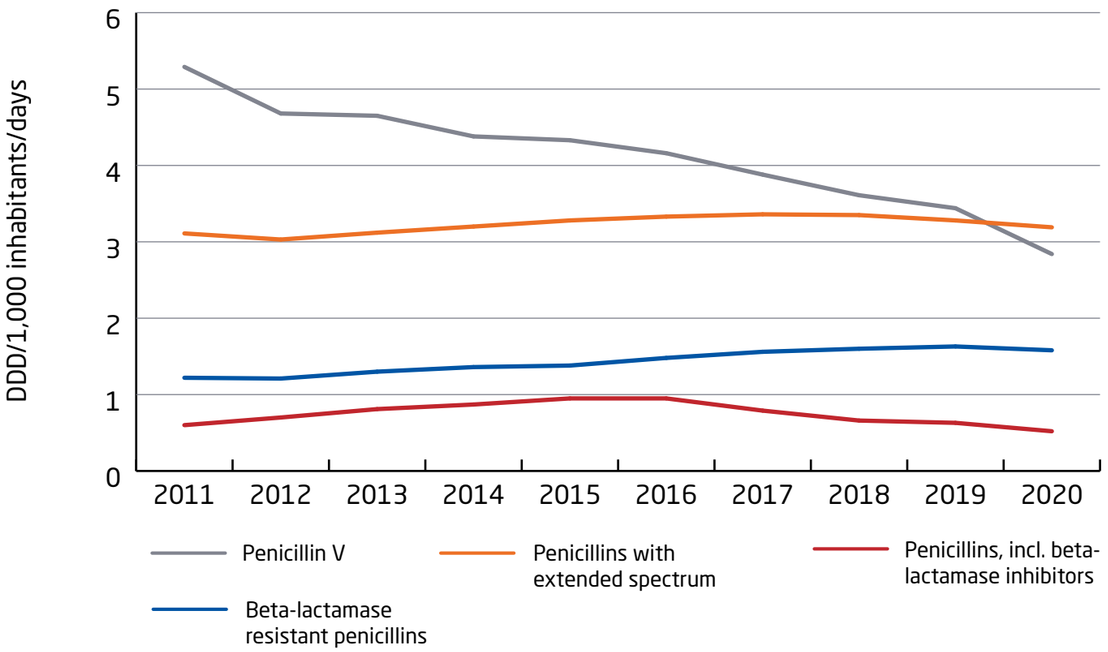
Antimicrobial consumption in hospitals increased further when measured per patients' bed-days or admissions to hospital

Antimicrobial consumption in Danish hospitals was 123.3 DBD in 2020. This represents a 33% increase compared to 2011 (92.5 DBD) and a 4% increase compared to 2019 (118.7 DBD). Measured in DAD, the consumption in 2020 (531.5 DAD) was 16% higher than in 2011 (459 DAD) and 1% higher than in 2019 (526 DAD).

Shift to broader-spectrum penicillins in primary health care and in hospitals

In 2020, penicillins accounted for 63% of antimicrobial consumption in primary health care and 55% of antimicrobial consumption in hospital care. For decades, penicillin V was the most used antimicrobial in primary health care in Denmark. This changed in 2020 where penicillins with extended spectrum were the most used group of antimicrobials (25% of total antimicrobial consumption), (Figure 3.2). In hospitals, the most used group of antimicrobials were penicillins incl. beta-lactamase inhibitors (18%) in 2020 with an increase of 197% over the past decade.

Figure 3.2 Consumption of different penicillins in primary health care, Denmark, 2011-2020



Marked changes in tetracycline and macrolide use in primary health care

During the last decade, the consumption of tetracyclines and macrolides decreased by 3% and 56%, respectively. However, in 2020, the consumption of tetracyclines increased by 15% compared to 2019, whereas consumption of macrolides showed a further marked reduction of 19%.This shift may reflect compliance with a new treatment guidance for chlamydia infections, which was published in 2019, and recommends doxycycline instead of azithromycin as first-line treatment.

The Danish Government's National Action Plan for reduction of antibiotics in humans

Following a joint One Health strategy with the Ministry of Food, Agricultur and Fisheries in 2017 on tackling AMR, the Ministry of Health also launched an Action plan for reduction of antimicrobial use in humans in 2017. The action plan included three measurable goals aimed at reducing human antimicrobial consumption – and thereby antimicrobial resistance - by 2020.

The Ministry of Health has extended the National Action Plan until 2021 acknowledging the significant impact the COVID-19 pandemic had on healthcare provision and allowing more time for achieving the goals.

Goal 1: The number of redeemed prescriptions for antibiotics in the primary health care sector should be reduced from 460 prescriptions per 1,000 inhabitants per year in 2016 to 350 prescriptions per 1,000 inhabitants per year in 2020 (prescriptions from hospital doctors are not included). **This goal was achieved** (Figure 3.3).

Goal 2: Narrow-spectrum antibiotics should be used more frequently in illness treatment. The use of penicillin V should be increased from approx. 31% in 2016 to constituting 36% of the total antibiotic use in the primary health care sector in 2020, measured by the number of prescriptions per 1,000 inhabitants. **This goal was not achieved** (the proportion of penicillin V used in primary health care decreased to 27% in 2020), (Figure 3.4).

Goal 3: The consumption of critically important* antibiotics (carbapenems, cephalosporins, fluoroquinolones) should be reduced by 10% by 2020 measured by DDD/100 bed-days for hospitalised patients, compared with consumption in 2016. **This goal was not achieved** (use of critically important antibiotics in hospitals decreased by 7.2% between 2020 and 2016), (Figure 3.5).

* as defined by The Danish Health Authority Guideline on antimicrobial prescription

Figure 3.3 Goal 1: Total number of prescriptions for antibiotics in primary health care, Denmark, 2016-2020

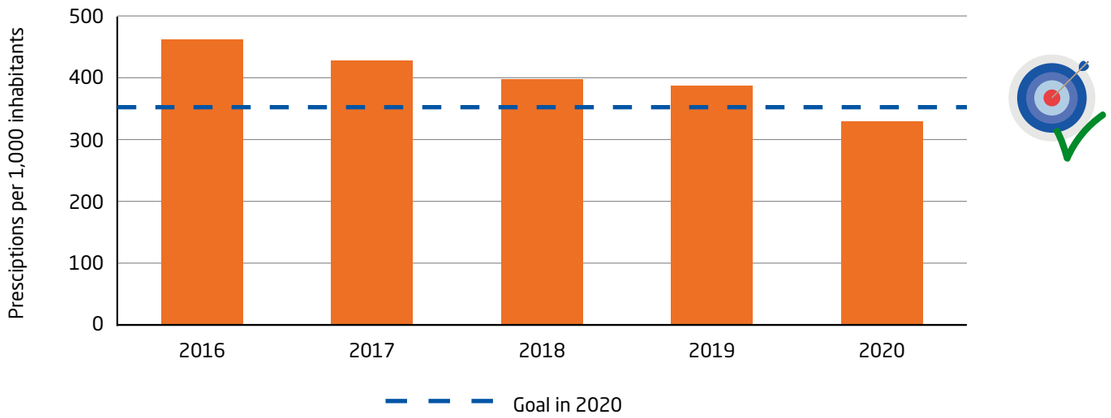


Figure 3.4 Goal 2: Proportion of penicillin V compared to total antibiotic consumption in primary health care, Denmark, 2016-2020

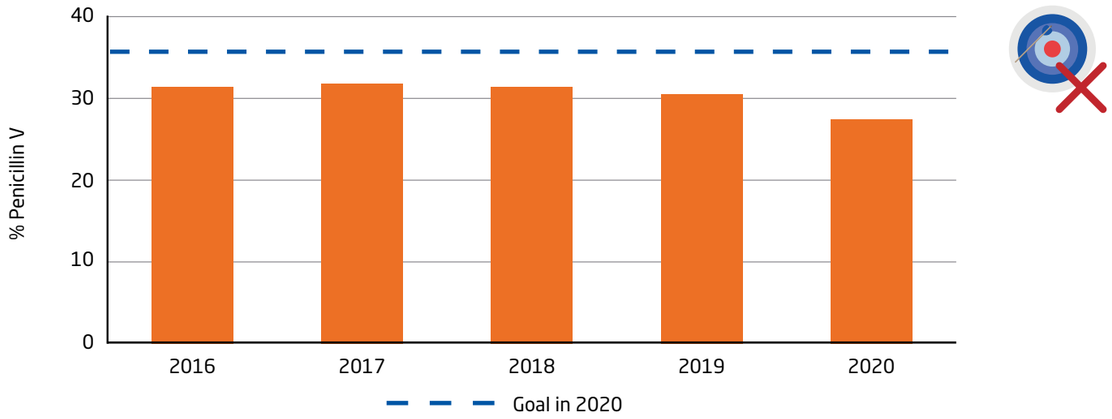
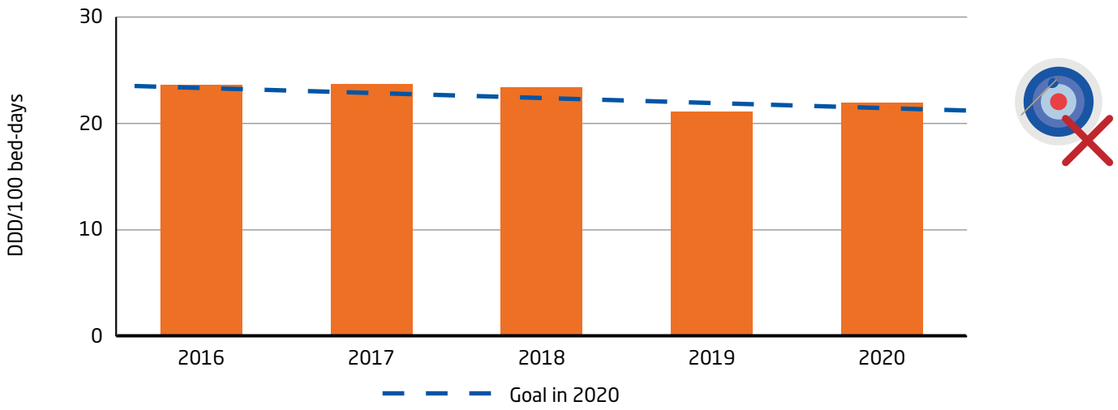


Figure 3.5 Goal 3: Consumption of critically important antibiotics (cephalosporins, fluoroquinolones, carbapenems) in hospitals, Denmark, 2016-2020



4. Impact of the COVID-19 pandemic on antimicrobial consumption

The first confirmed case of the novel coronavirus SARS-CoV-2 in Denmark was reported on 27 February 2020. The World Health Organization declared the rapidly spreading SARS-CoV-2 outbreak a pandemic in March 2020. Due to the high transmissibility of the virus and the clinical severity of the associated coronavirus disease (COVID-19), the Danish Government introduced a national lockdown in March 2020. Both the healthcare system and public life in Denmark were severely affected by the pandemic throughout 2020 and beyond. This chapter describes the impact of the pandemic on primary health care consultations, hospital admissions and antimicrobial consumption.

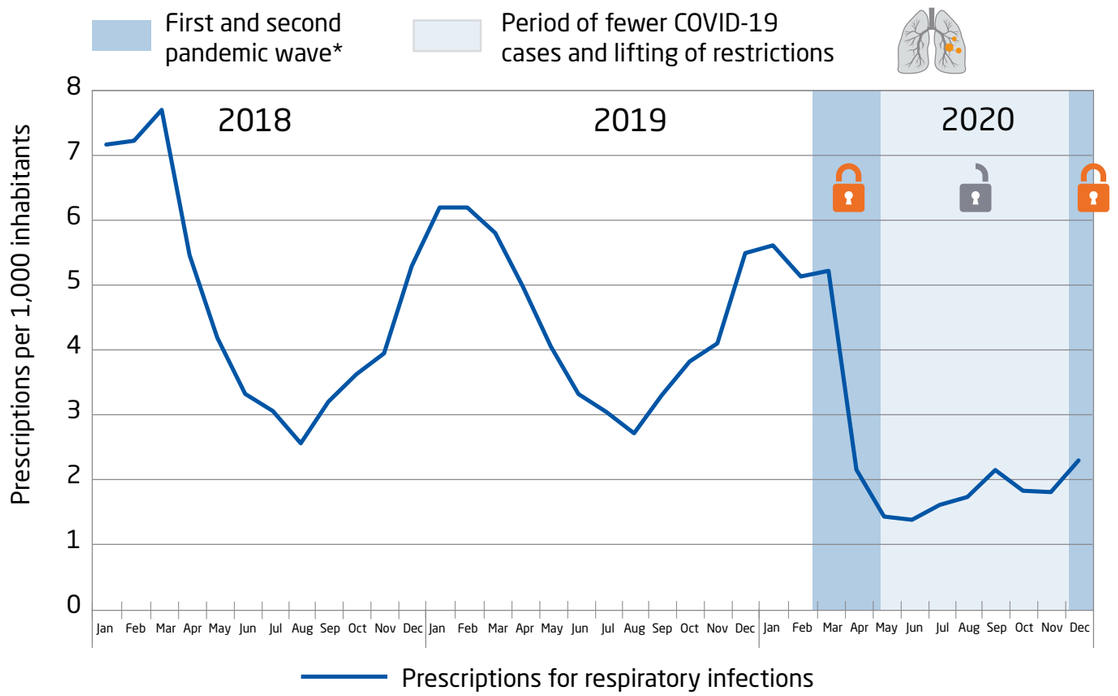
Consultation numbers in primary health care were 7% higher in 2020 compared to 2019 and shifted from face-to-face to remote consultations

Overall, consultation numbers in primary health care were 7% higher in 2020 compared with 2019. Consultation types changed during the pandemic with a shift to phone/video/email appointments - only 36% of consultations were held face-to-face in April 2020 compared to 57% in April 2019. The proportion of phone/video/email appointments decreased after easing of restrictions in May 2020 but continued to stay higher for the rest of the year compared to 2019.

Sharp drop in prescriptions for respiratory infections following national lockdown

The total number of antimicrobial prescriptions issued in primary health care per 1,000 inhabitants was 12% lower in 2020 than in 2019. The sharp drop in prescriptions of beta-lactamase sensitive penicillins and macrolides for respiratory infections following the first national lockdown in March probably reflects changes in patients' healthcare seeking behaviour and lower incidence of bacterial respiratory infections due to the measures aimed at reducing SARS-CoV-2 transmission (Figure 4.1). The reduction was most marked in children between 0 and 9 years of age (up to 54% reduction).

Figure 4.1 Consumption of beta-lactamase sensitive penicillins in primary health care with indication for respiratory diseases, prescriptions per 1,000 inhabitants, Denmark, 2018-2020



* The 'first wave' of the pandemic is defined as the period from 27 February 2020 (first SARS-CoV-2 cases in Denmark) to beginning of May 2020 (low incidence of SARS-CoV-2 cases, most restrictions lifted) and the 'second wave' as beginning of December 2020 (start of exponential growth of incidence and second series of restrictions/lockdown [large shops, high schools are closing])

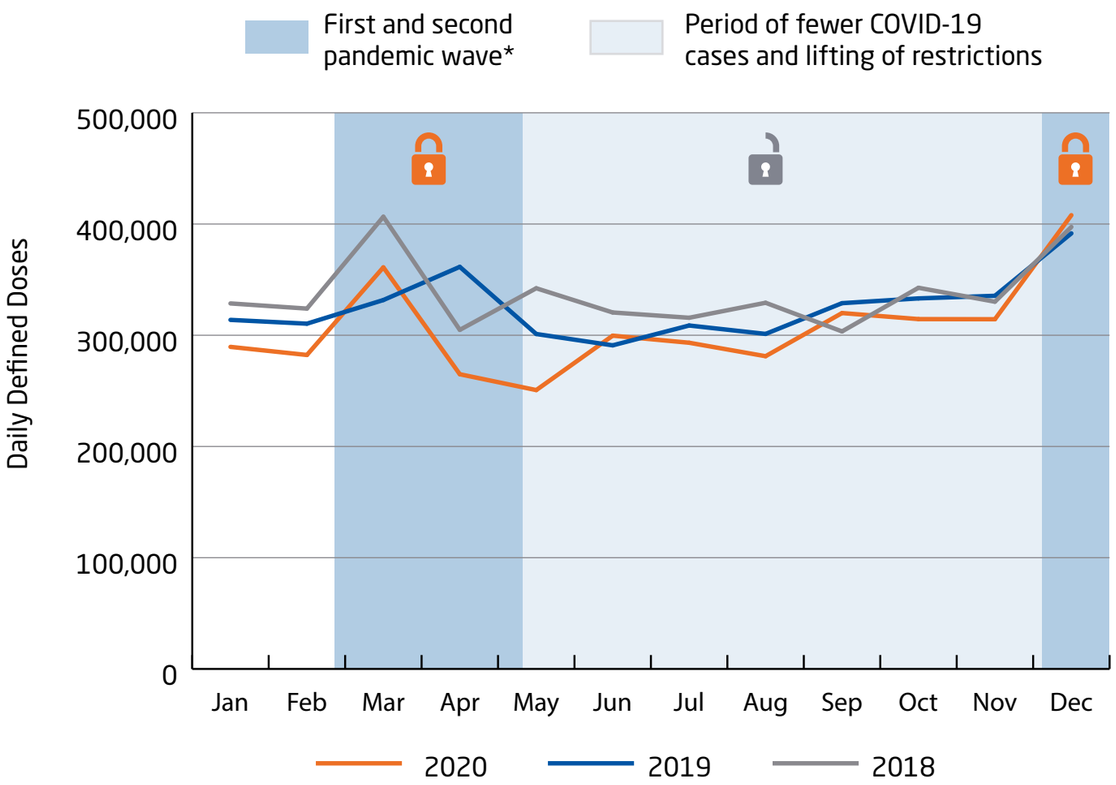
Hospital doctors issued more antimicrobial prescriptions for patients in the community compared to previous years

Doctors of different specialities in primary health care (e.g. general practitioners, ear-nose-throat specialists, dermato-venereology specialists, dentists and hospital doctors prescribing for patients in the community) issued fewer prescriptions during the first pandemic wave. Following the easing of restrictions, only hospital doctors issued more prescriptions for patients in the community than in previous years, possibly due to earlier discharge and fewer admissions of hospital patients.

Antimicrobial use per patient admitted to hospital was markedly higher during the first pandemic wave compared to the same time periods in 2018 and 2019

Total consumption of antimicrobials was lower in hospitals during the first pandemic wave when measured in Defined Daily Doses (DDD) and compared to the same time period in 2018 and 2019 (Figure 4.2). This reflects fewer patients being admitted to hospitals between February and June 2020, for example due to cancellations of non-urgent procedures. In contrast, consumption was higher during both pandemic waves compared to previous years when measured **per patient admission (DAD)** (Figure 4.3). This probably shows that more of the patients who were admitted to hospital during the pandemic waves were seriously ill.

Figure 4.2 Total consumption of antimicrobial agents for systemic use in somatic hospitals, Daily Defined Doses, Denmark, 2018-2020



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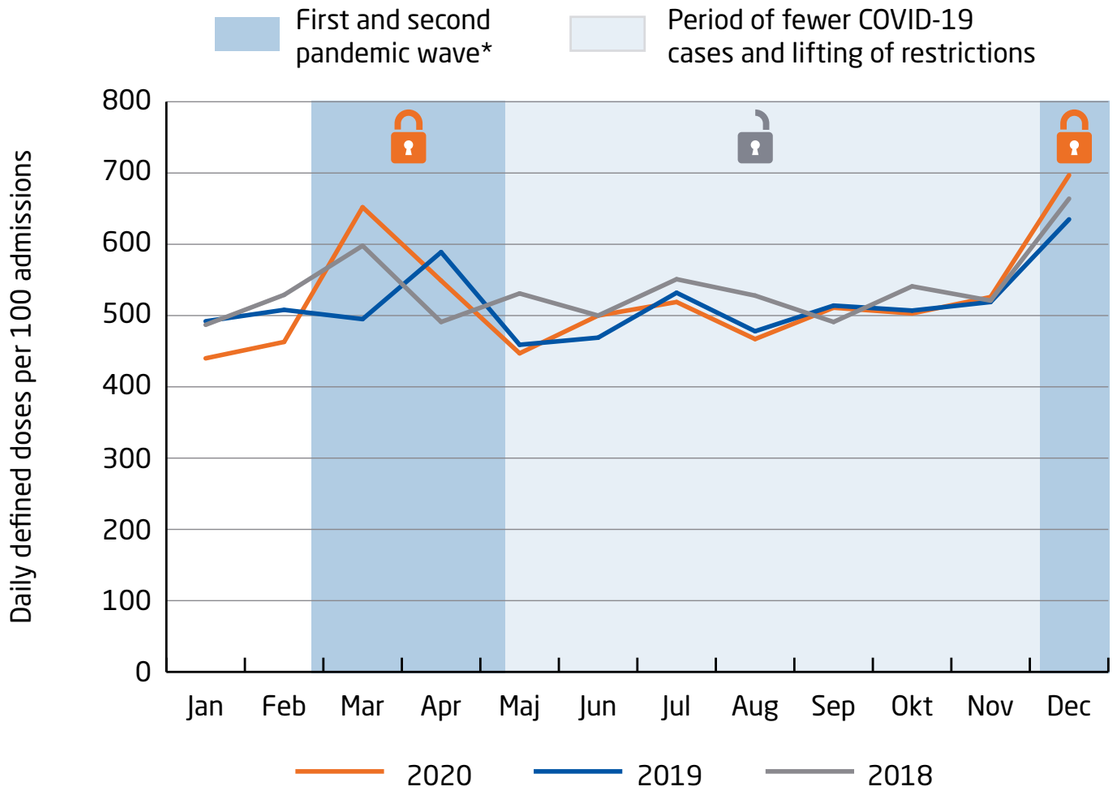
Somatic hospitals - definition

Somatic hospitals are public hospitals with acute care function. Psychiatric hospitals, private hospitals and hospices are not included since consumption at these facilities is minor.

Figure 4.3 Total consumption of antimicrobial agents for systemic use in somatic hospitals, Daily Defined Doses per 100 admissions, Denmark, 2018-2020



* The 'first wave' of the pandemic is defined as the period from 27 February 2020 (first SARS-CoV-2 cases in Denmark) to beginning of May 2020 (low incidence of SARS-CoV-2 cases, most restrictions lifted) and the 'second wave' as beginning of December 2020 (start of exponential growth of incidence and second series of restrictions/lockdown [large shops, high schools are closing])

This steep increase in consumption per patient admitted to hospital was also seen for key antimicrobials (carbapenems and penicillin and beta-lactamase inhibitor combinations), usually reserved for treatment of serious infections. The high use of these antimicrobials in March and April 2020 probably reflects the change in patient-mix in hospitals during this time which has already been described above. It may also reflect changes in behaviour, i.e. a more risk-averse approach by prescribers, due to high occupancy rates on many intensive care units and the uncertainty around treatment of COVID-19 patients in the first few weeks of the pandemic.

5. Resistance in zoonotic bacteria

Zoonoses are infectious diseases that can be transmitted between animals and humans, either through direct contacts or indirectly through contaminated water, food or the environment.

Surveillance of antimicrobial resistance in *Campylobacter* and *Salmonella* has been part of the DANMAP programme since the beginning. In 2020, *Campylobacter* and *Salmonella* remained the two most common causes of bacterial foodborne illness in Denmark, with 3,742 and 614 laboratory-confirmed human cases, respectively. In Denmark, antimicrobials are generally not recommended for treatment of diarrhoea in patients unless there is prolonged duration or the patient is severely ill. If treatment is required, macrolides (azithromycin) are recommended for treatment of *Campylobacter* infections. There are no general recommendations for treatment of zoonotic *Salmonella* infections in the primary sector, but for infections treated in hospitals, azithromycin or ciprofloxacin is recommended [http://pro.medicin.dk]. Macrolide resistance is monitored by erythromycin in *Campylobacter* and azithromycin in *Salmonella*, and ciprofloxacin is used for monitoring fluoroquinolone resistance in both *Campylobacter* and *Salmonella*.

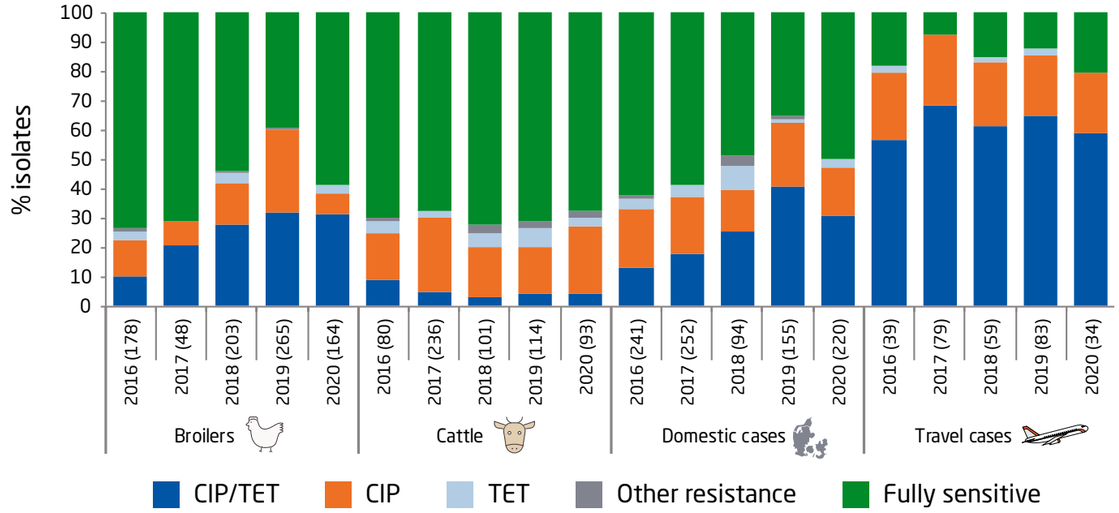
Resistance in *Campylobacter jejuni*

Campylobacter jejuni is the species most commonly associated with human infections. In 2020, the percentage of *Campylobacter jejuni* isolates that were sensitive to all antimicrobials tested increased for the first time since 2016. More than half (59%) of the isolates from Danish broilers, and 50% of isolates from human cases acquired in Denmark were fully sensitive to all of the antimicrobials tested (Figure 5.1). In contrast, only 21% of the isolates from human infections acquired abroad were sensitive to all antimicrobials in the test panels.

Fluoroquinolone (ciprofloxacin) resistance remained common in *Campylobacter jejuni* isolates from human cases (51%), broilers (38%) and cattle (27%), even though fluoroquinolones are not used in food production animals in Denmark.

As in previous years, macrolide (erythromycin) resistance was not observed in human isolates from domestically acquired infections, cattle and broilers.

Figure 5.1 Distribution (%) of AMR profiles in *Campylobacter jejuni* from broilers, cattle and human cases, Denmark, 2016-2020



Broilers include isolates from Danish broiler meat when available. CIP: all isolates with ciprofloxacin resistance, but without tetracycline resistance. TET: all isolates with tetracycline resistance, but without ciprofloxacin resistance. CIP/TET: all isolates with ciprofloxacin and tetracycline resistance. CIP/TET, CIP and TET isolates may be resistant to erythromycin, nalidixic acid or streptomycin

Salmonella - most *S.* Typhimurium isolates were resistant to several antimicrobials

DANMAP focuses on resistance in *Salmonella* Typhimurium, because this serotype is often associated with contaminated pork and present in clinical human isolates and in isolates from production animals.

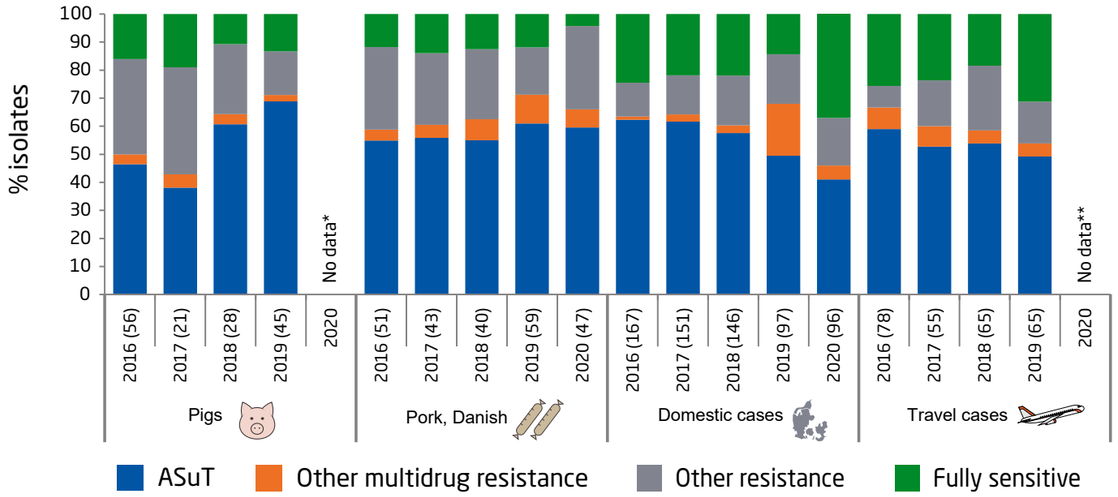
In 2020, most of the *S.* Typhimurium isolates were resistant to several antimicrobials. Only 4% of the isolates from pork and 39% of the isolates from human cases were fully sensitive to all antimicrobials tested, compared to 12% and 14% in 2019, respectively (Figure 5.2). Similar to previous year, the ASuT phenotypes was the most frequent resistance profile among *S.* Typhimurium from Danish pork and human cases.

In 2020, the level of macrolide (azithromycin) resistance in *Salmonella* Typhimurium isolates was 1% in isolates from humans, while no macrolide resistance was detected in isolates from Danish pork.

Among *S.* Typhimurium isolates from human cases acquired in Denmark, resistance to fluoroquinolones (ciprofloxacin) remained low (1%). Among all *S.* Typhimurium isolates from human cases (cases acquired in Denmark and abroad, and cases with unknown travel history), 3% of the were resistant to fluoroquinolones. This percentage is lower than in 2019 (6%) and likely affected by the reduction of travel-associated cases in 2020, due to the COVID-19 travel-restrictions. Fluoroquinolone resistance in *S.* Typhimurium from Danish pigs and pork is rare and has not been recorded since 2010 and 2007, respectively.

Similar to previous years, resistance to the critically important 3rd generation cephalosporins and carbapenems was not observed in *S.* Typhimurium isolates from Danish pork. Furthermore, no carbapenem resistance was observed in *S.* Typhimurium from humans and the level of resistance towards 3rd generation cephalosporins remained low (1%).

Figure 5.2 Relative distributions (%) of AMR profiles among *Salmonella* Typhimurium from pigs, pork and human cases, Denmark, 2016-2020



The number of isolates included each year is shown in parentheses. Includes isolates monophasic variants of *S.* Typhimurium with antigenic formulas *S.* 4,[5],12:i:-. An isolate is considered fully sensitive if susceptible to all antimicrobials tested, and multidrug-resistant if resistant to 3 or more of the 12 antimicrobial classes tested. ASuT are isolates that are resistant to ampicillin, sulfonamide and tetracycline
* No data
** Distribution not shown due to low number of isolates (14)

Resistance definitions

CIP: Resistance against ciprofloxacin.
TET: Resistance against tetracyclines.
CIP/TET: Resistance against ciprofloxacin and tetracyclines.
ASuT: Resistance against ampicillin, sulfonamide and tetracycline.

6. Resistance in indicator bacteria

Indicator bacteria such as *Escherichia coli* and *Enterococcus* are present as part of the normal gut flora of healthy animals and humans. However, they have the potential to cause infection especially in immunocompromised patients or patients with foreign body implants. *E. coli* and *Enterococcus* isolates from healthy food-producing animals are included in DANMAP to monitor the status of antimicrobial resistance in the animal reservoirs. Furthermore, in accordance with harmonised EU monitoring, particularly important types of resistant bacteria are included in the programme: *E. coli* exhibiting resistance to 3rd generation cephalosporins via production of extended-spectrum beta-lactamases (ESBLs) or AmpC beta-lactamases (AmpCs) and carbapenemase-producing *E. coli* (CPE). In 2020, ESBL/AmpC/CPE were monitored in broilers and broiler meat. No CPE isolates were detected.

Indicator *E. coli*

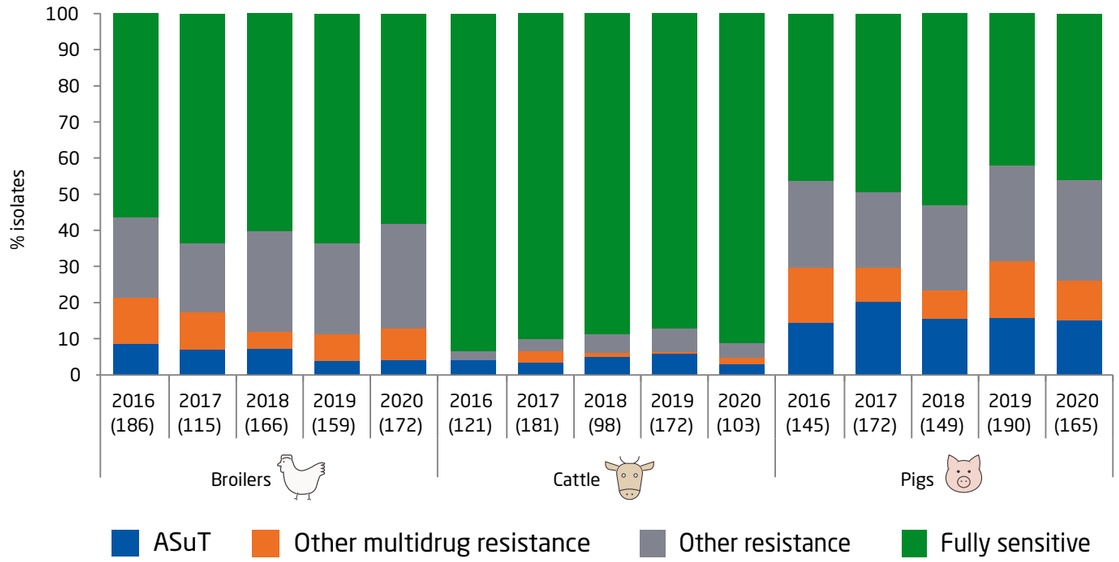
In 2020, the overall occurrence of antimicrobial resistance in indicator *E. coli* from broilers, pigs and cattle were similar to previous years. The level of resistance is much lower in isolates from cattle than in isolates from broilers and pigs. In 2020, 91% of the isolates from cattle, 58% of broiler isolates, and 46% of isolates from pigs were susceptible to all antimicrobials tested. The highest occurrence of multidrug resistance was also found in isolates from pigs (Figure 6.1).

The relative occurrence of multidrug-resistance in isolates from broilers decreased significantly between 2015 and 2019, but levelled out in 2020. Among the multidrug-resistant isolates, combined resistance to ampicillin, sulfonamide and tetracycline (ASuT) was commonly observed (32%).

In broilers, there has been an increasing trend in *E. coli* resistant to ciprofloxacin and nalidixic acid during the last decade, and a decrease in *E. coli* resistant to ampicillin, chloramphenicol, tetracycline and trimethoprim over the last 5 years.

The reduction in use of tetracycline and colistin and the increased use of macrolides and aminoglycosides since 2016, have not led to measurable changes in the resistance patterns in *E. coli* from pigs. The observed resistance phenotypes mostly relevant to human health were ciprofloxacin resistance in broiler isolates and azithromycin resistance in pig isolates since these are key antimicrobials in human treatment.

Figure 6.1 Relative distributions (%) of fully sensitive, resistant and multidrug-resistant *Escherichia coli* isolates from broilers, cattle and pigs, Denmark, 2016-2020



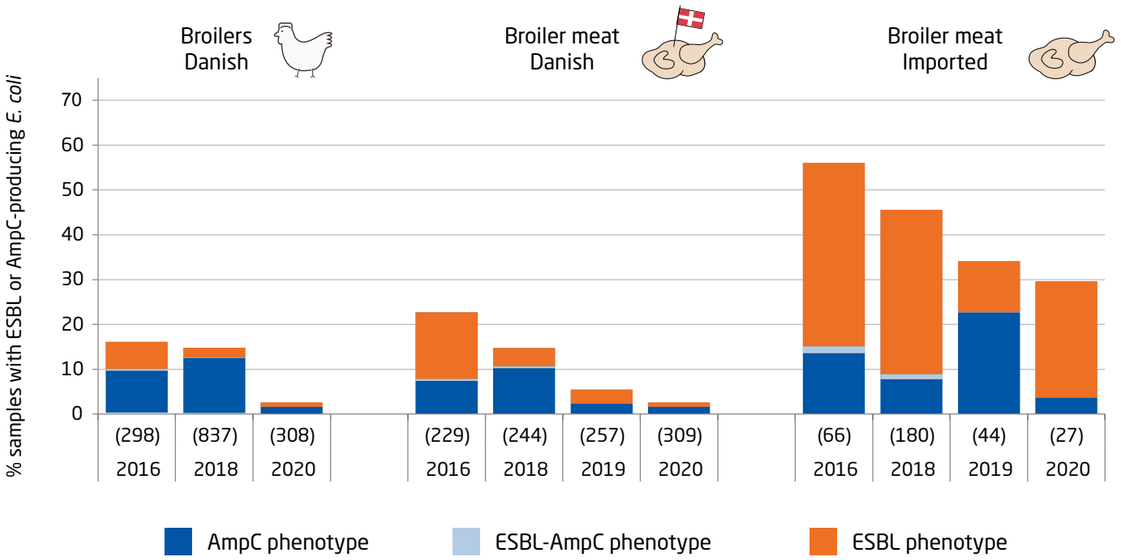
The number of isolates included each year is shown in parentheses. An isolate is considered fully sensitive if susceptible to all antimicrobial agents tested, and multidrug-resistant if resistant to 3 or more of the 12 antimicrobial classes tested. ASuT are the multidrug-resistant isolates resistant to ampicillin, sulfonamide and tetracycline, but may also be resistant to other antimicrobials

Decreasing trend for ESBL/AmpC-producing *E. coli* in Danish broilers and broiler meat

In the 6-year period with EU harmonised monitoring, the overall prevalence of ESBL/AmpC-producing *E. coli* showed a significant decreasing trend in Danish broilers and broiler meat, as well as in imported broiler meat.

In 2020, only one ESBL-producing isolate from broilers was found using non-selective methods. Using selective methods, ESBL/AmpC producing *E. coli* were found in 3% of the samples from Danish broilers and broiler meat and in 30% of samples from imported broiler meat (Figure 6.2). All the ESBL/AmpC-producing *E. coli* were resistant to 3rd generation cephalosporins and ampicillin. Resistance to 4th generation cephalosporins (cefepime) was found in all isolates from imported broiler meat and half of the isolates from Danish broilers and broiler meat. As previously, different combinations of additional multidrug resistance was observed.

Figure 6.2 Occurrence (%) of samples with phenotypic ESBL- or AmpC-producing *E. coli* from broilers and broiler meat recovered by selective enrichment, Denmark, 2016-2020



Number of samples tested per year is presented in parentheses. Classification of CPE, ESBL and AmpC phenotypes according to the scheme provided by EFSA. No samples were collected in 2017. Broilers were not sampled in 2019

Enterococci

Enterococci are commensal bacteria in the intestine in both animals and humans, however, both *E. faecalis* and *E. faecium* can cause human disease. In humans, an increase in infections caused by invasive enterococci, mainly *E. faecium*, has been observed since 2002, but did not increase further in 2020. The proportion of invasive vancomycin-resistant *E. faecium* isolates reported in MiBa is relatively high in Denmark (9.4% in 2020).

In 2020, resistance in Enterococci was monitored in broilers and found in 97% of 258 samples. Overall, 48% of the *E. faecium* isolates and 38% of the *E. faecalis* were susceptible to all antimicrobials tested, excluding quinupristin/dalfopristin. *E. faecalis* are assumed intrinsically resistant to streptogramins. Among *E. faecium* isolates, resistance to quinupristin/dalfopristin (44%) and tetracycline (12%) were the most common, whereas resistance to tetracycline (62%), and erythromycin (38%) were the most commonly observed among *E. faecalis*.

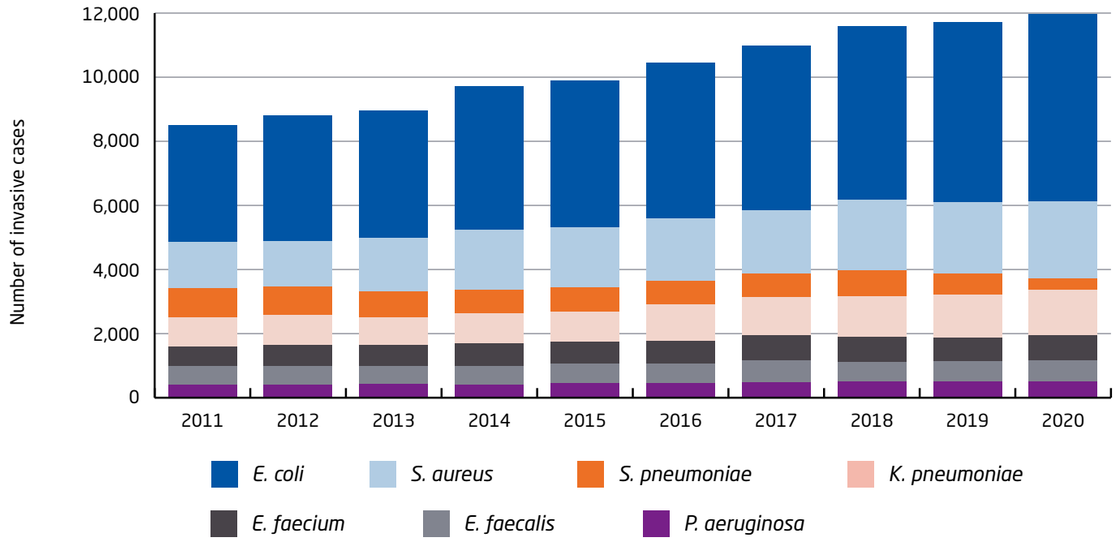
None of the *E. faecium* or *E. faecalis* isolates from broilers exhibited resistance to linezolid and tigecycline. None of the *E. faecalis* isolates exhibited teicoplanin or vancomycin resistance and <1% of the tested *E. faecium* isolates were found resistant to teicoplanin and vancomycin. This is important, since these antimicrobials are critically important to human medicine and are considered last resort compounds to treat severe infections caused by Gram positive bacteria.

7. Resistance in human clinical bacteria

DANMAP's surveillance of antimicrobial resistance in bacteria isolated from humans is based on the results of routine testing from all Departments of Clinical Microbiology reported to the Danish Microbiology Database (MiBa). DANMAP is also monitoring the testing results of specified isolates submitted to reference laboratories at SSI.

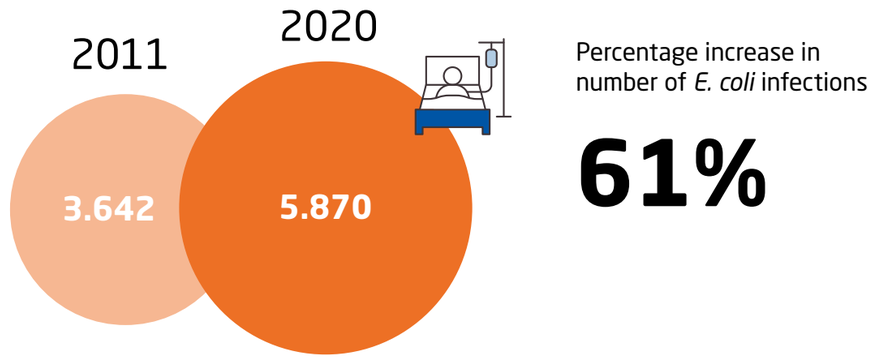
In addition, DANMAP also surveils the number of key invasive bacterial infections (blood and cerebrospinal fluid isolates) to be able to determine the proportion of invasive infections that are caused by resistant bacteria.

Figure 7.1 Number of invasive cases for bacterial species under surveillance, Denmark, 2011-2020



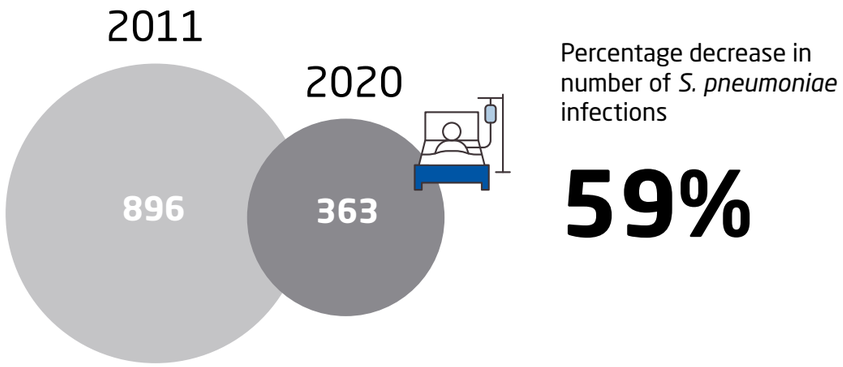
Escherichia coli was the most frequent cause of invasive infections (Figure 7.1) with a 61% increase in the number of invasive isolates over the last decade (Figure 7.2). This is most likely due to an increase in at-risk groups (elderly, immunocompromised/comorbid patients) and potentially in invasive medical procedures. However, many operations have become less invasive and safer due to new technology, same-day surgery and surgical patient safety initiatives. This trend warrants further investigations to inform prevention measures.

Figure 7.2 Increase in invasive infections caused by *E. coli*, Denmark, 2011 and 2020



Streptococcus pneumoniae was the only bacterial species for which invasive numbers decreased by 59% between 2011 and 2020 (Figure 7.3) including a marked reduction between 2019 and 2020 (Figure 7.1). The lower numbers of invasive *S. pneumoniae* infections are probably due to the introduction of the pneumococcal vaccine in the Danish childhood vaccination programme in 2007 and, more recently, the national restrictions aimed at preventing SARS-CoV-2 transmission in 2020.

Figure 7.3 Decrease in invasive infections caused by *S. pneumoniae*, Denmark, 2011 and 2020



The number of ESBL/AmpC positive invasive isolates of *Escherichia coli* has decreased

Monitoring the presence of ESBL/AmpC enzymes in invasive *E. coli* isolates is important since they confer resistance to most beta-lactam antibiotics, thereby limiting treatment options for infected patients. Between 2019 and 2020, the number of ESBL- and/or AmpC positive invasive *E. coli* isolates decreased by 6% (from 373 to 352 isolates).

Antimicrobial resistance in invasive isolates of *Klebsiella pneumoniae* has decreased for key antimicrobials including 3rd generation cephalosporins

Antimicrobial resistance decreased for key antimicrobials (3rd gen. cephalosporins, gentamicin, cefuroxime and ciprofloxacin) in invasive and urine *K. pneumoniae* isolates over the last ten years. Especially the reduced resistance to 3rd generation cephalosporins is a positive development potentially linked to lower use of 2nd and 3rd generation cephalosporins in hospitals since 2017.

In contrast, carbapenem resistance has increased in invasive *K. pneumoniae* isolates since 2011 but still remained at low levels (11 [0.8%] out of 1,411 invasive isolates) in 2020. Decreased susceptibility (=resistant and intermediate susceptible isolates) to piperacillin-tazobactam also went up from 5% in 2011 to 9% in 2020 potentially mirroring the increasing use of piperacillin-tazobactam in the hospital sector. Given that carbapenems and piperacillin-tazobactam are important antimicrobials for the treatment of patients with severe infections these trends need to be monitored carefully.

Carbapenemase-producing organisms (CPO) and Enterobacterales (CPE)

Carbapenemase-producing organisms (CPO) are of national and international concern as they are resistant to beta-lactam antimicrobials including carbapenems, which are used to treat serious infections, for example caused by multi-resistant bacteria. CPO infections are associated with high mortality and healthcare costs due to longer treatment and lengths of hospital stay. Importantly, CPO have the potential for transmission of resistance to other bacteria via mobile genetic elements and cause increasingly outbreaks in healthcare settings.

Detection of CPO was made notifiable in Denmark in September 2018.

CPO comprise of two main groups:

- Intestinal bacteria (Carbapenemase-producing Enterobacterales [CPE]) e.g. *Escherichia coli, Klebsiella pneumoniae*
- Environmental bacteria e.g. *Pseudomonas aeruginosa, Acinetobacter baumannii*

Nine new CPE hospital outbreaks were captured by SSI's outbreak database in 2020

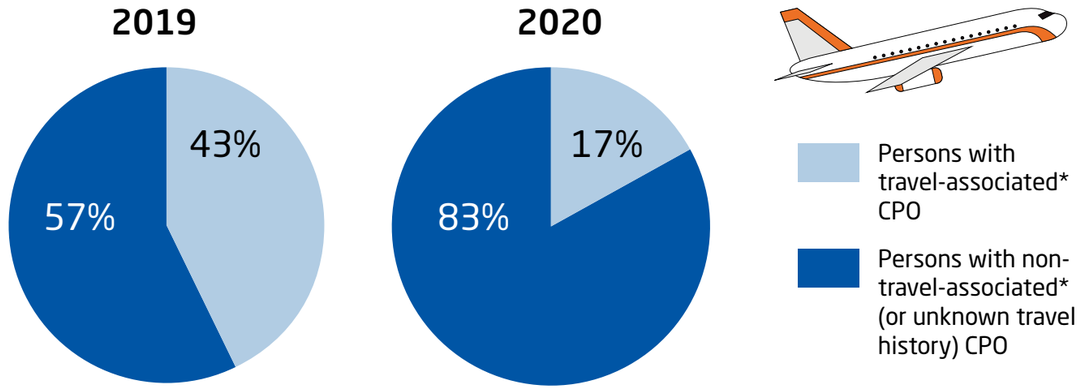
In 2020, SSI's national database for CPE outbreaks captured 9 CPE hospital outbreaks which were identified by whole genome sequencing. In addition, there were 11 already ongoing hospital outbreaks in Denmark.

Fewer CPO isolates were associated with travel in 2020 compared to 2019

The number of travel-associated CPO isolates decreased most likely due to COVID-19-related travel restrictions. Only 35 (17%) of patients with a CPO reported recent travel outside the Nordic countries compared to 80 (43%) patients in 2019 (Figure 7.4).

The continuous increase in the number of CPO isolates and CPE hospital outbreaks over the last ten years emphasizes the importance of the national guidance on prevention of the spread of CPO.

Figure 7.4 Percentage distribution of travel-associated and non-travel-associated infections with CPO, Denmark, 2019-2020



* Travels outside the Nordic countries

The number of invasive vancomycin-resistant and vancomycin-variable *enterococci* (VRE/VVE) stayed stable between 2019 and 2020

In 2020, 656 invasive VRE/VVE isolates were detected in Denmark - a similar number compared to the 660 isolates found in 2019. This is a positive development after the increases seen between 2011 and 2018. The plateauing number of invasive VRE/VVE isolates is probably the result of joint efforts by clinicians and infection prevention and control teams to control outbreaks in healthcare facilities and implement prevention strategies.

The numbers of linezolid-resistant *enterococci* (LRE) and linezolid-vancomycin-resistant *enterococci* (LVRE) were small in 2020 (7 and 8 isolates, respectively). These findings are still of concern, as treatment options for LVRE are very limited which emphasizes again the importance of antimicrobial stewardship and infection prevention and control measures.

Staphylococcus aureus - the number of bacteraemia cases continued to increase in 2020

Staphylococcus aureus is part of the normal flora of the skin and mucosa but may cause blood-stream infections. Methicillin-resistant *S. aureus* (MRSA) are resistant against the penicillins usually used to treat staphylococcal infections. Livestock-associated MRSA (LA-MRSA) are found in livestock, especially in pigs, unlike other variants of MRSA, which are primarily found in humans.

The number of patients where *S. aureus* was isolated from blood (=bacteraemia) increased by 5% from 2,233 cases in 2019 to 2,342 cases in 2020. Thirty-eight (2%) of the bacteraemia cases were methicillin-resistant (MRSA) out of which almost a third of cases (11) were LA-MRSA.

Surveillance of all MRSA cases, i.e. infected or colonized people (bacteria are present e.g. on skin, in the nose, but do not cause disease), showed a decrease of 21% in 2020 compared to 2019. This was most likely due to restrictions imposed on travel, social contacts and healthcare access during the COVID-19 pandemic. LA-MRSA constituted 32% of all new MRSA cases and primarily affected persons working with pigs and their households.

However, the number of MRSA outbreaks in hospitals, nursing homes and other institutions was higher in 2020 than in 2019 but involved fewer patients (31 outbreaks in 2020, 23 in 2019; 130 patients in 2020, 157 in 2019). This highlights again the importance of infection prevention and control measures and outbreak detection systems.

Neisseria gonorrhoeae – resistance levels to antimicrobials used for treatment of gonorrhoeae are currently not of concern in Denmark

Gonorrhoea, the second most common bacterial sexually transmitted infection in Denmark, is caused by *N. gonorrhoeae* (gonococci). In 2020, SSI's reference laboratory confirmed 1,278 cases of gonorrhoeae. The proportion of gonococci being resistant to the first- and second line antimicrobials used for treatment of gonorrhea (ceftriaxone, azithromycin, ciprofloxacin) were 0%, 2% and 41% respectively.

Although resistance levels among gonococci are currently not of concern in Denmark, the frequent emergence of resistance mechanisms in *N. gonorrhoeae* globally compromises the management and control of the infection in many countries and highlights that surveillance of resistance trends is vital to ensure that treatment for gonorrhoea remains effective.

For more details see DANMAP 2020 on www.danmap.org

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8. Concluding remarks

DANMAP was established in 1995 with the purpose of conducting continuous surveillance of antimicrobial resistance and antimicrobial use in the human, animal and food sectors. A number of structural changes and technological progress have happened over this 25-year time period. Thus, as many other surveillance programmes DANMAP has been challenged by the need to deliver and present comparable data over time and at the same time to ensure that the data are generated using the most recent methodologies.

A number of changes have occurred over time, both in relation to data and methodologies. This includes the shift from disk diffusion to MIC to determine susceptibility among bacteria from animals and food, new methods for calculating antimicrobial use so it better reflects the number of animals treated, implementation of the European Committee on Antimicrobial Susceptibility Testing methodologies in the Clinical Departments of Microbiology and the ability to extract national susceptibility data for human microorganisms from the MiBa database. In many cases, it has been possible to ensure retrospective comparability whereas unfortunately this has not been possible for all cases.

However, as this short report shows, DANMAP is until today providing a useful overview of the occurrence of antimicrobial resistance and use in Denmark. As also highlighted in this report, emergence of novel resistance mechanisms, changes in antimicrobial consumption caused by the COVID-19 pandemic, and going forward, by the withdrawal of medical zinc for use in the pig production, clearly call for continuous, updated and more real-time AMR surveillance.

It is our intention that DANMAP - while still ensuring retrospective comparability - should continue to evolve. In recent years, the introduction of next-generation sequencing has drastically changed microbiological research and outbreak investigations. It is also our expectation that this will become increasingly integrated in AMR surveillance. Focus on providing more real-time updates and not only an annual report, as well as more interactive access to the information, is also high on our agenda.

AMR surveillance is more needed than ever and it is our hope that also in the future DANMAP can provide such information for the different stakeholders, decision-makers and the general public.

Anders Rhod Larsen and Frank Møller Aarestrup

CELEBRATING 25 years

9. List of abbreviations

AGP	Antimicrobial growth promoter
AMU	Antimicrobial use
AMR	Antimicrobial resistance
ATC	Anatomical Therapeutic Chemical Classification System
ATCvet	Anatomical Therapeutic Chemical Classification System for veterinary medicines
ATU	Area of Technical Uncertanity
CA	Community-acquired
CC	Clonal complex
CDI	Clostridium difficile infections
CHR	Central Husbandry Register
CPE	Carbapenemase producing Enterobacterales
CPO	Carbapenemase producing organisms
CPR	Danish Civil Registry, register for social security numbers
DAD	Defined Daily Doses per 100 admissions
DADD	Defined Animal Daily Dose
DaDDD	Danish adjusted Defined Daily Doses
DAPD	Defined Animal Daily Dose per 1,000 animals per day
DBD	Defined Daily Doses per 100 occupied bed-days
DCM	Department of clinical microbiology
DDD	Defined Daily Dose
DID	Defined Daily Doses per 1,000 inhabitants per day (DDD/1000 inhabitants/day)
DTU	Technical University of Denmark
DVFA	Danish Veterinary and Food Administration
EARS-Net	The European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
ESC	Extended Spectrum cephalosporinase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GP	General Practitioner
HAI	Hospital-acquired infections
HCAI	Health care associated infections
HACO	Health care associated community onset
HAIBA	Hospital Acquired Infections Database
MiBa	The Danish Microbiology Database
MIC	Minimum inhibitory concentration
MDR	Multidrug-resistant
MRSA	Methicillin-resistant Staphylococcus aureus
NAAT	Nucleic acid amplification test
OIE	World Organisation for Animal Health
PCR	Polymerase chain reaction
PHC	Primary health care
RFCA	Regional Veterinary and Food Control Authorities
SEGES	Knowledge Centre for Agriculture
SS	Statens Serum Institut
ST	Serotype/Sequence type
VASC	Veterinary advisory service contracts
VMP	Veterinary medicinal products
VetStat	Danish Register of Veterinary Medicines
VRE	Vancomycin-resistant enterococci
VVE	Vancomycin-variable enterococci
WGS	Whole-genome sequencing
WHO	World Health Organization

SUMMARY • DANMAP 2020

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