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SUMMARY DANMAP 2021

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

Statens Serum Institut
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SUMMARY • DANMAP 2021

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1. Introduction

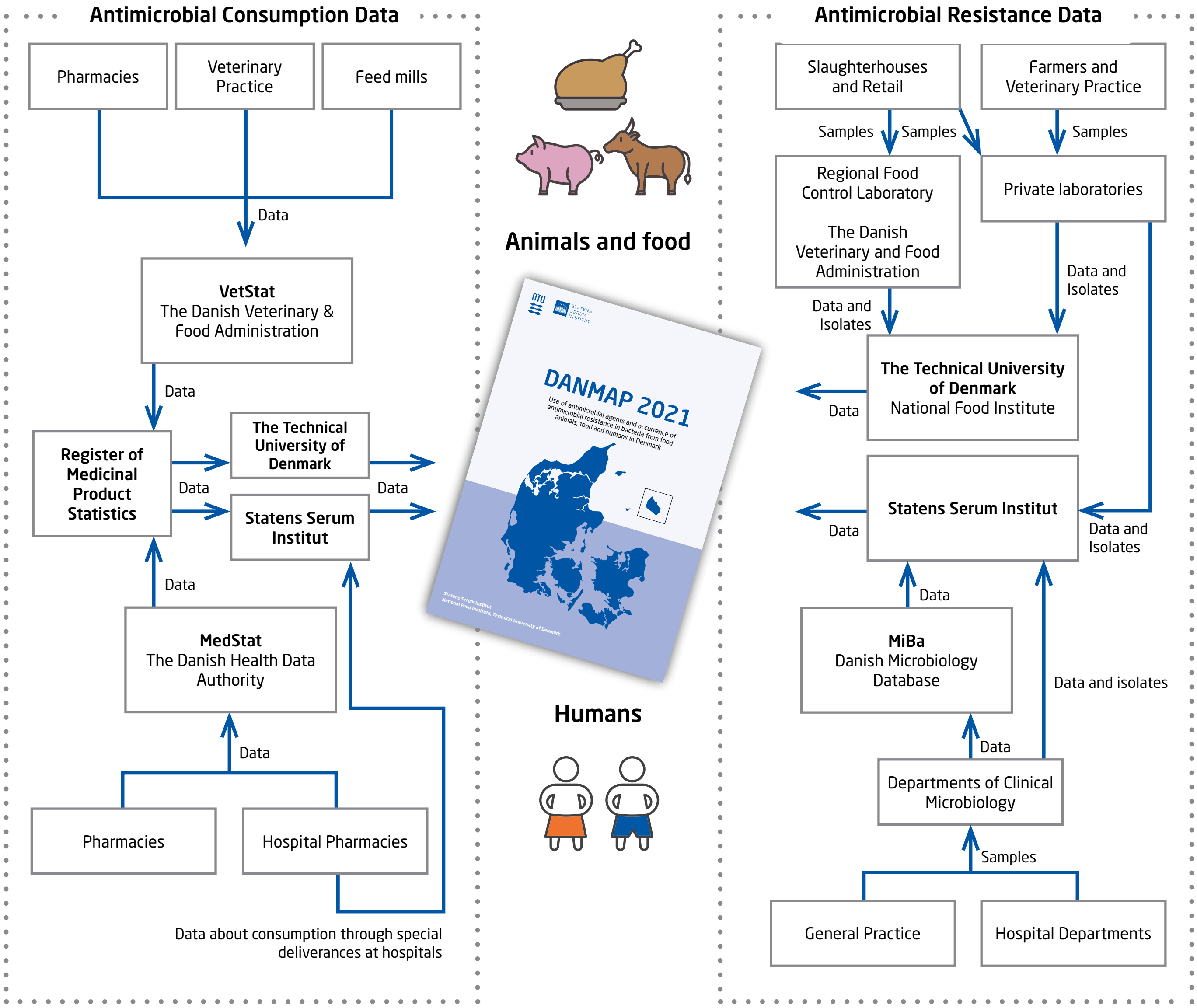
The Danish integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) is a governmentally financed surveillance programme that collects and presents antimicrobial use (AMU) and antimicrobial resistance (AMR) data in humans and animals in Denmark. The programme was established in 1995 and is based on clinical data from humans and clinical and survey data from animals.

DANMAP is based on the concept of 'One Health' – a collaborative, multidisciplinary initiative across human and animal sectors. The programme is managed by a collaborating team from the National Food Institute at the Technical University of Denmark, and the National AMR reference laboratory at Statens Serum Institut. The work is supported by internal and external technical experts and receives contributions from all Danish Clinical Microbiology departments, the Danish Veterinary and Food Administration and the Danish Health Data Authority.

This short report 2021 complements the more comprehensive DANMAP report 2021. It features the most important findings from the four main areas under surveillance and includes new perspectives on One Health and antimicrobial resistance. The summary aims to inform healthcare professionals, scientists, decision-makers, and everybody else with an interest in antimicrobial use and resistance and the monitoring of these.

More information about the surveillance programme and further data and analyses can be found at www.DANMAP.org, where you also find the full DANMAP 2021 and former reports.

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



2. Antimicrobial consumption in animals

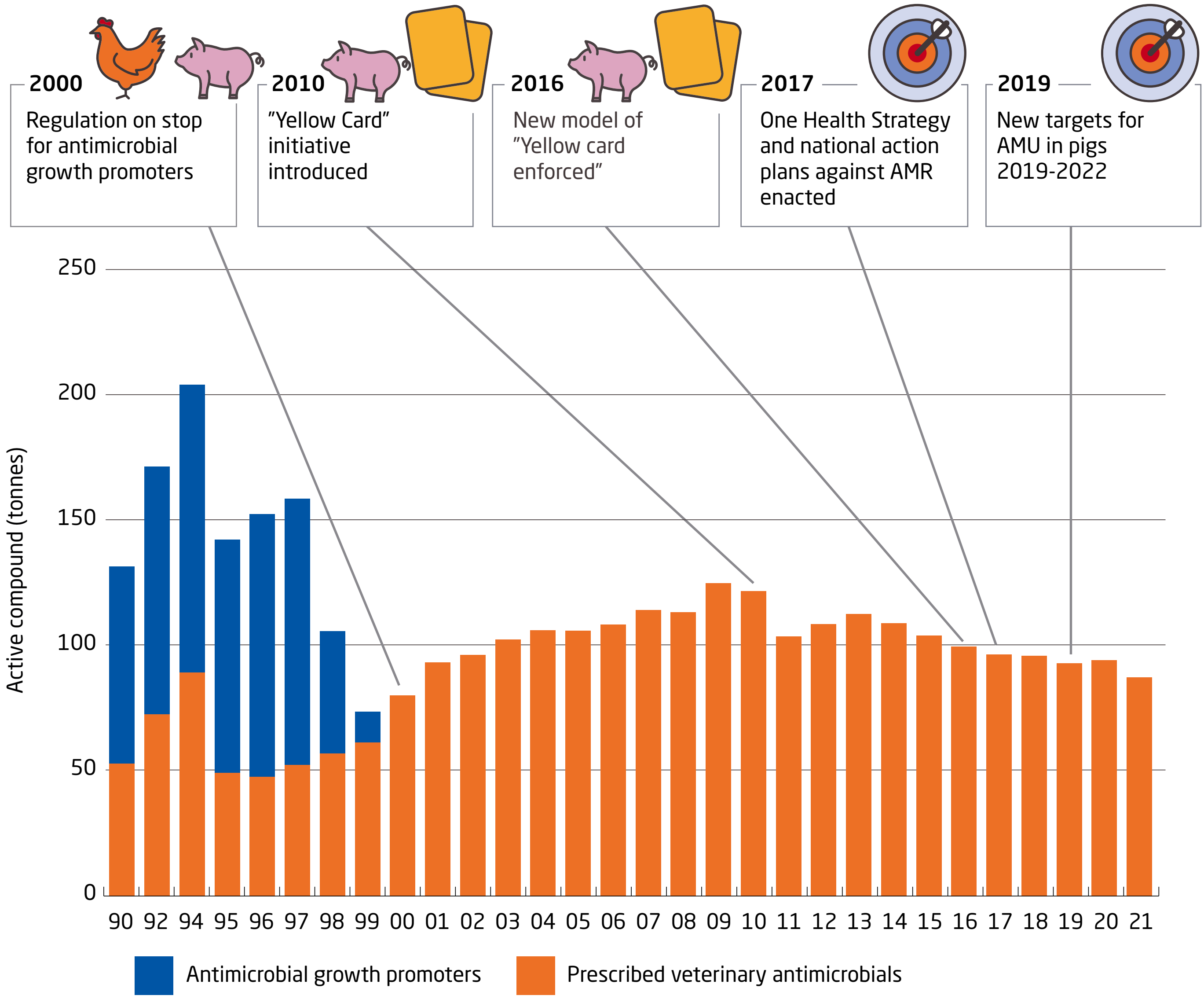
The surveillance of antimicrobial consumption in animals is based on sales data from pharmacies, veterinary practices and feed-mills. Since 2001, all medicines prescribed for use in animals have been recorded in the national database, VetStat, the Danish database collecting usage data on veterinary prescription medicines.

For DANMAP 2021, data on antimicrobial use in animals were extracted from the new VetStat data platform, which was launched by the Danish Veterinary and Food Administration in June 2021. The shift from the old to the new data platform affected the calculated total amount of active compound, but the overall trends and conclusions remain the same as in former reports. For further information, see Textbox 4.1 in DANMAP 2021 or https://vetstat.fvst.dk/vetstat/, which can be accessed by all Danish citizens with the appropriate logon credentials.

Since DANMAP was established, many initiatives have been taken on to reduce the use of antimicrobials in both animals and humans (Figure 2.1 and Chapter 8, Timeline). 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 2.1 shows the antimicrobial use in animals, along with some important initiatives that have had a marked effect on the antimicrobial use in animals, especially the AMU in pigs.

Over time, antimicrobial use in animals has changed, not only as a result of risk management measures established to reduce consumption, but also as a result of changes in the animal production, especially increases in the pig production.

Figure 2.1 Antimicrobial consumption in animals and some important initiatives to reduce antimicrobial use in animals, Denmark, 1990-2021



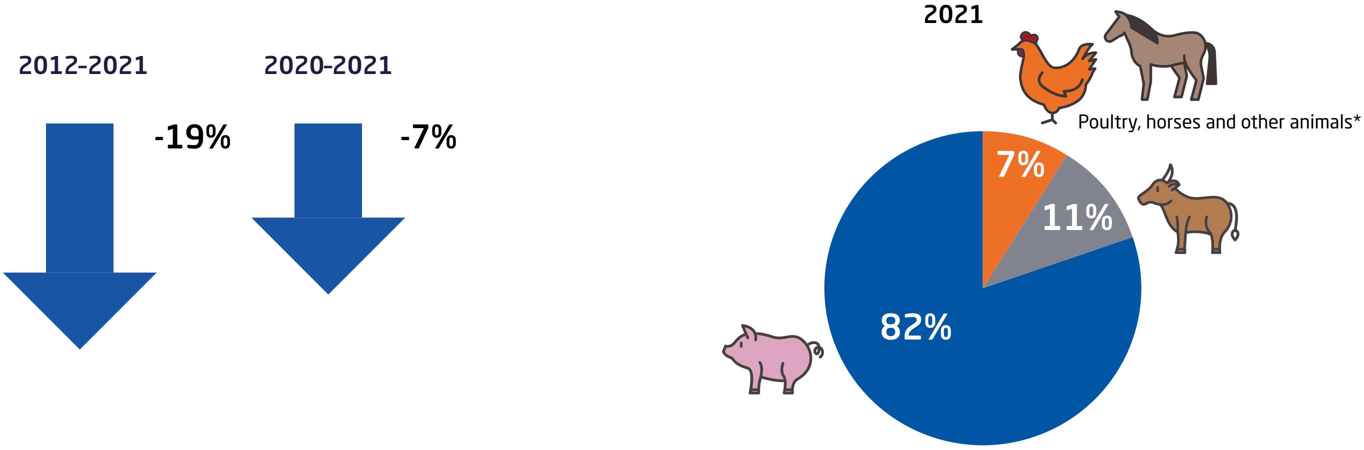
Overall reduction in antimicrobial use in animals

In 2021, approximately two thirds of all antimicrobials prescribed in Denmark were prescribed for veterinary use. The total use of antimicrobials for animals amounted to 88.0 tonnes active compound, (Figure 2.1 and Figure 2.4).

Since 2013, the overall use of antimicrobials in animals has decreased every year, except in 2020 (Figure 2.1). The total use was 21.3 tonnes (-19%) lower in 2021 compared with 2012, and 7.0 tonnes (-7%) lower than in 2020 (Figure 2.2). A substantial part of this reduction may be explained by lower use in pigs, poultry and not least, the almost zero use for fur animals, due to culling of all Danish mink. Antimicrobial use in the different animal species is shown in Table 2.1 and Figure 2.4.

The pig sector is the main driver of veterinary antimicrobial use in Denmark. Therefore, any major change in usage patterns in the pig sector also has a major impact on the overall antimicrobial use in animals. In 2021, approximately 82% of veterinary prescribed antimicrobials were used for pigs, amounting to 72.2 tonnes active compound and the overall use of antimicrobial for pigs decreased by approximately 2.0 tonnes from 2020 to 2021.

Figure 2.2 Changes in overall antimicrobial use and distribution (%)of antimicrobial use by main animals species



* Other animals include fur animals, aquaculture and pets

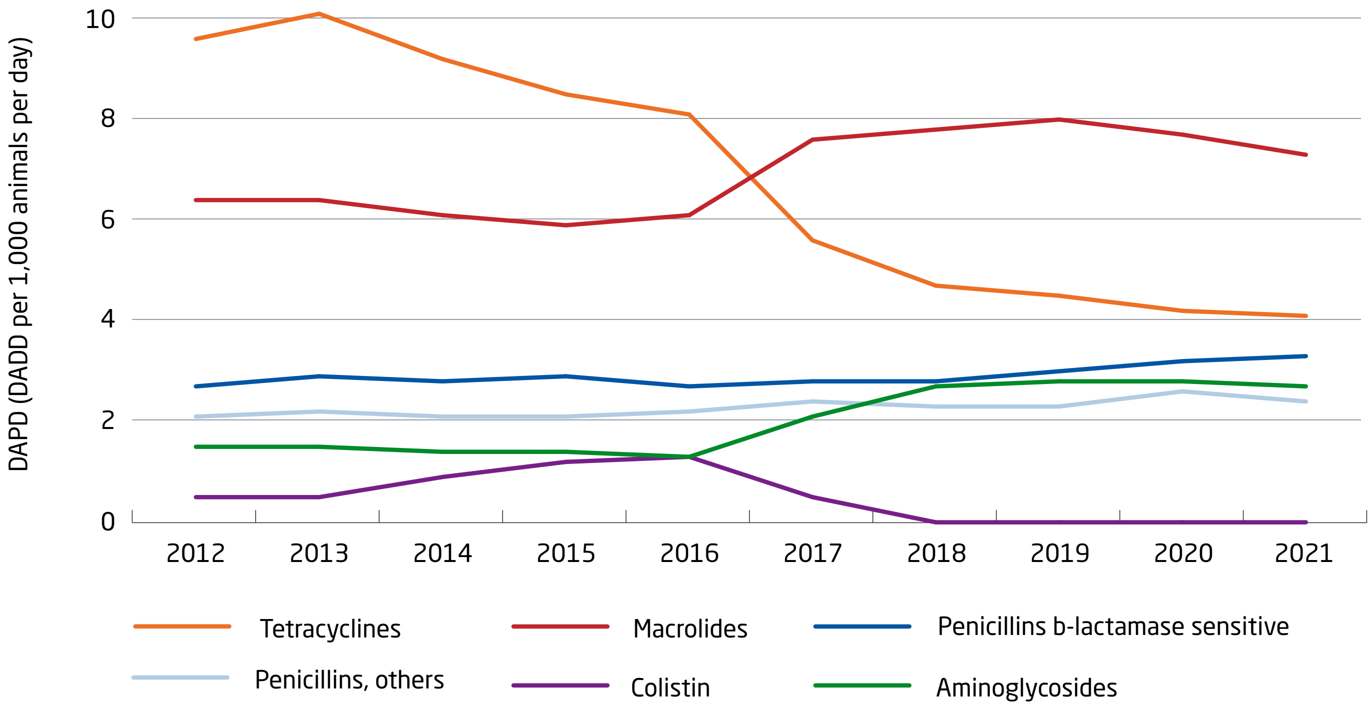
Table 2.1 Antimicrobial agents sold (kg active compound) by animal species, Denmark

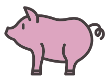
	Year									
	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Pigs	83814	88754	83613	79094	76348	73541	74006	71679	74382	72345
Cattle	11959	11230	11238	10934	10673	10148	10284	10082	10069	9425
Poultry	722	1303	1636	2569	1671	1610	1430	1719	2458	1196
Other production animals[a]	8782	8625	9544	8354	7861	8108	7392	6562	4469	1788
Companion animals[b]	2322	2143	2295	2189	2320	2339	2348	2316	2446	2520
Unspecified	1768	1471	1399	1654	1538	1564	1265	1295	1188	772
Total	109366	113525	109725	104796	100412	97310	96724	93653	95012	88045

a) Other production animals include aquaculture and fur animals
b) Companion animals includes pets and horses

Measured as treatment proportion, in 2021 an estimated 2.8% (28 DAPD) of all pigs received antimicrobial treatment on any given day. In 2010, before the introduction of the Yellow Card initiative, an estimated 3.6% 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 2021, approximately 1-2% of the sows and piglets and finisher pigs and 9% of the weaner pigs received antimicrobial treatment, similar to levels in 2020 and 2019, (Figure 2.3).

Figure 2.3 Antimicrobial use in the pig production, DAPD, Denmark, 2012-2021





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

Kg active compound: Provides 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 2021, Materials and Methods).

Changes in AMU for pigs driven by the Yellow Card initiative

Several initiatives have aimed at reducing the use of tetracyclines, since this may select for livestock-associated methicillin resistant *Staphylococcus aureus* (LA-MRSA). Similarly, initiatives have aimed at phasing out critically important antimicrobials such as fluoroquinolones, cephalosporins and colistin.

Since 2010, the use of tetracyclines has decreased significantly. During the same period, the use of macrolides and aminoglycosides has increased (Figure 2.3). Since 2019 the use of macrolides has remained at the same level. For a more historical view of the changes in AMU in the different age groups of pigs, please refer to DANMAP 2021.

The Yellow Card Initiative

In 2010 the Danish Veterinary and Food Administration (DVFA) introduced the Yellow Card initiative to reduce the use of antimicrobials in Danish pigs. The initiative targets farms with high consumption of antimicrobials and works as an incentive for pig producers to contribute to the goal of reducing AMU.

The initiative is based on monitoring AMU on detailed levels on each farm. If the average antibiotic consumption in a holding, within a nine-month period, exceeds the given threshold levels, the DVFA may issue an order or injunction (a yellow card) compelling the owner of the holding to reduce the antibiotic consumption below the maximum limits within nine months of the issuance of the injunction.

In 2016, the initiative was developed further and multiplication factors were added, to adjust the use of specific antimicrobial agents. Multiplication factors were determined by the DVFA and are used as risk mitigation tools for each class of antimicrobials. Fluoroquinolones and cephalosporins, which are classified as critically important for treatment of humans, have been given the highest multiplication factor of ten. Tetracyclines have been given the multiplication factor of 1.5, to promote further reduction in tetracycline use for pigs. Furthermore, colistin has also been given a multiplication factor of ten as a precautionary measure.

The differentiated Yellow Card has proven to be an efficient tool to reduce overall antimicrobial use in pig herds and to discourage use of certain critically important antimicrobials. For more information see DANMAP 2010 or www.fvst.dk.

Critically important antimicrobials

Antimicrobials that are used to treat serious infections caused by resistant bacteria are classified "highest priority critically important" by WHO.

Denmark has declared four types of antimicrobials as 'critically important', namely carbapenems, 3rd and 4th generation cephalosporins, fluoroquinolones and colistin.

Decrease in the use of medical zinc in pigs

Medical zinc is prescribed to newly weaned pigs to prevent or treat diarrhea, but use of medical zinc may select for antimicrobial resistant bacteria including LA-MRSA. Zinc is also known to accumulate in the environment, therefore in 2017, the European Commission announced an EU-wide withdrawal of medical zinc, effective per June 2022.

The use of medical zinc increased from 2012 to 2017, most likely due to an increase in the production of pigs, but has since shown decreasing trends. In 2021, the use of medical zinc oxide amounted to 462 tons, equivalent to a 7% decrease compared to 2020 and a 17% decrease compared to 2017. Nevertheless, the industry still remains far from the target of zero use by June 2022. It is generally feared that phasing out of medical zinc in weaning populations will increase the incidence of diarrhoea and lead to higher antimicrobial use. To investigate on possible impact and consequences the Danish Livestock industry is undertaking research on better feed and other measures to improve the health of weaners.

Antimicrobial use in other animals

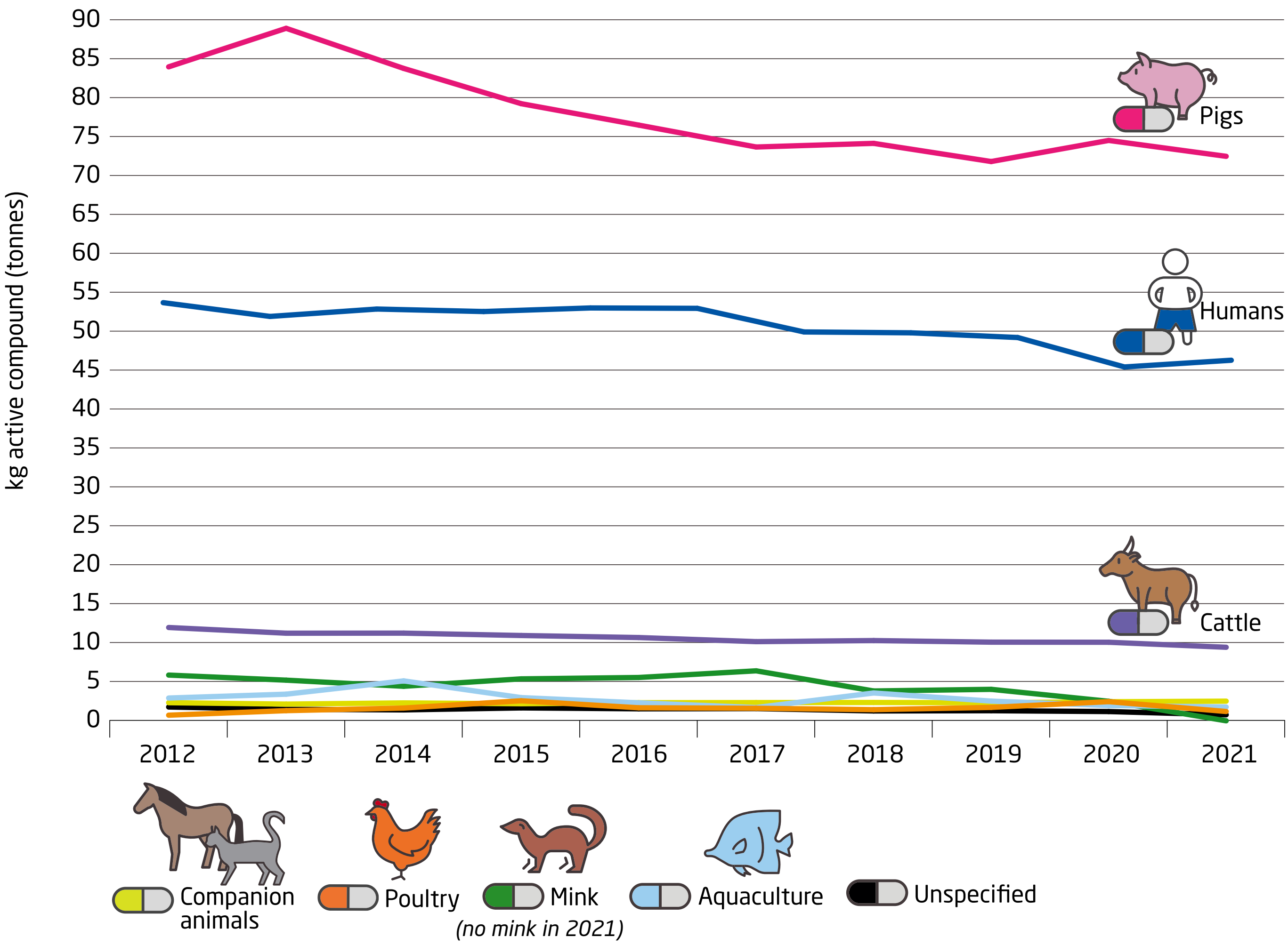
In 2021, a total of 9,425 kg were prescribed for **cattle**, of which approximately 70% was used for treating cattle older than 12 months, including 485 kg used for intramammary treatment. An overall decreasing trend has been observed over the last decade and in 2021 the use in cattle was 21% lower than in 2012 and 6% lower than in 2020. No fluoroquinolones or 3rd or 4th generation cephalosporins were registered for use in cattle.

Antimicrobial use in Danish **poultry** is generally low, and is therefore markedly affected by disease outbreaks, even in just a few farms. In 2021, the usage was at the lowest level in more than a decade at 1,196 kg, representing a decrease of approximately 50% compared to the usage in 2020. 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.

Antimicrobial use in **aquaculture** varies considerably with water temperatures because bacterial diseases are more likely to occur when temperatures are high. The AMU in 2021 was 1,771 kg, which was 10% lower than the use in 2020. Mainly three compounds are used to treat bacterial infections in aquaculture: sulfonamide/trimethoprim (61%), 1st generation quinolones (21%), and amphenicols (17%).

Data on AMU in **companion animals** is less detailed than for the food producing animals, because registering of species is not mandatory for companion animals. The use for companion animals was estimated to be 2,520 kg in 2021, which was 8% higher than in 2012 and 3% higher than in 2020. More than half of all cephalosporins, all 3rd and 4th generation cephalosporins, as well as almost all fluoroquinolones prescribed for veterinary use, were prescribed for companion animals, (Figure 2.4).

Figure 2.4 Total antimicrobial consumption of active ingredients (kg) by animal species and humans, Denmark 2017-2021



The Danish One Health AMR Strategy

In 2017, the Ministry of Food, Agriculture and Fisheries and the Danish Ministry of Health launched a joint One Health strategy on tackling antimicrobial resistance. The aim of the One Health strategy was to provide a framework for continued strong and coordinated efforts across sectors to combat antibiotic resistance. A former One Health AMR strategy from 2010 had established a cross-sectoral coordination mechanism, the National Antibiotic Council, which was tasked to oversee a broad range of initiatives e.g. improved microbiological diagnostics and the introduction of these into routine laboratory work, extension of the surveillance programmes and digital tools to undertake this, guidelines on the mitigation and control of *C. difficile* and LA-MRSA in hospitalized patients together with recommendations and treatment guidelines for both animal and human sectors. The aim of the new strategy was to strengthen the efforts and to focus on antimicrobial usage.

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

Together with the strategy, 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 particularly including measurable goals for the reduction of veterinary antimicrobial consumption. A new action plan was launched in 2021, (Figure 2.5).

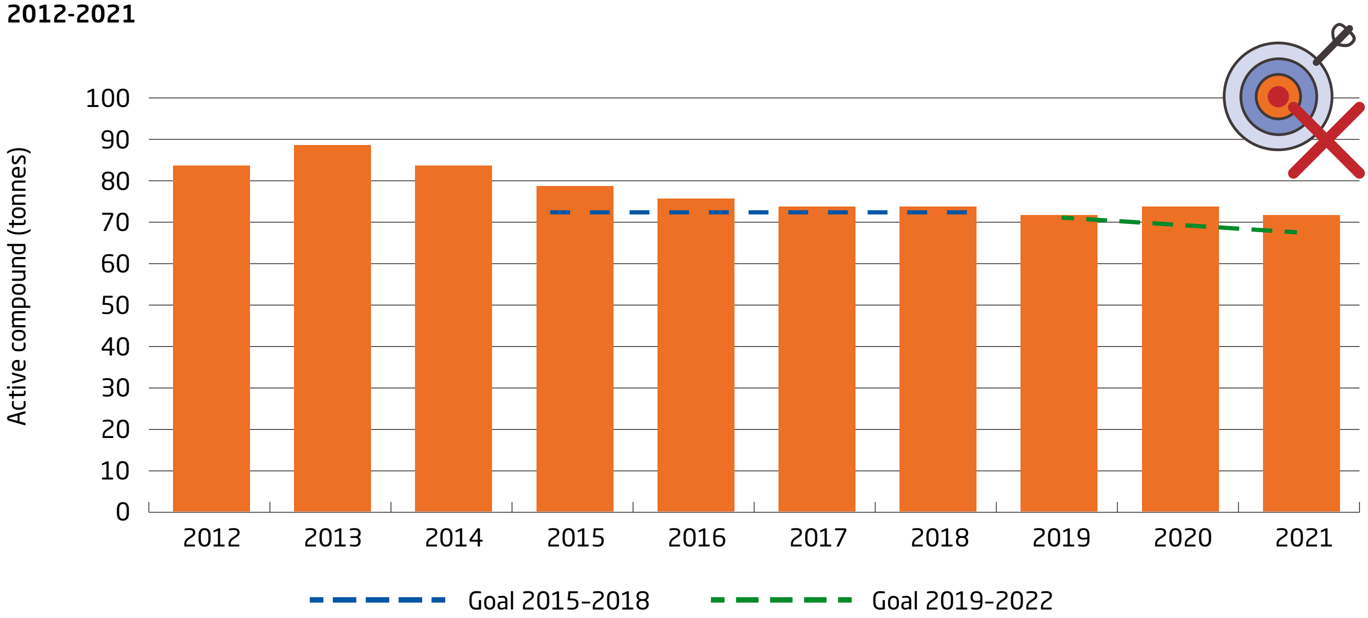
Goal 1: Achieve a reduction of 2 per cent per year (2019-2022) in the use of antibiotics for pigs, and maintain or reduce the use of antibiotics for other livestock species. This Goal was not achieved in 2021.

Goal 2: Maintain low use for production animals of those antibiotics that are critically important for treating humans (2019 level).

Goal 3: To maintain or, if possible, reduce the low incidence of resistance in food, with an emphasis on critically important resistance, by enhanced focus on biosecurity and hygiene in production animals and food production as well as on animal health.

Goal 4: To limit the spread of livestock-associated MRSA from pig herds and in the community.

Figure 2.5 Antimicrobial use in pigs and goals of the national action plan against antimicrobial resistance, Denmark, 2012-2021



3. Antimicrobial consumption in humans

Surveillance of antimicrobial consumption in humans is based on sales data from all public and private healthcare providers in Denmark. In the following sections, antimicrobial consumption data are presented at national level as well as at different health care sector levels, i. e. primary health care and hospital care.

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.

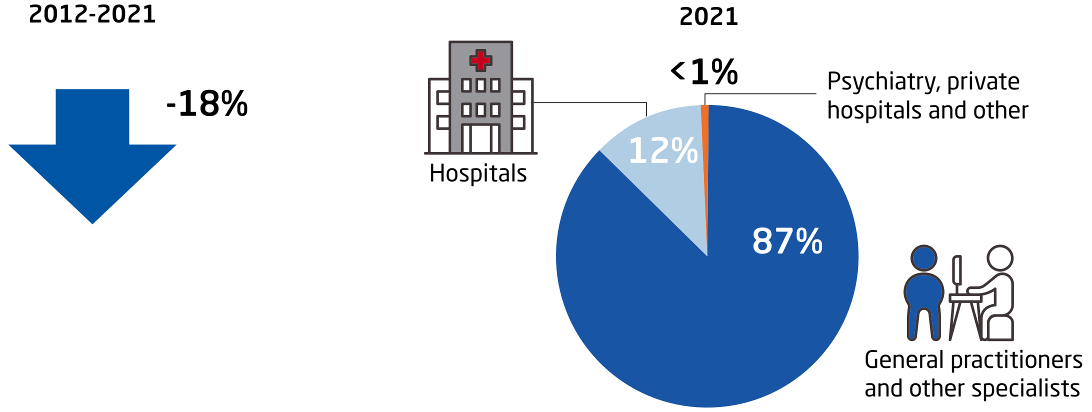
DID: DDD per 1,000 inhabitants per day. The unit takes changes in population size over time into account.

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 Change in total antimicrobial consumption and distribution by health care providers, Denmark, 2012-2021



Total consumption of antimicrobials in Denmark

Major part of antimicrobial consumption is prescribed in primary health care

Total antimicrobial consumption in Denmark in 2021 was 14.71 DID, of which 87% was prescribed in primary healthcare (Figure 3.1).

Decreased consumption of antimicrobials by 18% over the past decade

Over the past decade, total antimicrobial consumption in Denmark has decreased by 18%, while no change was observed from 2020 to 2021.

Increased antimicrobial consumption at hospitals

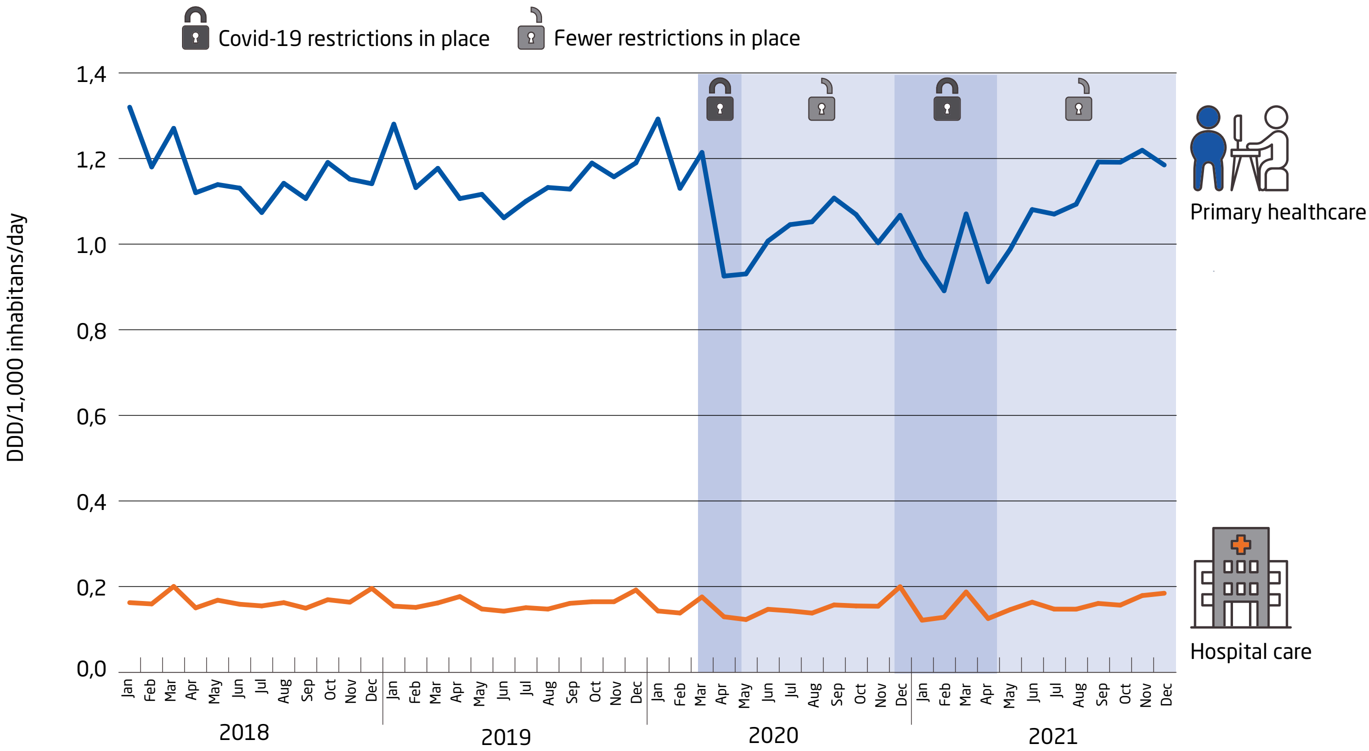
In contrast to primary health care, antimicrobial consumption at hospitals in 2021 has increased by 25% over the past decade, when standardized by changes in hospital activity over the years (124.01 DBD in 2021 versus 99.54 DBD in 2012).

Antimicrobial consumption in primary health care

Antimicrobial consumption seems to be returning to levels before the COVID-19 pandemic

The total antimicrobial consumption level in the second COVID-19 pandemic year, 2021, was the same as the in first pandemic year 2020, where the consumption decreased by 6.7% compared to 2019. However, analysis of monthly antimicrobial consumption data showed that consumption increased from August 2021, i.e. following the lifting of almost all COVID-19-related restrictions, to similar levels seen in corresponding months in 2018 and 2019 (Figure 3.2).

Figure 3.2 Antimicrobial consumption in primary healthcare and hospital care, Denmark, 2018-2021



Antimicrobial consumption among the youngest children increased in 2021

Analysis of antimicrobial consumption data by age groups showed a 16% increase in consumption of antimicrobials in 0-4 year olds in 2021 compared to 2020 following the 38% reduction observed from 2019 to 2020 (Figure 3.3). The second pandemic year, 2021, was characterized by fewer COVID-19 related restrictions and thus a more normalized risk of infection transmission.

This is also confirmed by the analysis of treatment indications for all age groups, which showed a marked drop in antimicrobials for respiratory infections during 2020 and beginning of 2021 but return to almost normal levels form the summer 2021 onwards (Figure 3.4).

However, the consumption of antimicrobials among 5-14 year olds continued to decrease in 2021 (11% lower than in 2020). For the 15-24 year olds, consumption increased (6%) in 2021 after significant decreases observed from 2019 to 2020.

Figure 3.3 Antimicrobial consumption for children from 0-4 years old in primary health care, Denmark, 2017-2021

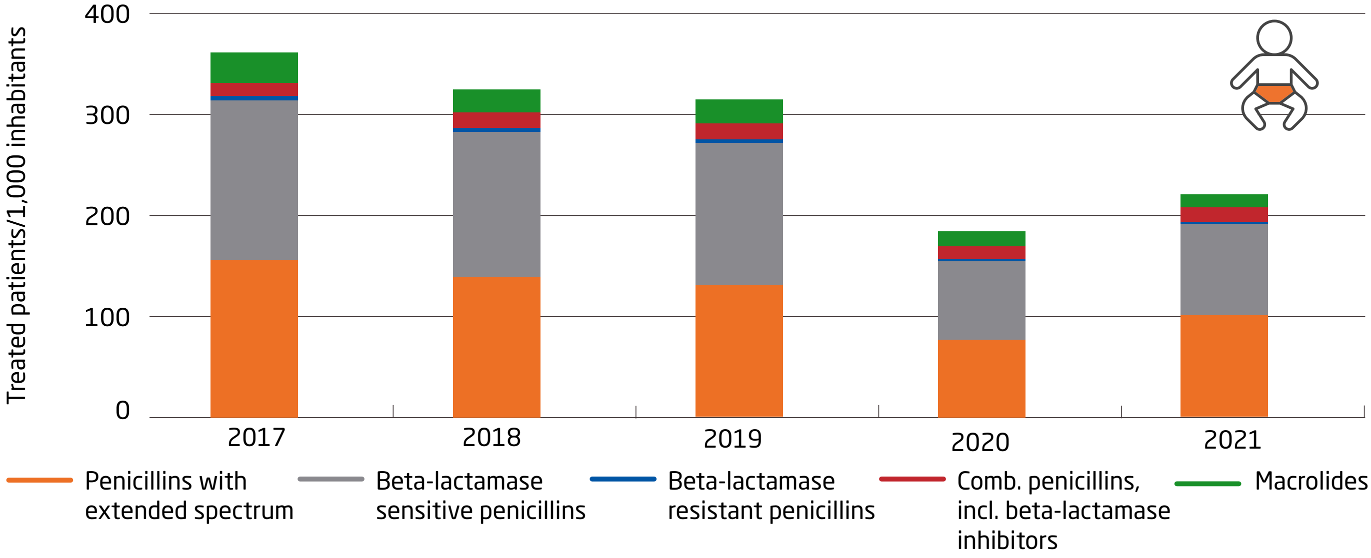
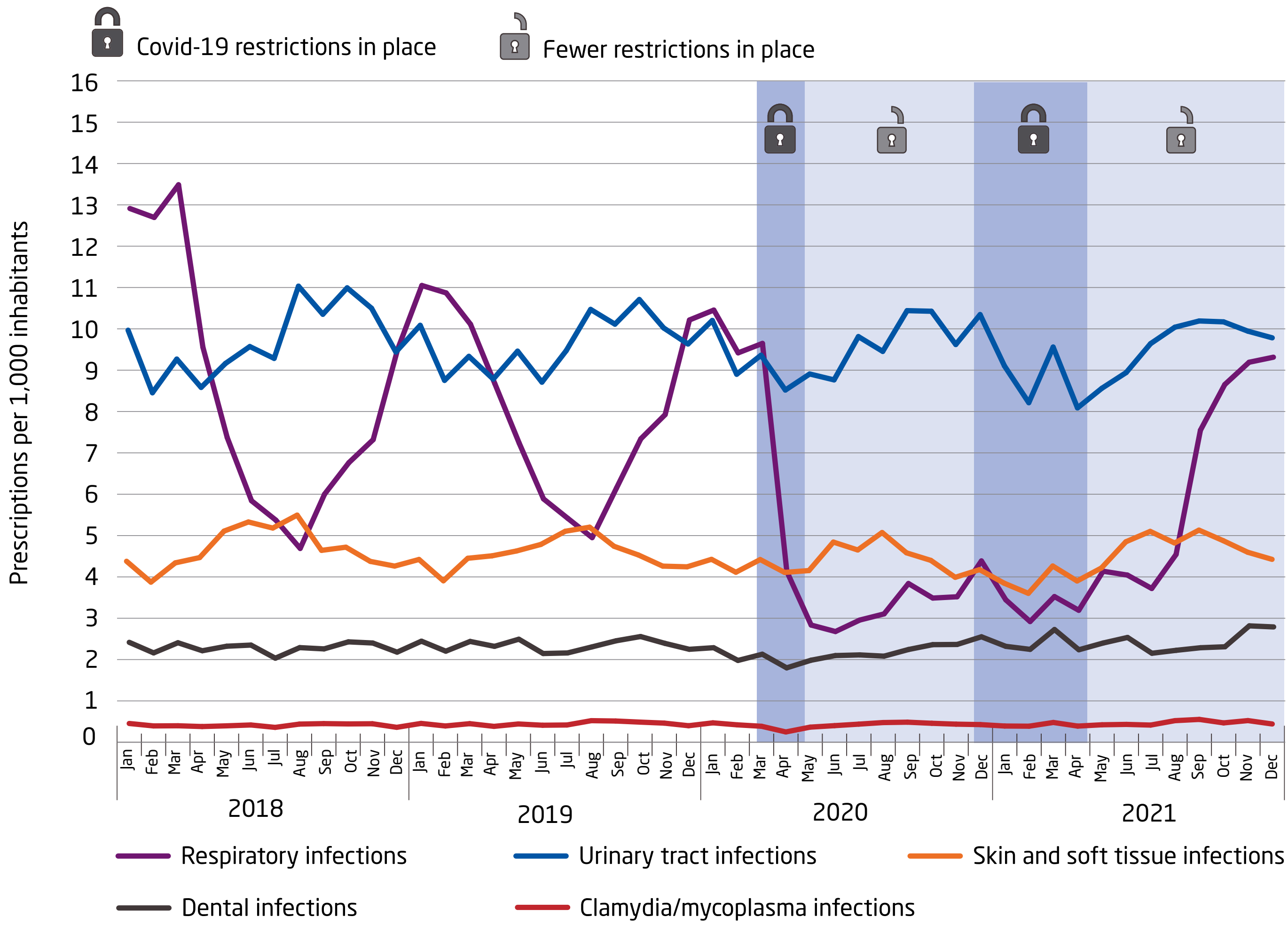


Figure 3.4 Monthly consumption of systemic antimicrobials by indication in primary health care, prescriptions per 1,000 inhabitants, Denmark, 2018-2021



Antimicrobial consumption in elderly residents living in care homes is higher than in elderly residents living in their own homes

Total antimicrobial consumption in elderly residents living in care homes was notably higher than in elderly residents living in their own homes in 2020. The biggest difference was observed in the treatment of urinary tract infections which was 2.5 times higher in care home residents than in elderly who lived in their own homes in 2020 (1382 prescriptions/1,000 inhabitants versus 559 prescriptions/1,000 inhabitants). However, the total consumption of antimicrobials in care home residents decreased by 23% from 2016 to 2020, mainly driven by fewer prescriptions for urinary tract infections. The Ministry of Health has focused on better prevention of urinary tract infections in the elderly through publication of campaigns and best practice booklets.

Figure 3.5 Antimicrobial consumption in elderly living at care homes and in elderly living in their own homes, Denmark, 2020

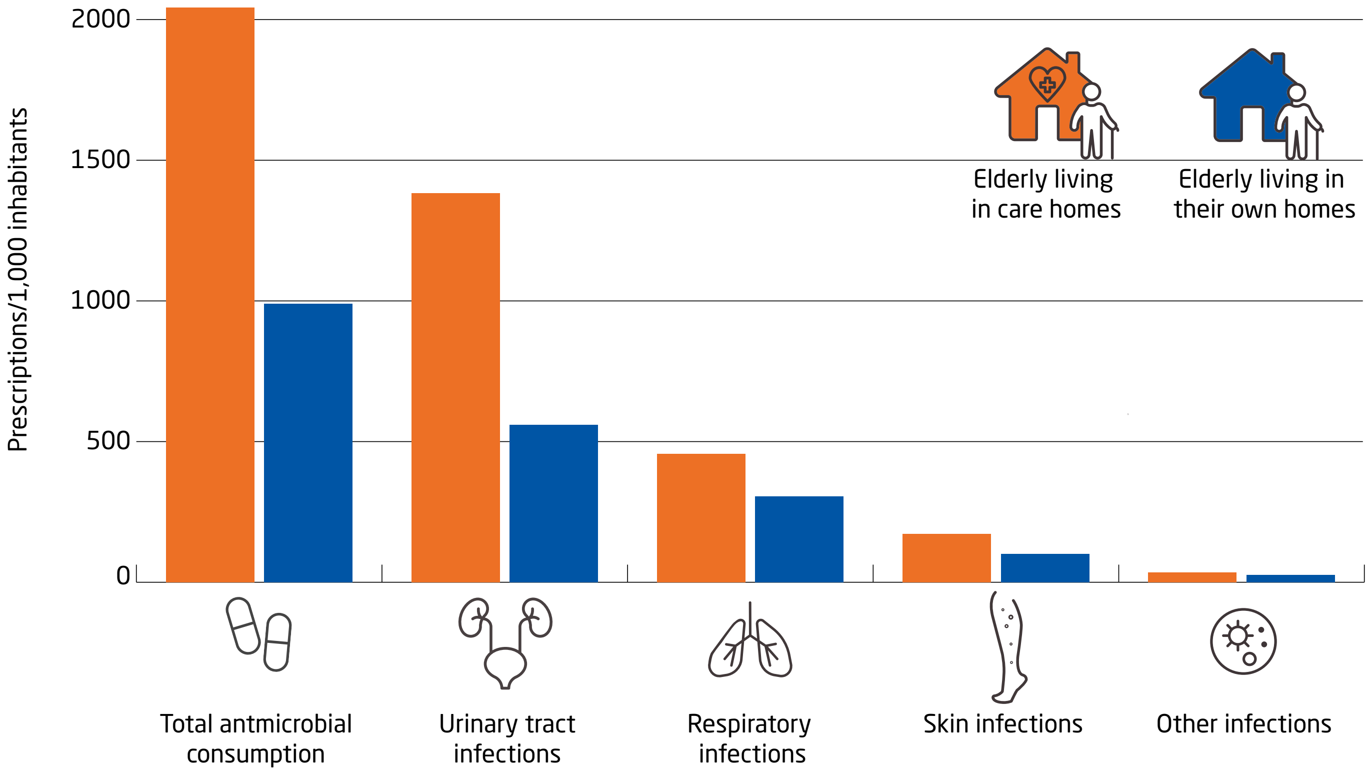


Table 3.1 Consumption of antimicrobial agents in primary health care, DDD per 1000 inhabitants per day, Denmark, 2012-2021

ATC group	Therapeutic group	Year 2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
J01AA	Tetracyclines	1.76	1.96	1.66	1.60	1.62	1.42	1.40	1.48	1.69	1.64
J01CA	Penicillins with extended spectrum	3.03	3.12	3.20	3.28	3.33	3.36	3.35	3.28	3.19	3.17
J01CE	Beta-lactamase sensitive penicillins	4.68	4.65	4.38	4.33	4.16	3.88	3.61	3.44	2.84	2.89
J01CF	Beta-lactamase resistant penicillins	1.21	1.30	1.36	1.38	1.48	1.56	1.60	1.63	1.58	1.61
J01CR	Combinations of penicillins, including beta-lactamase inhibitors	0.70	0.81	0.87	0.95	0.95	0.79	0.66	0.63	0.52	0.55
J01D	Cephalosporins and other betalactam antibiotics	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
J01EA	Trimethoprim and derivates	0.52	0.53	0.55	0.56	0.56	0.56	0.53	0.45	0.43	0.42
J01FA	Macrolides	2.20	1.94	1.79	1.77	1.82	1.62	1.46	1.41	1.15	1.11
J01GB	Aminoglycosides	0.02	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
J01MA	Fluroquinolones	0.55	0.52	0.50	0.49	0.48	0.44	0.41	0.37	0.33	0.32
J01XE	Nitrofuran derivates (nitrofurantoin)	0.50	0.49	0.48	0.45	0.43	0.26	0.15	0.27	0.27	0.28
	Other antibacerials	0.81	0.80	0.79	0.77	0.77	0.75	0.72	0.75	0.76	0.80
J01 and P01AB01	Antibacterial agents for systemic use (total)	16.03	16.19	15.64	15.66	15.67	14.71	13.97	13.77	12.83	12.86

Antimicrobial consumption at somatic hospitals

Change in use of antimicrobial groups during COVID19-pandemic

The increase in antimicrobial consumption at hospitals over the past decade was mainly driven by an increase in consumption of combination of penicillins including beta-lactamase inhibitors (119% increase from 2012 to 2021). These antimicrobials and carbapenems are used for treatment of critically ill patients at hospitals.

However, analysis of monthly consumption data showed that consumption of carbapenems and penicillin/beta-lactamase inhibitor combinations peaked during the COVID-19-related lockdowns in Denmark in 2020 and 2021 (Figure 4.5). This reflects most likely changes in hospital activity and in case mix in hospitals during these periods.

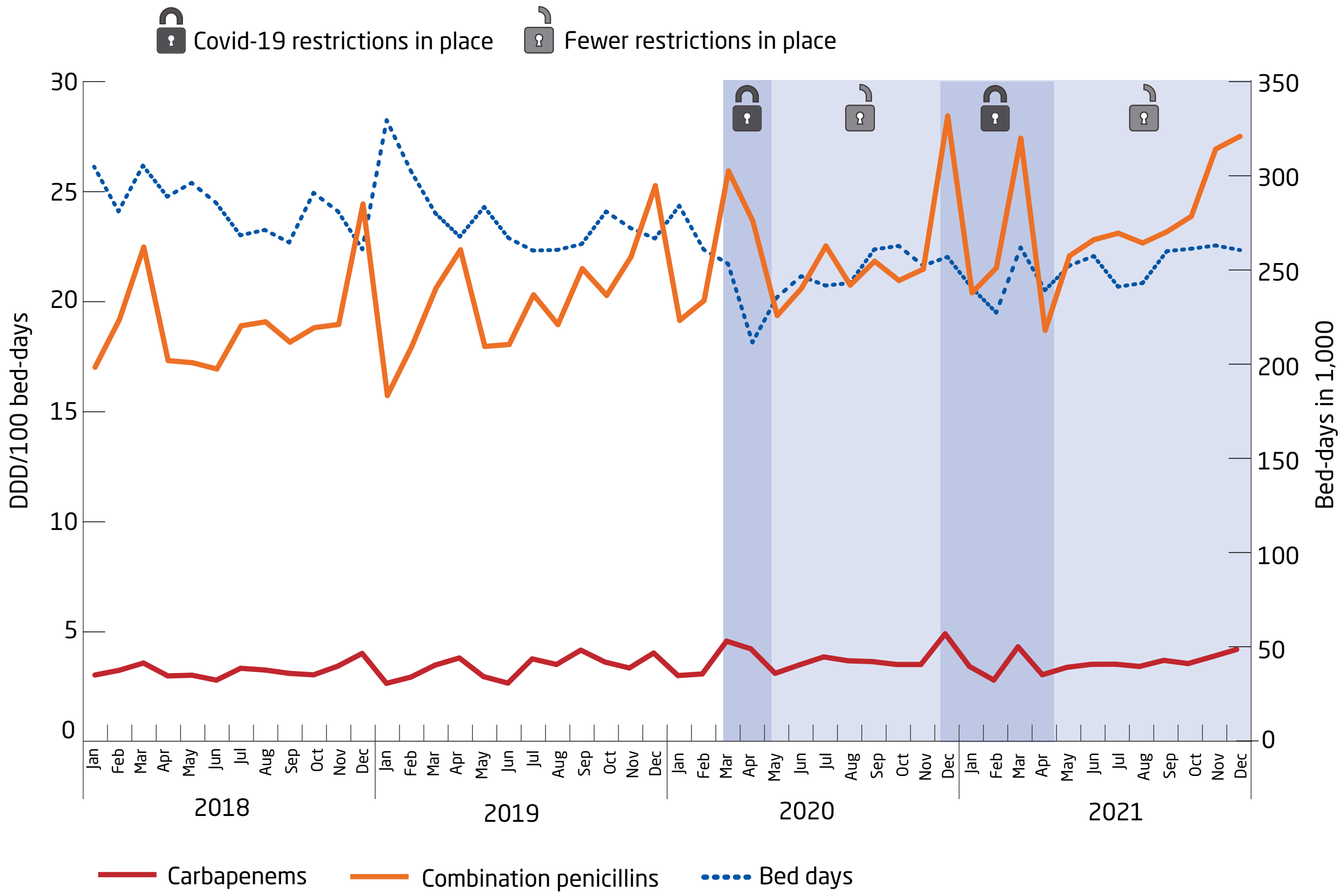
Somatic hospitals - definition

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.

Table 3.2 Consumption of antimicrobial agents at hospitals, DDD per 100 bed-days, Denmark, 2012-2021

	Year									
	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Macrolides (J01FA)	3.92	3.81	3.94	4.81	5.43	6.09	7.33	7.83	7.06	5.62
Aminoglycosides (J01GB)	2.44	2.50	2.21	2.39	2.25	2.38	2.51	2.84	2.94	2.79
Fluoroquinolones (J01MA)	9.70	10.03	9.33	9.17	8.66	7.69	8.19	7.89	8.11	8.36
Carbapenems (J01DH)	2.98	3.24	3.57	3.22	3.12	3.07	3.27	3.45	3.75	3.60
Cephalosporins (J01DB, DC, DD)	16.80	15.67	13.43	12.40	11.92	13.25	11.98	10.87	10.70	10.22
Combinations of penicillins, including beta-lactamase inhibitors (J01CR)	10.77	12.70	13.81	16.20	17.41	14.89	19.27	20.12	22.18	23.58
Beta-lactamase sensitive penicillins (J01CE)	10.79	10.94	10.07	10.04	10.61	10.88	12.17	11.40	11.49	10.70
Penicillins with extended spectrum (J01CA)	14.44	14.98	14.71	15.62	16.75	16.87	17.98	18.70	20.28	20.45
Others (A07, P01, J01A, J01DF, J01E, J01FF, J01X)	18.21	19.33	18.48	18.99	20.67	19.60	22.27	23.50	24.19	24.58
Beta-lactamase resistant penicillins (J01CF)	9.50	10.21	10.05	10.25	10.81	10.69	12.24	13.06	14.05	14.12
Total antimicrobial consumption	99.55	103.41	99.59	103.09	107.65	105.40	117.21	119.65	124.75	124.01

Figure 3.6 Consumption of key antimicrobials used for treatment of seriously ill patients in hospital, DDD per 100-bed-days, Denmark, 2018-2021



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

Together with the National One Health Strategy and the DVFAs Action Plan on the management of 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. Due to the SARS-CoV2 pandemic the period was extended to December 2021.

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 in 2016 to 350 prescriptions per 1,000 inhabitants in 2021 (prescriptions from hospital doctors are not included). **This goal was achieved** (Figure 3.7).

Goal 2: Narrow-spectrum antibiotics should be used more frequently in infection treatment. The use of penicillin V should increase from approximately 31% in 2016 to constituting 36% of the total antibiotic consumption in the primary health care sector in 2021, measured by the number of prescriptions per 1,000 inhabitants. **This goal was not achieved** (the proportion of penicillin V decreased to 28% in 2021), (Figure 3.8).

Goal 3: The consumption of critically important antibiotics* (carbapenems, cephalosporins, fluoroquinolones) should be reduced by 10% by 2021 measured by DDD/100 bed-days for hospitalised patients, compared with consumption in 2016. **This goal was achieved** (Figure 3.9).

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

Figure 3.7 Goal 1: Total number of prescriptions for antibiotics in primary health care, Denmark, 2016-2021

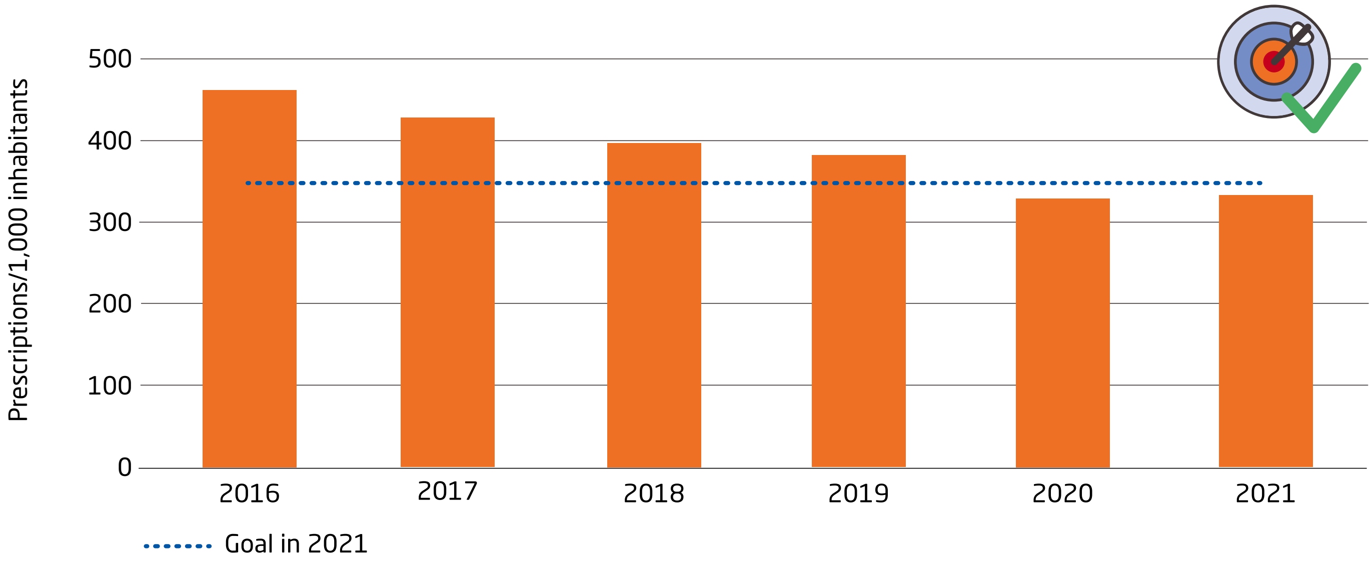


Figure 3.8 Goal 2: Proportion of penicillin V compared to total antibiotic consumption in primary health care, Denmark, 2016-2021

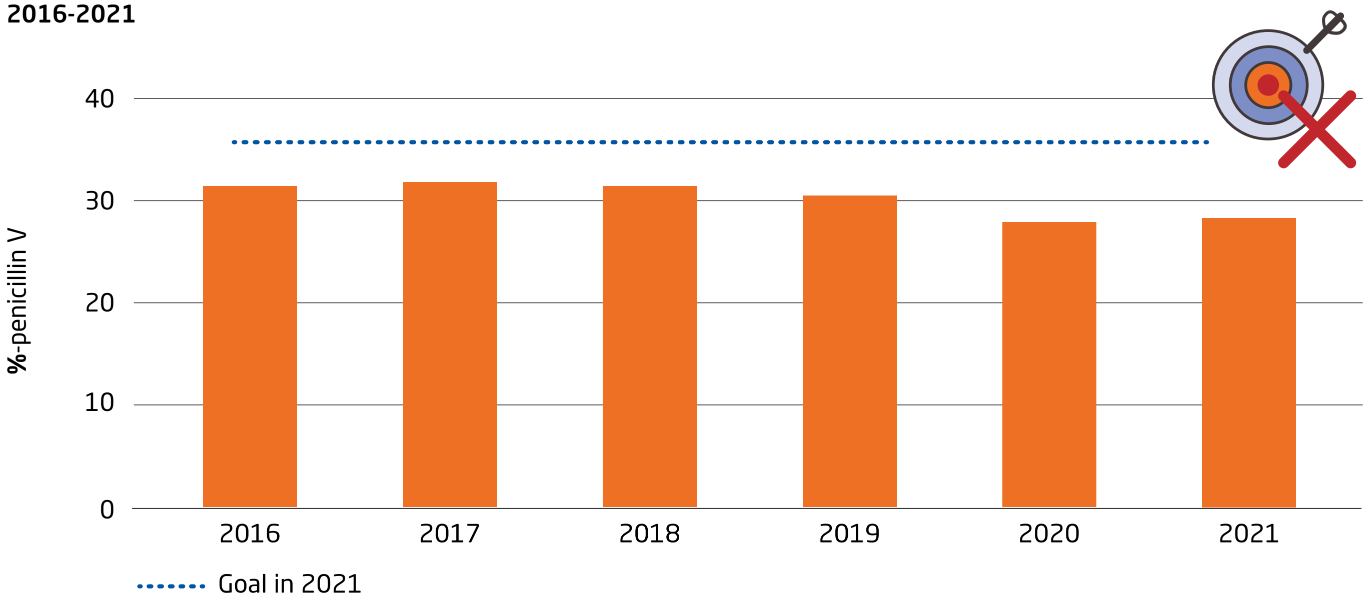
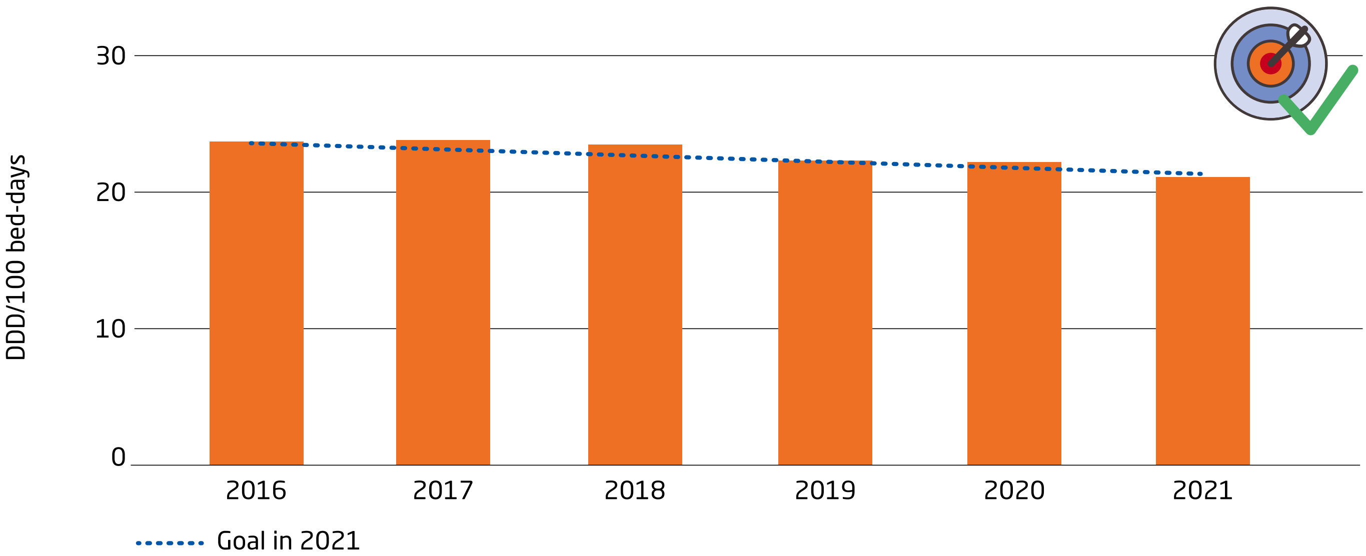


Figure 3.9 Goal 3: Consumption of critically important antibiotics (cephalosporins, fluoroquinolones, carbapenems) in hospitals, Denmark, 2016-2021



4. Resistance in zoonotic bacteria and animal pathogens

Zoonotic bacteria - increase in full sensitivity, decrease in multidrug resistance and detection of resistance to critically-important antimicrobials

Surveillance of antimicrobial resistance (AMR) in the zoonotic bacteria *Campylobacter* and *Salmonella* from healthy food-producing animals, fresh meat, and human clinical cases has been part of the DANMAP programme since 1995.

In Denmark, antimicrobials are only recommended for treatment of *Campylobacter* or *Salmonella* human infections in cases of diarrhoea of prolonged duration or in severely ill patients. If treatment is required, azithromycin (macrolide) is recommended to treat *Campylobacter* infections and less severe cases of *Salmonella* infections in hospital patients, but fluoroquinolones may also be used. Third generation cephalosporins are used to treat *Salmonella* infections in septic patients. In animal production, macrolides are often used to treat infections in Danish pigs, while the use of antimicrobials in Danish poultry is low and mainly limited to tetracyclines.

DANMAP *explorer* – Explore the DANMAP antimicrobial resistance results

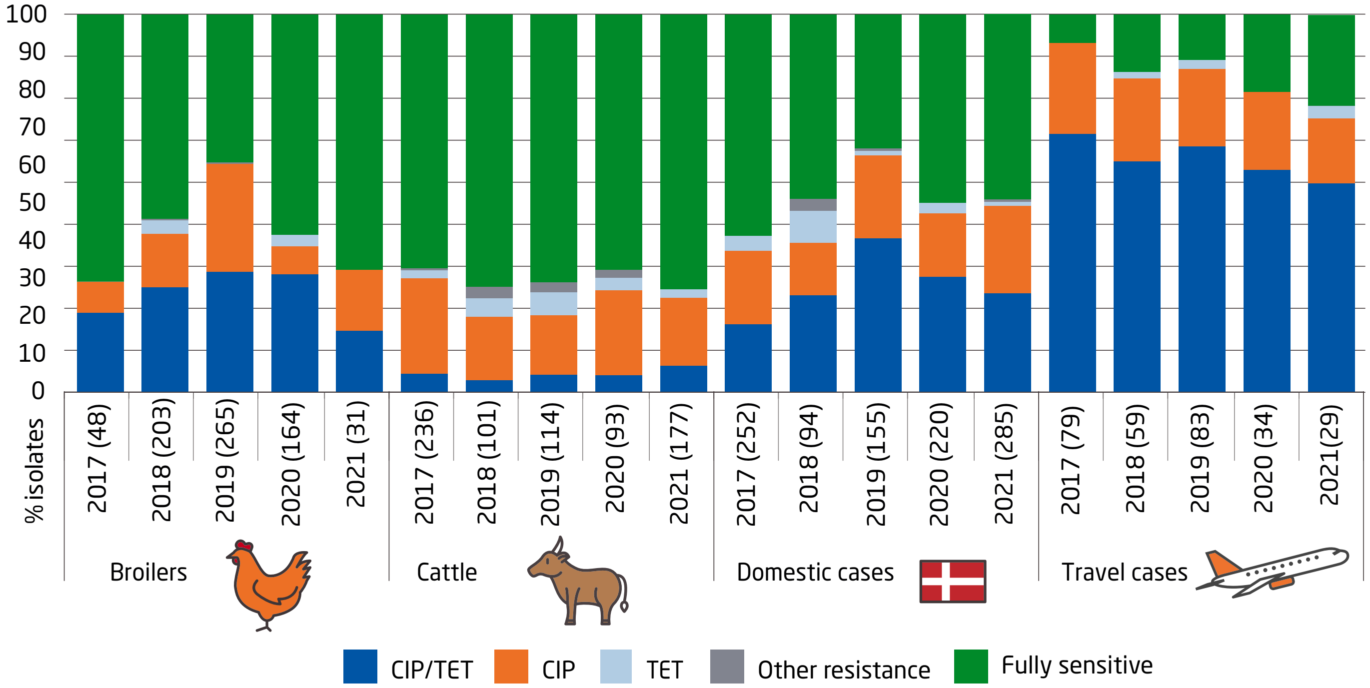
Monitoring results for prevalence of *Campylobacter* and *Salmonella* will soon be available for interactive visualization in DANMAP explorer, at www.DANMAP.org.

Resistance in *Campylobacter jejuni* and *Campylobacter coli*

C. jejuni is the *Campylobacter* species that most commonly is associated with foodborne gastro-intestinal human infections in Denmark. *C. jejuni* is also common in the guts of broilers and cattle, while *C. coli* is often present in pigs.

As in the previous years, occurrence of resistance in *C. jejuni* isolated from humans was higher than in isolates from broilers and cattle, and among the human infections the occurrence of resistance was higher in travel-associated cases compared to that of the domestically acquired infections. Compared to 2020, the percentage of fully sensitive *C. jejuni* increased in 2021 among isolates from both broilers (68% in 2021 vs 59% in 2020), cattle (73% in 2021 vs 68% in 2020) and travel-associated human infections (24% in 2021 vs 21% in 2020), while it remained at a very similar level in domestically acquired human infections (49% in 2021 vs 50% in 2020) (Figure 4.1).

Figure 4.1 Distribution (%) of AMR profiles among *Campylobacter jejuni* from broilers, cattle and human cases, Denmark, 2017-2021



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

Ciprofloxacin and tetracycline resistance in *C. jejuni* is common, whereas resistance is rarely observed for erythromycin and gentamicin. In 2021, macrolide (erythromycin) resistance in *C. jejuni* remained very low or was not detected, while fluoroquinolone (ciprofloxacin) resistance remained common (Table 4.1). Compared to 2020, combined resistance to ciprofloxacin and tetracycline decreased in isolates from broilers and humans (Figure 4.1).

C. coli from pigs were commonly resistant to ciprofloxacin (20%) and tetracycline (26%). Macrolide resistance (erythromycin) was observed in 6% of the isolates and no resistance to gentamicin was recorded.

The monitoring of amphenicol and carbapenem resistance in *Campylobacter* started in 2021, by including the antimicrobials chloramphenicol and ertapenem in the test panel, respectively. Ertapenem resistance was not observed in *C. jejuni* isolates from broilers and cattle, but one *C. coli* isolate from a pig (<1%) was resistant. Among *C. jejuni* from human infections, 4% and 14% of the isolates from domestically acquired and travel-associated infections, respectively, were resistant to ertapenem. No chloramphenicol resistance was observed among all *Campylobacter* isolates tested (Table 4.1).

Table 4.1 Resistance (%) in *Campylobacter jejuni* isolates from broilers, cattle and human cases, Denmark, 2021

	Broilers	Cattle	Human			
	Danish	Danish	Domestically acquired	Travel abroad reported	Unknown origin	Total
Antimicrobial agent	%	%	%	%	%	%
Chloramphenicol	0	0	0	0	0	0
Ciprofloxacin	32	25	49	72	57	52
Ertapenem	0	0	4	14	6	5
Erythromycin	0	0	0	0	2	<1
Gentamicin	0	0	0	0	0	0
Tetracycline	16	9	27	59	31	30
Fully sensitive (%)	68	73	49	24	41	46
Number of isolates	31	177	285	29	49	363

An isolate is categorised as domestically acquired if the patient did not travel outside Denmark one week prior to the onset of disease. Total number of human cases includes infections of unknown origin. In 2021, nalidixic acid and streptomycin were substituted by chloramphenicol and ertapenem in the antibiotic test panel for *Campylobacter*

Resistance in *Salmonella* Typhimurium

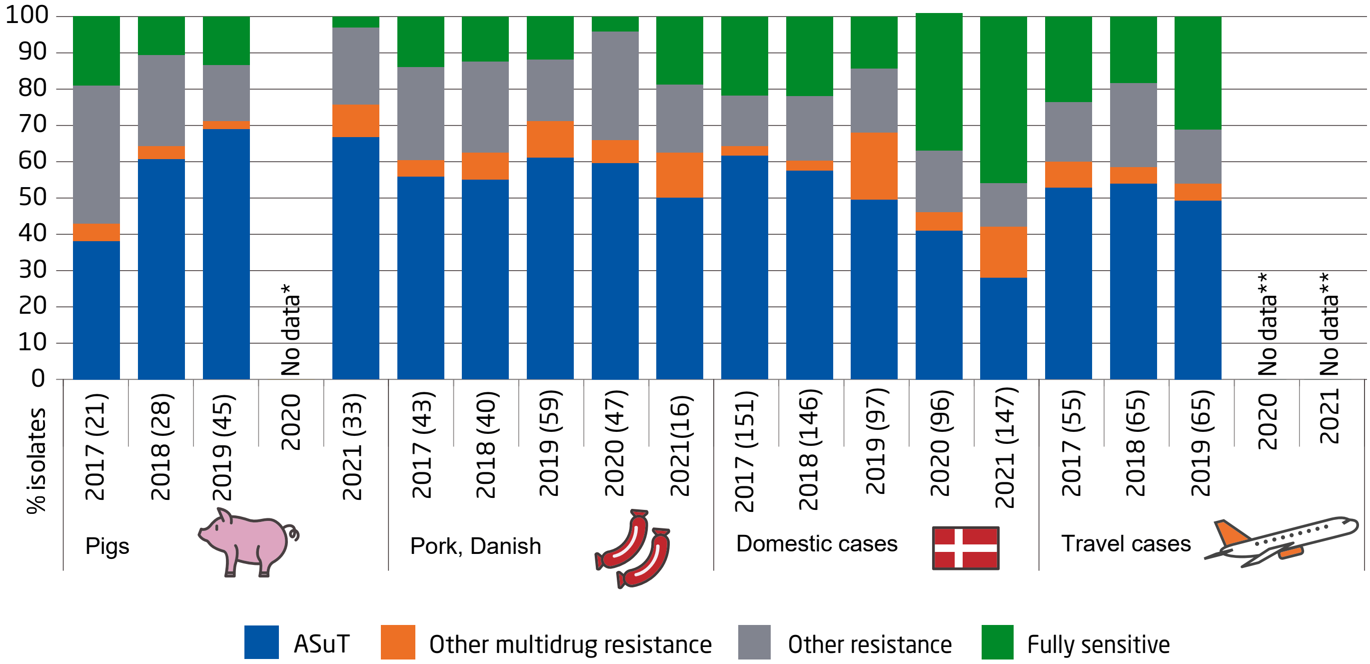
DANMAP focuses on resistance in *Salmonella* Typhimurium, including the monophasic variants with antigenic formula S. 4,[5],12:i:-, as this serotype is present among clinical human isolates and in isolates from pigs and contaminated pork. Genomic islands conferring combined resistance to ampicillin, sulfonamide and tetracycline (the ASuT profile) occur commonly in *S.* Typhimurium and contribute to a high level of multidrug-resistance.

As in most previous years, ASuT resistance represented the majority of multidrug-resistance profiles among all isolates, and was relatively higher among Danish pig- and pork isolates than among human isolates from domestically acquired infections. The percentage of fully sensitive human isolates from domestic cases was higher (47%) compared to fully sensitive isolates from pigs (3%) and from Danish pork (15%). The occurrence of fully sensitive *S.* Typhimurium isolates from domestic human cases increased from 2020 to 2021, however, in 2021, this could have been partially caused by two outbreaks involving fully sensitive strains. For Danish pork, in comparison with the previous year, the prevalence of fully sensitive isolates has increased, and the relative proportion of ASuT resistance has decreased (Figure 4.2).

Fluoroquinolone (ciprofloxacin) resistance was observed in 7% percent of the human isolates from domestically acquired infections, which represents an increase in comparison with the previous 10 years of monitoring. In 2021, ciprofloxacin resistance remained absent among isolates from Danish pork and Danish pigs (Table 4.2).

The level of macrolide (azithromycin) resistance remained low as in previous years in isolates from domestically acquired human infections and from Danish pork. However, unlike the previous years, where azithromycin resistance was not detected in isolates from pigs, in 2021, 9% (3 isolates) of *S.* Typhimurium recovered from pigs were azithromycin resistant (Table 4.2). Resistance to the critically important 3rd generation cephalosporins and carbapenems are rare in *S.* Typhimurium. In 2021, 3rd generation cephalosporin resistance was observed in less than 1% of the human isolates and was not observed in isolates from pigs and Danish pork, and carbapenem resistance was not observed (Table 4.2).

Figure 4.2 Relative distributions (%) of AMR profiles among *Salmonella* Typhimurium from pigs, pork and human cases, Denmark, 2017-2021



The number of isolates included each year is shown in parentheses. Includes isolates verified as 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 all antimicrobial agents included in the test panel. ASuT are isolates that are resistant to ampicillin, sulfonamide and tetracycline

* No data available

** Distribution not shown due to low number of isolates (<15)

Table 4.2 Resistance (%) in *Salmonella* Typhimurium isolates from pigs, domestic pork and humans, Denmark, 2021

	Pigs	Pork	Human	
	Danish	Danish	Domestically acquired	Total
Antimicrobial agent	%	%	%	%
Amikacin	0	0	1	1
Ampicillin	79	79	45	43
Azithromycin	9	3	0	<1%
Cefotaxime	0	0	1	<1%
Ceftazidime	0	0	1	<1%
Chloramphenicol	9	21	5	5
Ciprofloxacin	0	0	7	6
Colistin	0	0	0	<1%
Gentamicin	3	0	1	1
Meropenem	0	0	0	0
Nalidixic acid	0	0	5	5
Sulfonamide	82	79	45	43
Tetracycline	88	67	51	51
Tigecycline	9	3	3	3
Trimethoprim	18	31	5	4
Fully sensitive (%)	3	15	46	47
Number of isolates	33	39	147	205

Includes isolates verified as monophasic variants of *S*. Typhimurium with antigenic formulas s. 4,[5],12:i:-. Isolates of Danish pork were recovered from carcass swabs collected at slaughter. An isolate is categorised as domestically acquired if the patient did not travel outside Denmark one week prior to the onset of disease. Total number of human cases includes travel cases and infections of unknown origin. An isolate is considered fully sensitive if susceptible to all antimicrobial agents included in the test panel. Amikacin was included in the test panel for *Salmonella* in 2021

Resistance in pathogenic bacteria from pigs – high concordance between phenotypic and genotypic results

Phenotypic susceptibility testing for surveillance of AMR in pathogenic bacteria from pigs, including *Actinobacillus pleuropneumoniae*, *Escherichia coli* and *Streptococcus suis*, has been part of the DANMAP programme since 2015. In 2021, whole-genome sequencing (WGS) was implemented in the surveillance of AMR in those bacteria as a basis to detect resistance genes and point mutations.

Overall, *A. pleuropneumoniae*, haemolytic *E. coli* and *S. suis* displayed similar levels of resistance as in previous years (Table 4.3).

There was a high concordance between antimicrobial susceptibility testing results and presence/absence of corresponding resistance genes/point mutations in pathogenic bacteria from pigs (100% for *A. pleuropneumoniae*, 96% for haemolytic *E. coli* and 90% for *S. suis*).

Resistance to the critically important 3rd generation cephalosporin cefotaxime was identified in 7% of the haemolytic *E. coli* isolates and was always associated with presence of either the $bla_{\text{CTX-M-1}}$ gene or point mutations in the *ampC* promoter.

The *optrA* gene, which has been associated with resistance to oxazolidinones (e.g., linezolid used in human medicine) and phenicols (e.g., florfenicol used in veterinary medicine) was identified in 2% of the *S. suis* isolates.

A mutation in the *pmrB* gene associated with resistance to colistin was identified in 14% of the haemolytic *E. coli* isolates, but only one of the 15 isolates with this point mutation was phenotypically resistant to colistin.

Table 4.3 Resistance among clinical *Actinobacillus pleuropneumoniae*, haemolytic *Escherichia coli* and *Streptococcus suis* isolates from pigs, Denmark, 2021

Antimicrobial agent	*Actinobacillus pleuropneumoniae* (n=159)	*Haemolytic Escherichia coli* (n=242)	*Streptococcus suis* (n=149)
	non-wild-type/R (%)	non-wild-type/R (%)	non-wild-type/R (%)
Ampicillin	1.3	66.9	ND
Amoxicillin-clavulanic acid	ND	5.4	ND
Cefotaxime	ND	4.1	ND
Ceftiofur	0.0	0.8	ND
Chloramphenicol	ND	22.7	0.0
Ciprofloxacin	ND	9.1	ND
Colistin	ND	0.8	ND
Erythromycin	ND	ND	59.7
Florfenicol	0.0	16.5	1.3
Gentamicin	ND	12.8	ND
Neomycin	ND	25.6	ND
Penicillin	ND	ND	2.7
Spectinomycin	ND	62.4	ND
Streptomycin	ND	76.4	ND
Tetracycline	3.8	57.0	73.8
Tiamulin	0.0	ND	ND
Trimethoprim	ND	61.2	ND
Trimethoprim-sulfamethoxazole	0.0	ND	14.8

Data are based on ECOFFs and clinical breakpoints when ECOFFs are unavailable
Abbreviations: ECOFF, epidemiological cut-off; R, resistant; ND, not determined

5. Resistance in indicator bacteria

Escherichia coli and Enterococci (*E. faecalis*) are included in the DANMAP programme to monitor occurrence of antimicrobial resistance in different production animals, both at slaughter and at retail. They are considered indicator bacteria because they are commensals in the gut of healthy animals and humans, they can acquire antimicrobial resistance via mutations in chromosomal genes and by horizontal gene transfer, they have the potential to transfer antimicrobial resistance genes to pathogenic bacteria within and across species, and they can cause infections in both animals and humans.

E. coli exhibiting resistance to 3rd generation cephalosporins via production of extended-spectrum cephalosporinases (ESC), including beta-lactamases (ESBL) and AmpC beta-lactamases (AmpC), are spreading fast in both humans and production animals worldwide. Carbapenemase-producing Enterobacteriaceae (CPE) are a great threat to human health, due to the importance of carbapenems as last-line antimicrobials. In recent years, CP-producing *E. coli* have been sporadically, but increasingly detected in production animals in EU. ESC- and CP-producing *E. coli* are monitored in DANMAP in healthy animals at slaughter and in fresh meat of domestic- and imported origin, via antimicrobial susceptibility testing and whole genome sequencing.

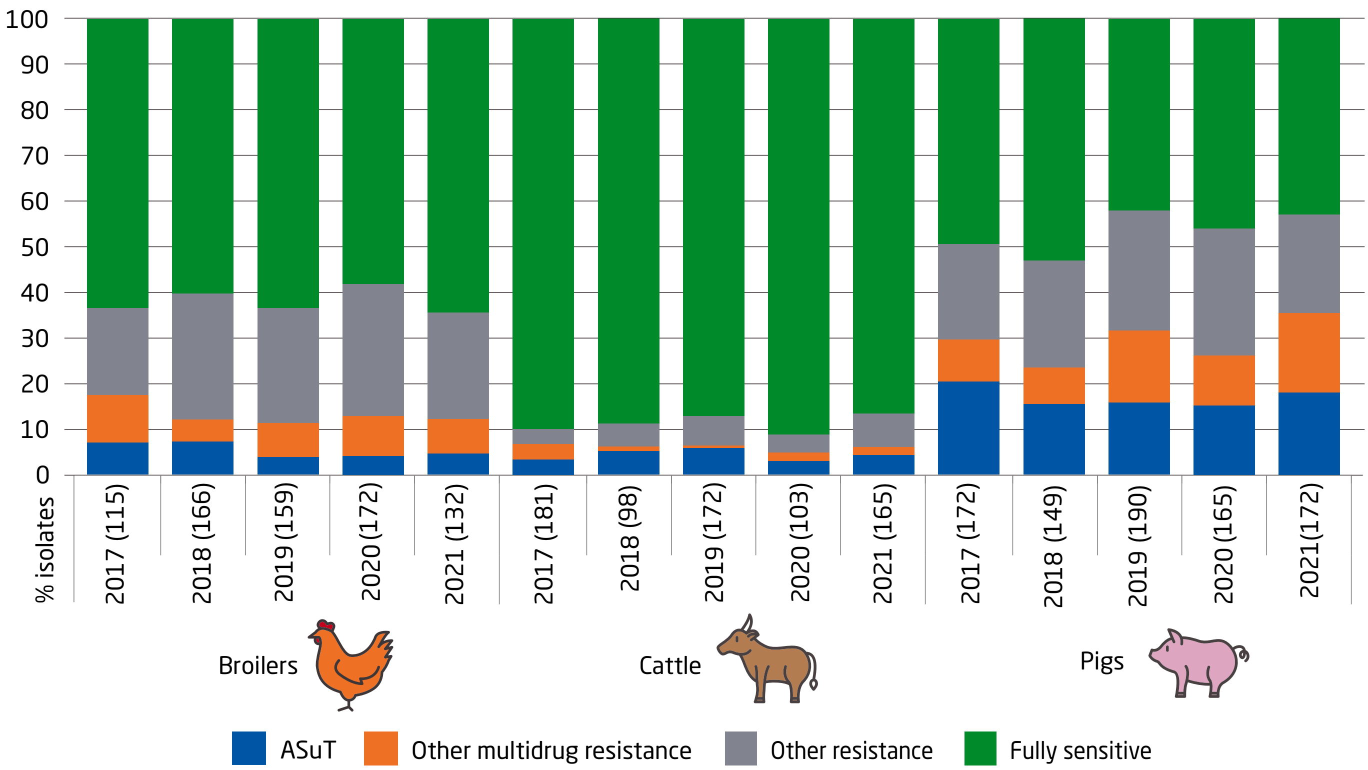
DANMAP *explorer* – Explore the DANMAP antimicrobial resistance results

Monitoring results for prevalence of indicator *E. coli*, indicator *E. faecalis* and ESC-producing *E. coli* will soon be available for interactive visualization in DANMAP explorer, at www.DANMAP.org.

Indicator *E. coli* – overall increase in resistance in isolates from pigs

Although no significant trend has been detected in the prevalence of fully sensitive indicator *E. coli* from Danish production animals over the last 5-year monitoring period, from 2020 to 2021, the prevalence of fully sensitive *E. coli* increased in broilers (from 58% in 2020 to 64% in 2021) and decreased in pigs (from 46% in 2020 to 43% in 2021) and in cattle (from 91% in 2020 to 87% in 2021) (Figure 5.1).

Figure 5.1 Relative distributions (%) of fully sensitive, resistant and multidrug-resistant *Escherichia coli* isolates from broilers, cattle and pigs, Denmark 2017-2021



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 all antimicrobial agents included in the test panel. ASuT are the multidrug-resistant isolates resistant to ampicillin, sulfonamide and tetracycline, which may also be resistant to other antimicrobials

The relative occurrence of multidrug-resistant indicator *E. coli* increased among isolates from pigs. Combined resistance to ampicillin, sulfamethoxazole and tetracycline (ASuT) continued to be the most common multidrug-resistance profile in isolates from all monitored animal populations in 2021 (Figure 5.1). Compared to 2020, resistance to ampicillin, sulfamethoxazole and tetracycline decreased in *E. coli* isolates from broilers and increased in isolates from cattle and pigs. In pigs, the prevalence of resistance to chloramphenicol and to trimethoprim also increased in 2021 (Table 5.1).

As in previous years, no colistin, meropenem or tigecycline resistance was detected in indicator *E. coli*. Resistance to ciprofloxacin continued to be low among cattle- and pig isolates and levelled out in isolates from broilers. In 2021, azithromycin resistance was detected in few isolates from pigs (3%) (Table 5.1).

Table 5.1 Resistance (%) in *Escherichia coli* isolates from broilers, cattle and pigs, Denmark, 2021

	Broilers	Cattle	Pigs
	Danish	Danish	Danish
Antimicrobial agent	%	%	%
Amikacin	0	0	0
Ampicillin	16	7	38
Azithromycin	0	0	3
Cefotaxime	0	<1	1
Ceftazidime	0	<1	1
Chloramphenicol	0	5	12
Ciprofloxacin	16	<1	1
Colistin	0	0	0
Gentamicin	2	0	1
Meropenem	0	0	0
Nalidixic acid	14	0	1
Sulfamethoxazole	16	9	43
Tetracycline	8	11	37
Tigecycline	0	0	0
Trimethoprim	11	1	34
Fully sensitive (%)	64	87	43
Number of isolates	132	165	172

An isolate is considered fully sensitive if susceptible to all antimicrobial agents included in the test panel. Amikacin was included in the test panel for *E. coli* in 2021

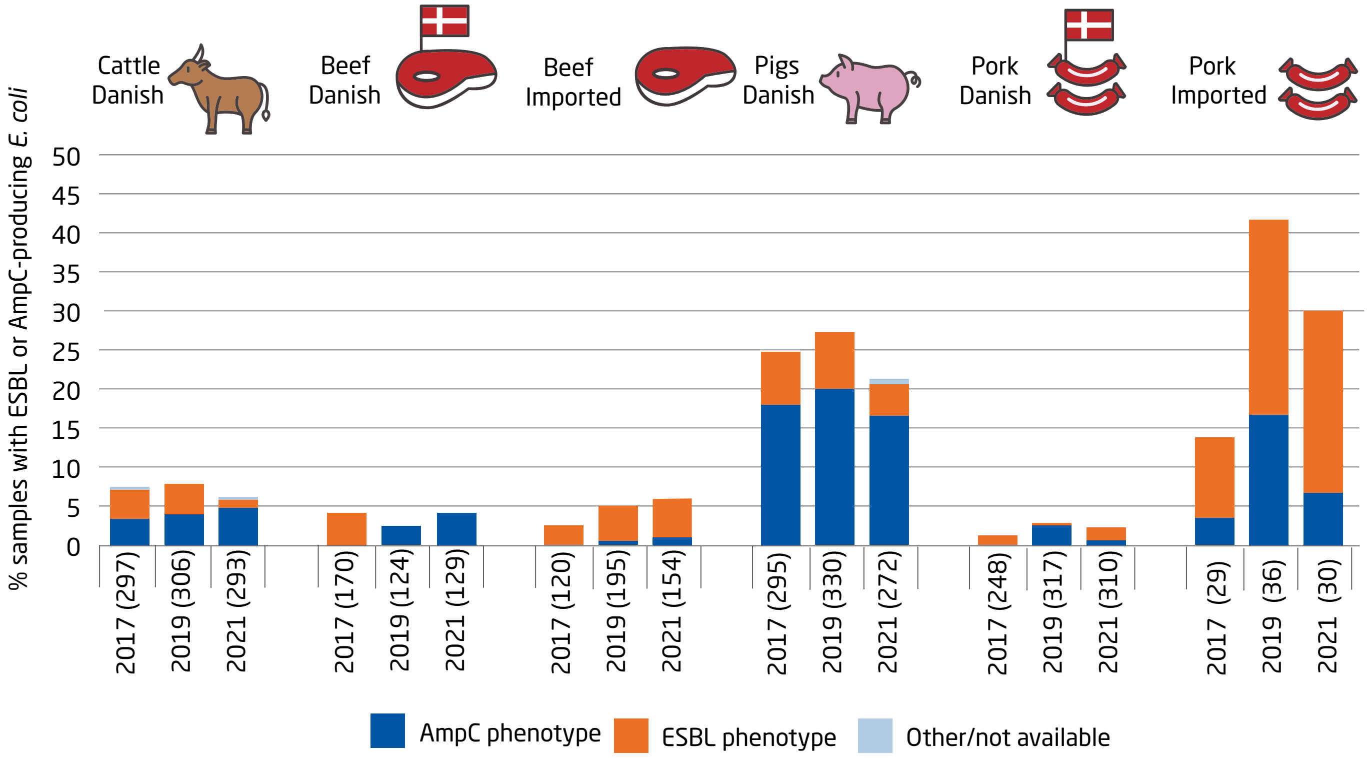
ESC-producing *E. coli* - possible development of increasing trend in imported beef

The occurrence of *E. coli* producing extended-spectrum cephalosporinases (ESC) decreased in Danish pigs and imported pork, and continued to increase in imported beef. As in previous years, no samples from animals or meat were found positive for carbapenemase-producing *E. coli* (Figure 5.2).

The phenotypic and genotypic resistance profiles of ESC-producing *E. coli* were mostly in concordance, however whole genome sequencing revealed occurrence of both ESBL and AmpC encoding genes in 17 isolates, while susceptibility testing did not show combined ESBL and AmpC resistance (Table 5.2).

Among the AmpC-producing isolates, resistance was mainly conferred by upregulated AmpC promotor C-42T mutations, while among ESBL-producing isolates, 25 different ESBL genes were detected, with most variation among isolates from pigs. Overall, the most commonly observed ESBL encoding genes were CTX-M-1 and TEM-1B (Table 5.2).

Figure 5.2 Occurrence (%) of samples with phenotypic ESBL- or AmpC-producing *E. coli* from animals and meat recoved by selective enrichment, Denmark 2017-2021



Number of samples tested per year is presented in the parentheses. Classification of ESBL and AmpC phenotypes is based on the antimicrobial susceptibility testing. Other/not available does not include any ESBL- and AmpC-producing *E. coli*, as this phenotype was not detected. The total number of samples of imported beef includes 151 samples collected at retail and 3 samples collected at border control posts (BCPs). The total number of samples of imported pork includes 27 samples collected at retail and 3 samples collected at BCPs

Table 5.2 Number of ESBL and AmpC enzymes detected in ESC-producing *E. coli* isolates from animals and meat recovered by selective enrichment, Denmark, 2021

	Cattle	Beef		Pigs	Pork	
Genotypes based on AmpC/ESBL enzymes	Danish %	Danish %	Import %	Danish %	Danish %	Import %
Number of AmpC genotypes	14	4	1	24	2	1
Number of ESBL genotypes	3	0	8	9	4	5
Number of AmpC+ESBL genotypes	1	0	1	14	0	1
Not available	1	1	0	11	1	2
Number (%) positive samples	18 (6%)	5 (4%)	10 (6%)	58 (21%)	7 (2%)	9 (30%)
Number of tested samples	293	129	154	272	310	30

Number (%) positive samples are isolates recovered by selective enrichment methods for specific monitoring of ESC-producing *E. coli*. ESBL/AmpC enzymes were determined by whole genome sequencing (WGS) of the recovered isolates. Not available refers to isolates without available WGS results

Enterococcus faecalis from pigs - lower resistance levels compared to previous monitoring year

In 2021, 21% of *E. faecalis* isolated from pigs were fully sensitive. No resistance to ampicillin, linezolid, teicoplanin, tigecycline, vancomycin, ciprofloxacin or daptomycin was detected in any of the isolates. Resistance to all other antibiotics in the test panel decreased in 2021 compared to 2019. Combined resistance to tetracycline and erythromycin continued to be the most common resistance profile, followed by a profile with additional resistance to chloramphenicol.

6. Resistance in human pathogens

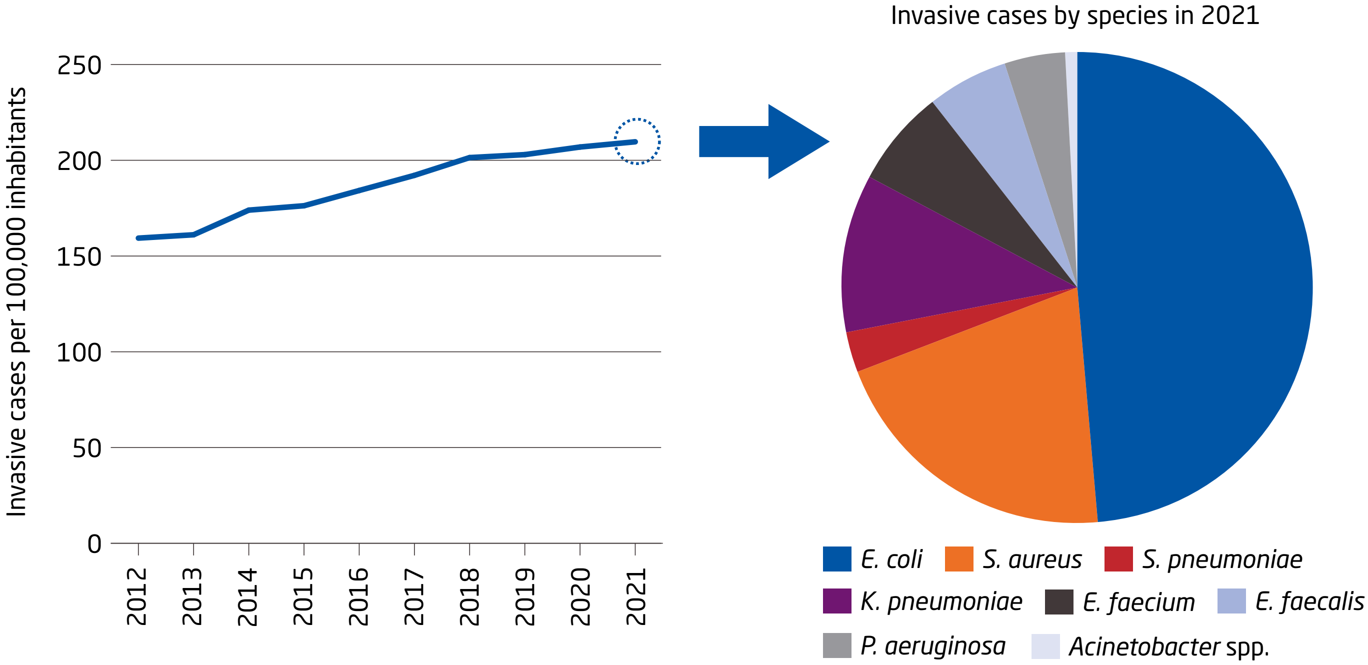
DANMAP's surveillance of antimicrobial resistance in bacteria from humans is based on clinical isolates and covers all antimicrobial susceptibility testing performed in Denmark. Data include phenotypic results from all Departments of Clinical Microbiology (DCMs) and phenotypic and/or genotypic results of isolates submitted to national reference laboratories (NRL) at SSI. Data for DANMAP is either extracted from the Danish Microbiological database (MiBa) or collected from the registers at the NRL.

Continued increases in invasive bacterial species monitored in Denmark

Escherichia coli was the most frequent cause of invasive infections (5,981 in 2021) with a 52% increase in the number of invasive isolates over the last decade. *Staphylococcus aureus* bacteraemia accounted for 2,506 patient cases (1,431 in 2012, 75% increase), followed by *Klebsiella pneumonia* with 1,336 patient cases (948 in 2012, 41% increase), (Figure 6.1).

The increasing numbers of invasive infections mirror an increase in hospitalised patients and at-risk groups (elderly and immunocompromised/chronically ill patients) and may in addition be associated with a higher use of invasive medical procedures. In addition, the number of microbiological samples received for analysis at the DCM has increased considerably during the past decade as well as the number of samples taken per patient. In 2021, a total of 3,129 patients per 100,000 inhabitants had at least one blood culture taken compared to 2,266 patients per 100,000 inhabitants in 2012, an increase of 38%. Simultaneously, the number of positive blood cultures from bacterial species under surveillance in DANMAP increased markedly, by an equal 38%, Figure 6.1.

Figure 6.1 Number of monitored invasive cases, Denmark, 2012-2021



Resistance in monitored bacterial species in Denmark

Resistance in *E. coli* has remained below the 10% percentile for most antimicrobials for the past decade with particularly decreasing trends for resistance to ciprofloxacin, cephalosporins and gentamicin and increasing trends for resistance to piperacillin-tazobactam. For *K. pneumoniae* similar trends were observed, the decreases in resistance to cephalosporins, fluoroquinolones and gentamicin being even more notable.

Table 6.1 Resistance (%) in *E. coli* and *K. pneumoniae* from urines and blood cultures, 2012-2021

	E. coli				*K. pneumoniae*			
	Urines from praxis 2012	Urines from praxis 2021	Invasive 2012	Invasive 2021	Urines from praxis 2012	Urines from praxis 2021	Invasive 2012	Invasive 2021
Ampicillin	40	34	45	41	-	100	-	100
Mecillinam	6.1	4.6	9.4	13	11	8.6	8.9	12
Trimethoprim	-	19	-	-	-	14	-	-
Amoxicillin/ clavulanic acid	-	-	-	25	-	-	-	14
Piperacillin-tazobactam	-	-	4.1	6.0	-	-	5.6	7.6
Cefuroxim	-	-	9.2	8.7	-	-	14	7.9
3rd gen. cephalosporins	3.5	4.4	7.1	5.4	4.7	3.7	8.9	4.9
Ciprofloxacin	10	6.9	14	10	8.3	4.9	8.8	6.7
Carbapenem	-	-	0.0	0.0	-	-	0.3	0.5

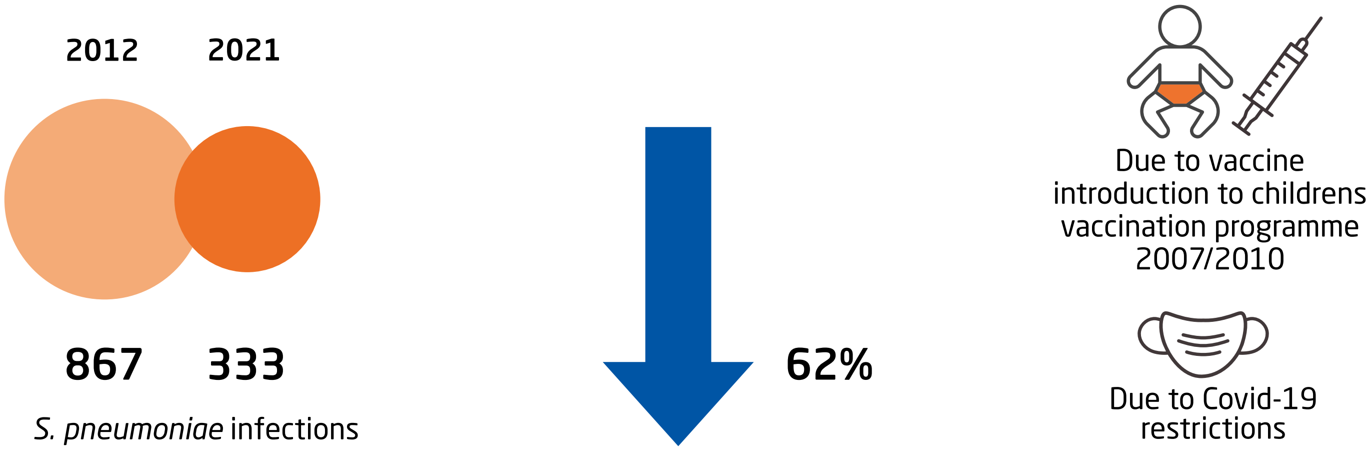
Continued decrease in the number of invasive pneumococcal infections

Invasive pneumococcal disease caused by *Streptococcus pneumoniae* has been a mandatory notifiable disease since the introduction of the pneumococcal PCV-7 vaccine in the Danish childhood vaccination programme in 2007. Over the last ten years, the number of cases has decreased by 62% (Fig. 6.3), largely due to vaccine and COVID-19 restrictions. Resistance to penicillin and erythromycin has slowly increased over the past 25 years, but fluctuates with the circulating serotypes.

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

Since 2016, 3rd generation cephalosporin resistant *E. coli* have been submitted to the reference laboratory at SSI on a voluntary basis. Monitoring the presence of ESBL/AmpC enzymes in invasive *E. coli* isolates is important since they confer resistance to most beta-lactam antibiotics, which limits treatment options for infected patients. Between 2020 and 2021, the number of ESBL- and/ or AmpC positive invasive *E. coli* isolates decreased by 28% (from 352 to 254 isolates).

Figure 6.2 Decrease in invasive infections caused by *S. pneumoniae*, Denmark, 2012 and 2021



Increasing numbers of CPO isolates associated with outbreaks and travel

Carbapenemase-producing organisms (CPO) have been notifiable since 2018. A substantial increase in CPO isolates related to outbreaks in Danish hospitals has been observed from 2019 to 2021 with 42 and 97 isolates, respectively (Figure 6.4a). In 2021, there were 15 registered on-going outbreaks. Acting in accordance with the CPO guidelines is of utmost important in order to prevent the further spread of CPO.

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.

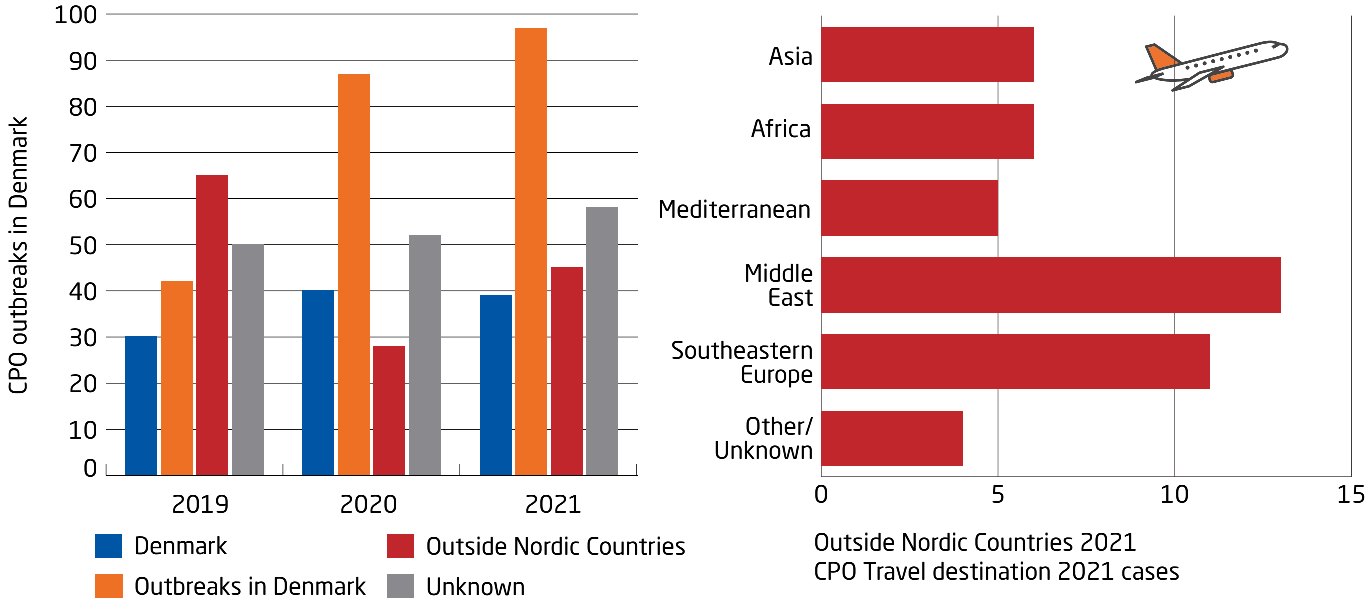
Detection of CPO was made notifiable in Denmark in September 2018.

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*

Following the easing of COVID-19 restrictions, an increasing number of CPO isolates related to travel has also been observed. In 2021, 45 CPO isolates were related to travel compared to 28 in 2020. The regions where the patients had travelled to can be seen in Figure 6.4b.

Figure 6.3 CPO a) Classification of CPO cases from 2019 through 2021 b) world regions where the patients with travel related cases had travelled



The number of vancomycin-resistant and vancomycin-variable enterococci (VRE/VVE) increased from 2020 to 2021

Voluntary submission of VRE from the DCMs to the SSI reference laboratory has been on-going since 2005. In 2021, 733 VRE/VVE isolates were detected in Denmark – a 12% increase compared to the 656 isolates found in 2020. This is a worrying development after the stable numbers found in 2020. The increasing numbers warrants intensified efforts by clinicians and infection prevention and control teams to control outbreaks in healthcare facilities and implement prevention strategies in order to curb the numbers.

The numbers of linezolid-resistant enterococci (LRE) and linezolid-vancomycin-resistant enterococci (LVRE) were small in 2021 (1 and 14 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 – continued increases in the number of bacteraemia cases in 2021

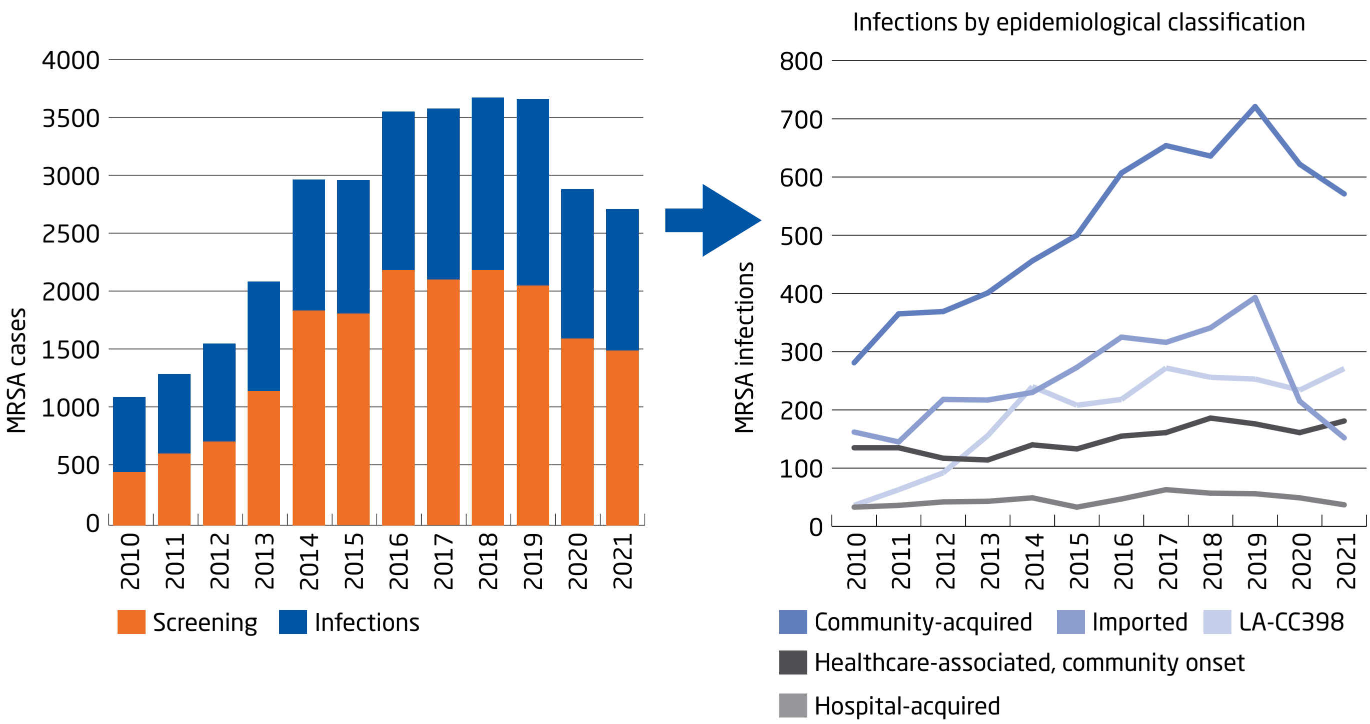
Since 1957 isolates from invasive infections with *Staphylococcus aureus* have on a voluntary basis been referred to the reference laboratories at Statens Serum Institut. Since 2006, the isolation of methicillin resistant *S. aureus* (MRSA) from either infected or non-infected (colonized) persons has been notifiable and guidelines were issued by the Danish Health Authority regarding the detection, prevention and management of MRSA. Revision of the guidelines in 2012 included an extension with specific focus on livestock-associated MRSA (LA-MRSA), which is found especially in pigs, but may be found in other livestock and horses and can be transmitted to humans. The 3rd revision of the MRSA guidelines is currently in use and includes an update on screening procedures and community-management of MRSA.

In 2021, the number of invasive *S. aureus* isolates from blood had increased by 7% from 2,342 cases in 2020 to 2,512 cases in 2021. Forty (2%) of the bacteraemia cases were caused by methicillin-resistant (MRSA) out of which six were LA-MRSA.

Surveillance of all MRSA cases, e.g. infected and colonized persons, showed a continued decrease of 6% in 2021 (2712 cases) compared to 2020 (2883 cases) and a 74% increase compared to 2012 (1557cases), figure 6.4. LA-MRSA constituted 36% of all new MRSA cases and primarily affected persons working with pigs and their households. Trends in MRSA in infected persons is presented in Figure 6.4.

The number of MRSA outbreaks in hospitals, nursing homes and other institutions stayed at the same low levels as in 2020, but involved fewer patients (30 outbreaks in 2021, 31 in 2020; 109 patients in 2020, 130 in 2020).

Figure 6.4 Number of MRSA under surveillance (screening and infections), Denmark, 2010-2021



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

Gonorrhoea, the second most common sexually transmitted bacterial infection in Denmark, is caused by *N. gonorrhoeae* (gonococci) and the DCMs have submitted isolates to SSI since 1962. In 2021, SSI's reference laboratory confirmed 1,408 cases of gonorrhoea. The proportion of gonococci being resistant to the first- and second line antimicrobials used for treatment of gonorrhoea (ceftriaxone, azithromycin, ciprofloxacin) were 0%, 3% and 48% respectively.

Although the occurrence of resistance among gonococci is currently not of concern in Denmark, the frequent emergence of resistance mechanisms in *N. gonorrhoeae* globally compromises the management, prevention 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.

7. One Health AMR – new perspectives

The health and functioning of the animal and human sectors are interrelated, and thus intersectorial studies are vital for monitoring coinciding trends and identifying possible AMR transmission between these sectors.

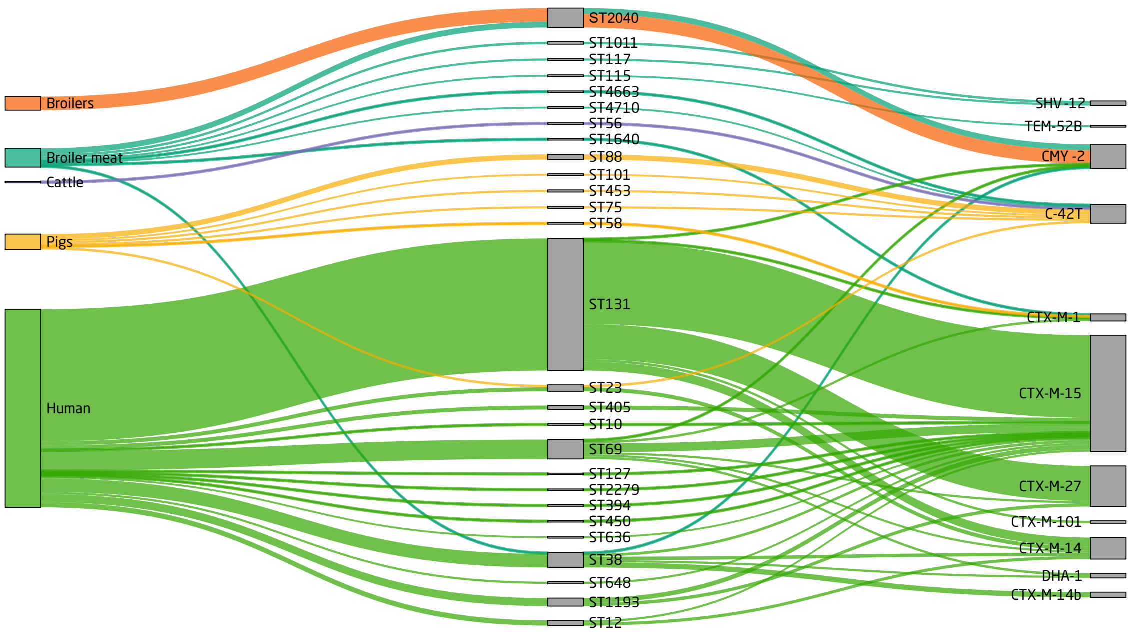
In order to determine similarities in AMR between the animal and food production and the human sector, a two-stranded approach was concocted.

First, an analysis was performed involving the phenotypic resistance profiles of human clinical *E. coli* UTI isolates from primary health care and indicator and clinical *E. coli* isolates from livestock animals from 2021. Altogether, 399 isolates from broilers, calves and pigs (including 191 clinical pig isolates) and 971 human UTI isolates were included in the analysis. Isolates were classified as either resistant or susceptible towards ampicillin, ciprofloxacin, sulfamethoxazole, trimethoprim or a 3rd generation cephalosporin. The results indicated that human UTI isolates have overall higher occurrence of resistance and are associated with resistance towards the critically important antibiotics, ciprofloxacin and 3rd generation cephalosporins. Indicator isolates from pigs correlated with resistance towards trimethoprim and sulfamethoxazole, both of which are commonly used in the treatment of pigs.

When including human UTI isolates, indicator *E. coli* from healthy pigs, and clinical *E. coli* from sick pigs in a second step, the results changed slightly. Here, the clinical isolates from pigs correlated with higher overall occurrence of resistance, particularly towards trimethoprim and sulfamethoxazole. Indicator isolates and human UTI isolates had lower overall occurrence of resistance, but again the human UTI isolates correlated with resistance towards ciprofloxacin and 3rd generation cephalosporins.

The second part of the analysis involved *E. coli* ESBL/AmpC isolates from human blood stream infections, food production animals and meat. A total of 1457 isolates from 2018 through 2021 were included with 884 from humans, 284 from meat and 289 from animals. Sequence types (ST) and ESBL genes were compared using a Sankey diagram (Fig. 7.1). Overlaps were seen for ST23 and ST38, but in both of these cases the ESBL genes were different. ST23 was found in both humans and pigs, but the human isolates carried the CTX-M-14 gene, whereas the pig isolates carried the C-42T promoter mutation. The same was observed with the ST38 isolates, where the broiler meat isolates carried the CMY-2 gene and the human isolates carried several different ESBL/AmpC genes that were all exclusively found in humans.

Figure 7.1 A Sankey diagram showing source, MLST and ESBL/AmpC gene of the included isolates. Flows of minimum five are shown



The results suggest that there is little to no overlap between the human health sector and the animal and food production sector. However, a more comparable dataset with isolates from healthy humans and/or diarrhoeal cases is suggested.

8. Timeline

Early 1980's

Clinical microbiology and principles of rational antibiotic use introduced as part of medical training at universities

1986

Antimicrobial prescription guidelines for doctors in "The little green" published by Danish Medical Association

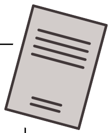
1993

Cascade rules for veterinary medicines

1994

MedStat Database with human use of medicinal products

1995



DANMAP Surveillance in food animals, food and humans

1995-1996

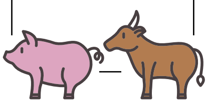
- VASC* contracts with farmers
- Veterinarians non profit on sale

1995-1999

Industry stop for antimicrobial growth promotors

1996

Guidelines for antimicrobial use in pigs and cattle



1997

1998

1999

2000

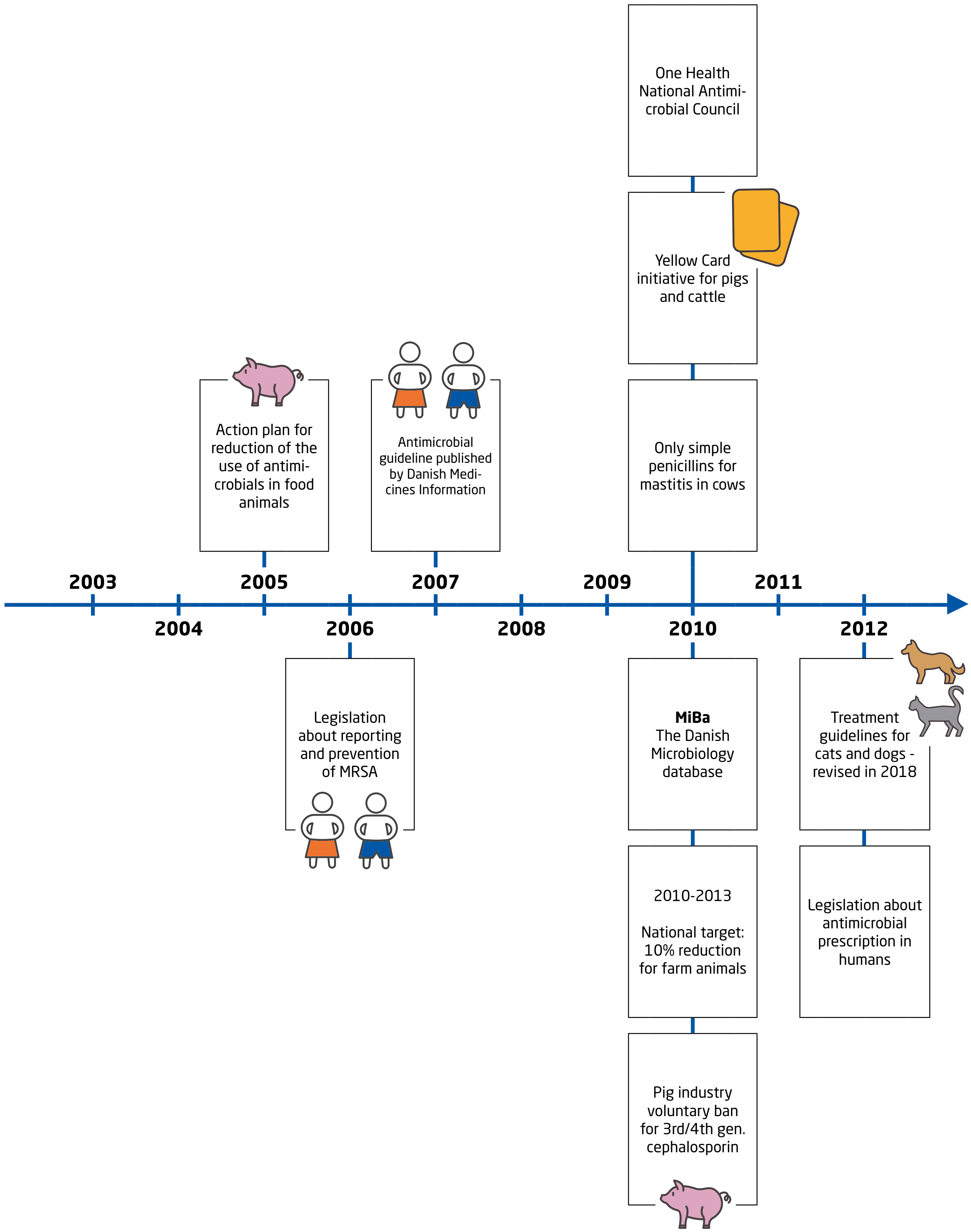
VetStat data collection

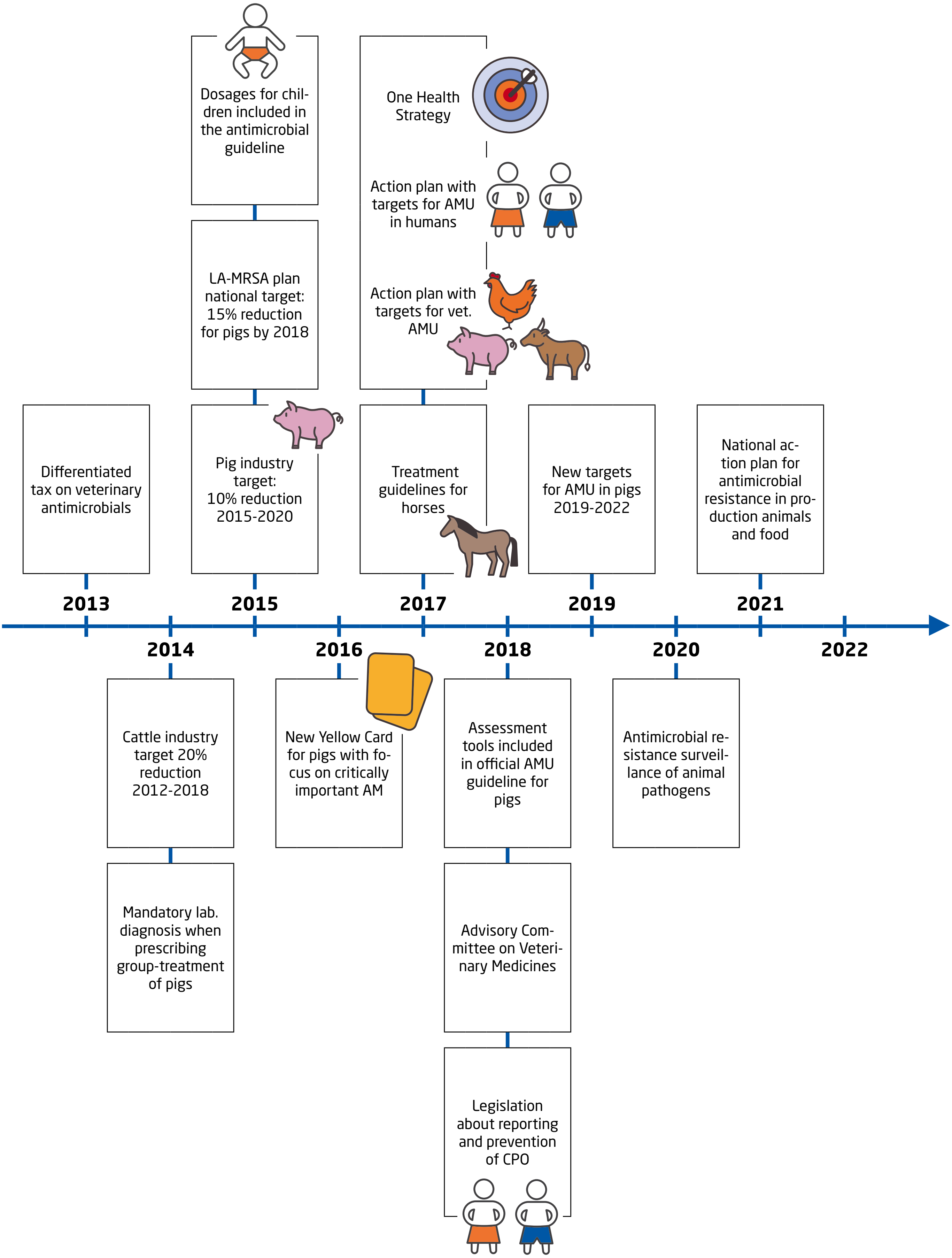
2001

2002

Restrictions on fluoroquinolones for food animals

* Veterinary Advisory Service contracts


One Health National Antimi-crobial Council
Yellow Card initiative for pigs and cattle
Only simple penicillins for mastitis in cows
Action plan for reduction of the use of antimi-crobials in food animals
Antimicrobial guideline published by Danish Medi-cines Information
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
Legislation about reporting and prevention of MRSA
MiBa The Danish Microbiology database
2010-2013
National target: 10% reduction for farm animals
Pig industry voluntary ban for 3rd/4th gen. cephalosporin
Treatment guidelines for cats and dogs - revised in 2018
Legislation about antimicrobial prescription in humans


2013
Differentiated tax on veterinary antimicrobials
2014
Cattle industry target 20% reduction 2012-2018
Mandatory lab. diagnosis when prescribing group-treatment of pigs
2015
Dosages for children included in the antimicrobial guideline
LA-MRSA plan national target: 15% reduction for pigs by 2018
Pig industry target: 10% reduction 2015-2020
2016
New Yellow Card for pigs with focus on critically important AM
2017
One Health Strategy
Action plan with targets for AMU in humans
Action plan with targets for vet. AMU
Treatment guidelines for horses
2018
Assessment tools included in official AMU guideline for pigs
Advisory Committee on Veterinary Medicines
Legislation about reporting and prevention of CPO
2019
New targets for AMU in pigs 2019-2022
2020
Antimicrobial resistance surveillance of animal pathogens
2021
National action plan for antimicrobial resistance in production animals and food
2022

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 Uncertainty
CA	Community-acquired
CC	Clonal complex
CDI	*Clostridium difficile* infections
CHR	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
SSI	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 2021